Cautionary and advisory labels—now user-tested, see Appendix 9

British National Formulary

BNF

61

March 2011

bnf.org

Medicines information services

Information on any aspect of drug therapy can be obtained from Regional and District Medicines Information Services. Details regarding the *local* services provided within your Region can be obtained by telephoning the following numbers.

England	
Birmingham	(0121) 424 7298
Bristol	(0117) 342 2867
Ipswich	(01473) 704 431
Leeds	(0113) 206 5377
Leicester	(0116) 255 5779
Liverpool	(0151) 794 8113/4/5/7 (0151) 794 8206
London	
Guy's Hospital	(020) 7188 8750 (020) 7188 3849 (020) 7188 3855
Northwick Park Hospital	(020) 8869 2761 (020) 8869 3973
Newcastle	(0191) 282 4631
Southampton	(023) 8079 6908/9
Wales	
Cardiff	(029) 2074 2979 (029) 2074 2251
Scotland	
Aberdeen	(01224) 552 316
Dundee	(01382) 632 351 (01382) 660 111 Extn 32351
Edinburgh	(0131) 242 2920
Glasgow	(0141) 211 4407
Northern Ireland	
Belfast	(028) 9063 2032 (028) 9063 3847
Republic of Ireland	
Dublin	Dublin 473 0589 Dublin 453 7941 Extn 2348

United Kingdom Medicines Information Pharmacists Group (UKMIPG) website

www.ukmi.nhs.uk

Telephone numbers and email addresses of manufacturers listed in BNF Publications are shown in the Index of Manufacturers

UK Teratology Information Service

Information on drug and chemical exposures in pregnancy

Tel: 0844 892 0909

Information on drug therapy relating to **dental treatment** can be obtained by telephoning

Liverpool (0151) 794 8206

Driver and Vehicle Licensing Agency (DVLA)

Information on the national medical guidelines of fitness to drive is available from:

www.dvla.gov.uk/medical.aspx

Patient Information Lines

NHS Direct 0845 4647

Poisons Information Services

UK National Poisons Information Service 0844 892 0111

Sport

Information on substances currently permitted or prohibited is provided in a card supplied by UK Anti-doping.

Further information regarding medicines in sport is available from: www.ukad.org.uk

Tel: (020) 7766 7350

information@ukad.org.uk

Travel Immunisation

Up-to-date information on travel immunisation requirements may be obtained from:

National Travel Health Network and Centre (for healthcare professionals only) 0845 602 6712 (09.00–12.00 and 14.00–16.30 hours weekdays)

Travel Medicine Team, Health Protection Scotland (0141) 300 1130 (14.00–16.00 hours weekdays)

www.travax.nhs.uk (for registered users of the NHS website Travax only)

Welsh Assembly Government (029) 2082 5397 (09.00–17.30 hours weekdays)

Department of Health and Social Services (Belfast) (028) 9052 2118 (weekdays)

List of Registered Medical Practitioners

Details on whether doctors are registered and hold a licence to practise medicine in the UK can be obtained from the General Medical Council.

Tel: (0161) 923 6602

www.gmc-uk.org/register

British National Formulary

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BMA

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The UK health departments distribute BNFs to NHS hospitals, doctors, dental surgeons, and community pharmacies. In England, BNFs are mailed individually to NHS general practitioners and community pharmacies; contact the DH Publication Orderline for extra copies or changes relating to mailed BNFs.
Tel: 0300 123 1002
In Wales, telephone the Business Services Centre
Tel: (01495) 332 000
For further information on the supply of copies of the BNF to NHS organisations, see www.library.nhs.uk/orderingbnf

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. *BNF for Children* should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services (see inside front cover).

Preface

The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society. It is published biannually under the authority of a Joint Formulary Committee which comprises representatives of the two professional bodies and of the UK Health Departments. The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the Group includes representatives of the British Dental Association. The Nurse Prescribers' Advisory Group advises on the content relevant to nurses.

The BNF aims to provide prescribers, pharmacists and other healthcare professionals with sound up-to-date information about the use of medicines.

The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified. Little or no information is included on medicines promoted for purchase by the public.

Information on drugs is drawn from the manufacturers' product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies. Advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources. The BNF also takes account of authoritative national guidelines and emerging safety concerns. In addition, the editorial team receives advice on all therapeutic areas from expert clinicians; this ensures that the BNF's recommendations are relevant to practice.

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. *BNF for Children* should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services (see inside front cover).

It is **vital** to use the most recent edition of the BNF for making clinical decisions. The more important changes for this edition are listed on p. xvi.

The website (bnf.org) includes additional information of relevance to healthcare professionals. Other digital formats of the BNF—including intranet and versions for mobile devices—are produced in parallel with the printed version.

The BNF welcomes comments from healthcare professionals. Comments and constructive criticism should be sent to:
British National Formulary,
Royal Pharmaceutical Society,
1 Lambeth High Street, London SE1 7JN.
editor@bnf.org

Contents

Preface iii
Acknowledgements iv
How the BNF is constructed viii
How to use the BNF x
Changes for this edition xvi
Significant changes xvi
Dose changes xvii
Classification changes xvii
New names xvii
Deleted preparations xvii
New preparations included in this edition xviii
Guidance on prescribing 1
General guidance 1
Prescription writing 5
Emergency supply of medicines 7
Controlled Drugs and drug dependence 8
Adverse reactions to drugs 12
Prescribing for children 15
Prescribing in hepatic impairment 17
Prescribing in renal impairment 17
Prescribing in pregnancy 19
Prescribing in breast-feeding 19
Prescribing in palliative care 20
Prescribing for the elderly 24
Prescribing in dental practice 26
Drugs and sport 31
Emergency treatment of poisoning 32

Notes on drugs and Preparations
1: **Gastro-intestinal system** 43
2: **Cardiovascular system** 81
3: **Respiratory system** 170
4: **Central nervous system** 207
5: **Infections** 320
6: **Endocrine system** 418
7: **Obstetrics, gynaecology, and urinary-tract disorders** 485
8: **Malignant disease and immunosuppression** 518
9: **Nutrition and blood** 576
10: **Musculoskeletal and joint diseases** 629
11: **Eye** 666
12: **Ear, nose, and oropharynx** 685
13: **Skin** 700
14: **Immunological products and vaccines** 746
15: **Anaesthesia** 775

Appendices and indices
Appendix 1: **Interactions** 800
Appendix 2: **Liver disease** 17
Appendix 3: **Renal impairment** 17
Appendix 4: **Pregnancy** 19
Appendix 5: **Breast-feeding** 19
Appendix 6: **Intravenous additives** 892
Appendix 7: **Borderline substances** 903
Appendix 8: **Wound management products and elasticated garments** 935
Appendix 9: **Cautionary and advisory labels for dispensed medicines** 957
Dental Practitioners' Formulary 972
Nurse Prescribers' Formulary 974
Non-medical prescribing 978
Index of manufacturers 979
Index 990

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How the BNF is constructed

The BNF is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information, enabling healthcare professionals to select safe and effective medicines for individual patients.

Information in the BNF has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts.

Hundreds of changes are made between editions, and the most clinically significant changes are listed at the front of each edition (pp. xvi–xviii)

Joint Formulary Committee

The Joint Formulary Committee (JFC) is responsible for the content of the BNF. The JFC includes doctors appointed by the BMJ Publishing Group, pharmacists appointed by the Royal Pharmaceutical Society, and representatives from the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK health departments. The JFC decides on matters of policy and reviews amendments to the BNF in the light of new evidence and expert advice. The Committee meets quarterly and each member also receives proofs of all BNF chapters for review before publication.

Editorial team

BNF staff editors are pharmacists with a sound understanding of how drugs are used in clinical practice. Each staff editor is responsible for editing, maintaining, and updating specific chapters of the BNF. During the publication cycle the staff editors review information in the BNF against a variety of sources (see below).

Amendments to the text are drafted when the editors are satisfied that any new information is reliable and relevant. The draft amendments are passed to expert advisers for comment and then presented to the Joint Formulary Committee for consideration. Additionally, for each edition, sections are chosen from every chapter for thorough review. These planned reviews aim to verify all the information in the selected sections and to draft any amendments to reflect the current best practice.

Staff editors prepare the text for publication and undertake a number of checks on the knowledge at various stages of the production.

Expert advisers

The BNF uses about 60 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with the production of each edition. The role of these expert advisers is to review existing text and to comment on amendments drafted by the staff editors. These clinical experts help to ensure that the BNF remains reliable by:

- commenting on the relevance of the text in the context of best clinical practice in the UK;
- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- advising on areas where the BNF diverges from summaries of product characteristics;
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, children, the elderly, palliative care, and the emergency treatment of poisoning.

In addition to consulting with regular advisers, the BNF calls on other clinical specialists for specific developments when particular expertise is required.

The BNF also works closely with a number of expert bodies that produce clinical guidelines. Drafts or prepublication copies of guidelines are routinely received for comment and for assimilation into the BNF.

Sources of BNF information

The BNF uses a variety of sources for its information; the main ones are shown below.

Summaries of product characteristics The BNF receives summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are the principal source of product information and are carefully processed, despite the ever-increasing volume of information being issued by the pharmaceutical industry. Such processing involves:

- verifying the approved names of all relevant ingredients including 'non-active' ingredients (the BNF is committed to using approved names and descriptions as laid down by the Medicines Act);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breast-feeding;
- incorporating the information into the BNF using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by two staff editors before submitting to a senior editor; changes relating to doses receive an extra check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- careful validation of any areas of divergence of the BNF from the SPC before discussion by the Committee (in the light of supporting evidence);
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs.

Much of this processing is applicable to the following sources as well.

Expert advisers The role of expert clinical advisers in providing the appropriate clinical context for all BNF information is discussed above.

Literature Staff editors monitor core medical and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in the BNF and the paper is noted, the new information is assessed for reliability and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Joint Formulary Committee. The BNF enjoys a close working relationship with a number of national information providers.

Systematic reviews The BNF has access to various databases of systematic reviews (including the Cochrane Library and various web-based resources). These are used for answering specific queries, for reviewing existing text and for constructing new text. Staff editors receive training in critical appraisal, literature evaluation, and search strategies. Reviews published in Clinical Evidence are used to validate BNF advice.

Consensus guidelines The advice in the BNF is checked against consensus guidelines produced by expert bodies. A number of bodies make drafts or pre-publication copies of the guidelines available to the BNF; it is therefore possible to ensure that a consistent message is disseminated. The BNF routinely processes guidelines from the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

Reference sources Textbooks and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNF team works closely with the editorial team that produces *Martindale: The Complete Drug Reference*. The BNF has access to *Martindale* information resources and each team keeps the other informed of significant developments and shifts in the trends of drug usage.

Statutory information The BNF routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescription only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that the BNF complies with the relevant sections of the Medicines Act. The BNF itself is named as an official compendium in the Medicines Act.

The BNF maintains close links with the Home Office (in relation to controlled drug regulations) and the Medicines and Healthcare products Regulatory Agency (including the British Pharmacopoeia Commission). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug use issued by the UK health departments are processed as a matter of routine.

Relevant professional statements issued by the Royal Pharmaceutical Society are included in the BNF as are guidelines from bodies such as the Royal College of General Practitioners.

The BNF reflects information from the Drug Tariff, the Scottish Drug Tariff, and the Northern Ireland Drug Tariff.

Pricing information NHS Prescription Services (from the NHS Business Services Authority) provides information on prices of medicinal products and appliances in the BNF.

Comments from readers Readers of the BNF are invited to send in comments. Numerous letters and emails are received during the preparation of each edition. Such feedback helps to ensure that the BNF provides practical and clinically relevant information. Many changes in the presentation and scope of the BNF have resulted from comments sent in by users.

Comments from industry Close scrutiny of the BNF by the manufacturers provides an additional check and allows them an opportunity to raise issues about the BNF's presentation of the role of various drugs; this is yet another check on the balance of the BNF's advice. All comments are looked at with care and, where necessary, additional information and expert advice are sought.

Virtual user groups The BNF has set up virtual user groups across various healthcare professions (e.g. doctors, pharmacists, nurses, dentists). The aim of these groups will be to provide feedback to the editors and publishers to ensure that BNF publications continue to serve the needs of its users.

Market research Market research is conducted at regular intervals to gather feedback on specific areas of development, such as drug interactions or changes to the way information is presented in digital formats.

The BNF is an independent professional publication that is kept up-to-date and addresses the day-to-day prescribing information needs of healthcare professionals. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately.

How to use the BNF

In order to achieve the safe, effective, and appropriate use of medicines, healthcare professionals must be able to use the BNF effectively, and keep up to date with significant changes in each new edition of the BNF that are relevant to their clinical practice. *How to Use the BNF* is aimed as a quick refresher for all healthcare professionals involved with prescribing, monitoring, supplying, and administering medicines, and as a learning aid for students training to join these professions. While *How to Use the BNF* is linked to the main elements of rational prescribing, the generic structure of this section means that it can be adapted for teaching and learning in different clinical settings.

Structure of the BNF

The Contents list (on p. iii) shows that information in the BNF is divided into:

- *How the BNF is Constructed* (p. viii);
- *Changes for this Edition* (p. xvi);
- *Guidance on Prescribing* (p. 1), which provides practical information on many aspects of prescribing from writing a prescription to prescribing in palliative care;
- *Emergency Treatment of Poisoning* (p. 32), which provides an overview on the management of acute poisoning;
- *Classified notes on clinical conditions, drugs, and preparations*, these notes are divided into 15 chapters, each of which is related to a particular system of the body (e.g. chapter 2, Cardiovascular System) or to an aspect of medical care (e.g. chapter 5, Infections). Each chapter is further divided into classified sections. Each section usually begins with *prescribing notes* followed by relevant drug *monographs* and *preparations* (see fig. 1). Drugs are classified in a section according to their pharmacology and therapeutic use;
- *Appendices and Indices*, includes 5 Appendices (providing information on drug interactions, intravenous additives, Borderline substances, wound management, and cautionary and advisory labels for dispensed medicines), the Dental Practitioners' Formulary, the Nurse Prescribers' Formulary, Non-medical Prescribing, Index of Manufacturers, and the main Index. The information in the Appendices should be used in conjunction with relevant information in the chapters.

Finding information in the BNF

The BNF includes a number of aids to help access relevant information:

- *Index* (p. 990), where entries are included in alphabetical order of non-proprietary drug names, proprietary drug names, clinical conditions, and prescribing topics. A specific entry for 'Dental Prescribing' brings together topics of relevance to dental surgeons. The page reference to the drug monograph is shown in **bold** type. References to drugs in Appendices 1 and 9 are not included in the main Index;
- *Contents* (p. iii), provides a hierarchy of how information in the BNF is organised;
- The beginning of each chapter includes *a classified hierarchy* of how information is organised in that chapter;
- *Running heads*, located next to the page number on the top of each page, show the section of the BNF that is being used;
- *Thumbnails*, on the outer edge of each page, show the chapter of the BNF that is being used;
- *Cross-references*, lead to additional relevant information in other parts of the BNF.

Finding dental information in the BNF

Extra signposts have been added to help access dental information in the BNF:

- *Prescribing in Dental Practice* (p. 26), includes a contents list dedicated to drugs and topics of relevance to dentists, together with cross-references to the prescribing notes in the appropriate sections of the BNF. For example, a review of this list shows that information on the local treatment of oral infections is located in chapter 12 (Ear, Nose, and Oropharynx) while information on the systemic treatment of these infections is found in chapter 5 (Infections). This section also includes advice on Medical Emergencies in Dental Practice (p. 26) and Medical Problems in Dental Practice (p. 28). Guidance on the prevention of endocarditis and advice on the management of anticoagulated patients undergoing dental surgery can also be found here;
- *Side-headings*, in the prescribing notes, side-headings facilitate the identification of advice on oral conditions (e.g. Dental and Orofacial Pain, p. 257);
- *Dental prescribing on NHS*, in the body of the BNF, preparations that can be prescribed using NHS form FP10D (GP14 in Scotland, WP10D in Wales) can be identified by means of a note headed 'Dental prescribing on NHS' (e.g. Aciclovir Tablets, p. 393).

Identifying effective drug treatments

The prescribing notes in the BNF provide an overview of the drug management of common conditions and facilitate rapid appraisal of treatment options (e.g. hypertension, p. 104). For ease of use, information on the management of certain conditions has been tabulated (e.g. acute asthma, p. 173). Information is also provided on the prevention of disease (e.g. malaria prophylaxis for travellers, p. 404). Cardiovascular risk prediction charts for the primary prevention of cardiovascular disease can be found in the glossy pages at the back of the BNF.

Advice issued by the National Institute for Health and Clinical Excellence (NICE) is integrated within the BNF prescribing notes if appropriate. Summaries of NICE technology appraisals, and relevant short guidelines, are included in blue panels. The BNF also includes advice issued by the Scottish Medicines Consortium (SMC) when a medicine is restricted or not recommended for use within NHS Scotland.

In order to select safe and effective medicines for individual patients, information in the prescribing notes must be used in conjunction with other pre-

scribing details about the drugs and knowledge of the patient's medical and drug history.

A brief description of the clinical uses of a drug can usually be found in the Indications section of its monograph (e.g. bendroflumethiazide, p. 84); a cross-reference is provided to any indications for that drug that are covered in other sections of the BNF.

The symbol ◢ is used to denote preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing. Although such preparations may not be considered as drugs of first choice, their use may be justifiable in certain circumstances.

Drug management of medical emergencies

Guidance on the drug management of medical emergencies can be found in the relevant BNF chapters (e.g. treatment of anaphylaxis is included in section 3.4.3); advice on the management of medical emergencies in dental practice can be found in Prescribing in Dental Practice, p. 26. A summary of drug doses used for Medical Emergencies in the Community can be found in the glossy pages at the back of the BNF. An algorithm for Adult Advanced Life Support can also be found within these pages.

Figure 1 Illustrates the typical layout of a drug monograph and preparation records in the BNF

DRUG NAME ◢

Indications details of clinical uses

Cautions details of precautions required and also any monitoring required

Counselling Verbal explanation to the patient of specific details of the drug treatment (e.g. posture when taking a medicine)

Contra-indications circumstances when a drug should be avoided

Hepatic impairment advice on the use of a drug in hepatic impairment

Renal impairment advice on the use of a drug in renal impairment

Pregnancy advice on the use of a drug during pregnancy

Breast-feeding advice on the use of a drug during breast-feeding

Side-effects very common (greater than 1 in 10) and common (1 in 100 to 1 in 10); *less commonly* (1 in 1000 to 1 in 100); *rarely* (1 in 10 000 to 1 in 1000); *very rarely* (less then 1 in 10 000); also reported, frequency not known

Dose

- Dose and frequency of administration (max. dose); CHILD and ELDERLY details of dose for specific age group
- By alternative route, dose and frequency

[1]**Approved Name** (Non-proprietary) PoM

Pharmaceutical form, sugar-free, active ingredient mg/mL, net price, pack size = basic NHS price. Label: (as in Appendix 9)

1. Exceptions to the prescribing status are indicated by a note or footnote.

Proprietary Name (Manufacturer) PoM NHS

Pharmaceutical form, colour, coating, active ingredient and amount in dosage form, net price, pack size = basic NHS price. Label: (as in Appendix 9)

Excipients include clinically important excipients

Electrolytes clinically significant quantities of electrolytes

Note Specific notes about the product e.g. handling

Preparations

Preparations are included under a non-proprietary title, if they are marketed under such a title, if they are not otherwise prescribable under the NHS, or if they may be prepared extemporaneously.

Drugs

Drugs appear under pharmacopoeial or other non-proprietary titles. When there is an *appropriate current monograph* (Medicines Act 1968, Section 65) preference is given to a name at the head of that monograph; otherwise a British Approved Name (BAN), if available, is used.

The symbol ◢ is used to denote those preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing. Although such preparations may not be considered as drugs of first choice, their use may be justifiable in certain circumstances.

Prescription-only medicines PoM

This symbol has been placed against those preparations that are available only on a prescription issued by an appropriate practitioner. For more detailed information see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available).

The symbol CD indicates that the preparation is subject to the prescription requirements of the Misuse of Drugs Act. For regulations governing prescriptions for such preparations see p. 8.

Preparations not available for NHS prescription NHS

This symbol has been placed against those preparations included in the BNF that are not prescribable under the NHS. Those prescribable only for specific disorders have a footnote specifying the condition(s) for which the preparation remains available. Some preparations which are not *prescribable* by brand name under the NHS may nevertheless be *dispensed* using the brand name providing that the prescription shows an appropriate non-proprietary name.

Prices

Prices have been calculated from the basic cost used in pricing NHS prescriptions, see also Prices in the BNF, p. xiv for details.

How to use the BNF

Minimising harm in patients with co-morbidities

The drug chosen to treat a particular condition should have minimal detrimental effects on the patient's other diseases and minimise the patient's susceptibility to adverse effects. To achieve this, the *Cautions*, *Contra-indications*, and *Side-effects* of the relevant drug should be reviewed, and can usually be found in the drug monograph. However, if a class of drugs (e.g. tetracyclines, p. 346) share the same cautions, contra-indications, and side-effects, these are amalgamated in the prescribing notes while those unique to a particular drug in that class are included in its individual drug monograph. Occasionally, the cautions, contra-indications, and side-effects may be included within a preparation record if they are specific to that preparation or if the preparation is not accompanied by a monograph.

The information under Cautions can be used to assess the risks of using a drug in a patient who has co-morbidities that are also included in the Cautions for that drug—if a safer alternative cannot be found, the drug may be prescribed while monitoring the patient for adverse-effects or deterioration in the co-morbidity. Contra-indications are far more restrictive than Cautions and mean that the drug should be avoided in a patient with a condition that is contra-indicated.

The impact that potential side-effects may have on a patient's quality of life should also be assessed. For instance, in a patient who has difficulty sleeping, it may be preferable to avoid a drug that frequently causes insomnia. The prescribing notes in the BNF may highlight important safety concerns and differences between drugs in their ability to cause certain side-effects.

Prescribing for patients with hepatic or renal impairment

Drug selection should aim to minimise the potential for drug accumulation, adverse drug reactions, and exacerbation of pre-existing hepatic or renal disease. If it is necessary to prescribe drugs whose effect is altered by hepatic or renal disease, appropriate drug dose adjustments should be made, and patients should be monitored adequately. The general principles for prescribing are outlined under *Prescribing in Hepatic Impairment* (p. 17) and *Prescribing in Renal Impairment* (p. 17). Information about drugs that should be avoided or used with caution in hepatic disease or renal impairment can be found in drug monographs under *Hepatic Impairment* and *Renal Impairment* (e.g. fluconazole, p. 374). However, if a class of drugs (e.g. tetracyclines, p. 346) share the same recommendations for use in hepatic disease or renal impairment, this advice is presented in the prescribing notes under *Hepatic Impairment* and *Renal Impairment* and any advice that is unique to a particular drug in that class is included in its individual drug monograph.

Prescribing for patients who are pregnant or breast-feeding

Drug selection should aim to minimise harm to the fetus, nursing infant, and mother. The infant should be monitored for potential side-effects of drugs used by the mother during pregnancy or breast-feeding. The general principles for prescribing are outlined under *Prescribing in Pregnancy* (p. 19) and *Prescribing in Breast-feeding* (p. 19). The prescribing notes in the BNF chapters provide guidance on the drug treatment of common conditions that can occur during pregnancy and breast-feeding (e.g. asthma, p. 170). Information about the use of specific drugs during pregnancy and breast-feeding can be found in their drug monographs under *Pregnancy* and *Breast-feeding* (e.g. fluconazole, p. 374). However, if a class of drugs (e.g. tetracyclines, p. 346) share the same recommendations for use during pregnancy or breast-feeding, this advice is amalgamated in the prescribing notes under *Pregnancy* and *Breast-feeding* while any advice that is unique to a particular drug in that class is included in its individual drug monograph.

Minimising drug interactions

Drug selection should aim to minimise drug interactions. If it is necessary to prescribe a potentially serious combination of drugs, patients should be monitored appropriately. The mechanisms underlying drug interactions are explained in Appendix 1 (p. 800).

Details of drug interactions can be found in Appendix 1 of the BNF (p. 801). Drugs and their interactions are listed in alphabetical order of the non-proprietary drug name, and cross-references to drug classes are provided where appropriate. Each drug or drug class is listed twice: in the alphabetical list and also against the drug or class with which it interacts. The symbol ● is placed against interactions that are potentially serious and where combined administration of drugs should be avoided (or only undertaken with caution and appropriate monitoring). Interactions that have no symbol do not usually have serious consequences.

If a drug or drug class has interactions, a cross reference to where these can be found in Appendix 1 is provided under the Cautions of the drug monograph or prescribing notes.

Prescribing for the elderly

General guidance on prescribing for the elderly can be found on p. 24.

Prescribing for children

General guidance on prescribing for children can be found on p. 15. For detailed advice on medicines used in children, consult *BNF for Children*.

Selecting the dose

The drug dose is usually located in the *Dose* section of the drug monograph or preparation record. The dose of a drug may vary according to different indications and routes of administration. If no indication is given by the dose, then that dose can be used for the conditions specified in the Indications section of that drug monograph, but not for the conditions cross-referring to other sections of the BNF. The dose is located within the preparation record when the dose varies according to different formulations of that drug (e.g. amphotericin, p. 378) or when a preparation has a dose different to that in its monograph (e.g. *Sporanox*® liquid, p. 376). Occasionally, drug doses may be included in the prescribing notes for practical reasons (e.g. doses of drugs in *Helicobacter pylori* eradication regimens, p. 50). The right dose should be selected for the right indication, route of administration, and preparation.

Doses are either expressed in terms of a definite frequency (e.g. 1 g 4 times daily) or in the total daily dose format (e.g. 6 g daily in 3 divided doses); the total daily dose should be divided into individual doses (in the second example, the patient should receive 2 g 3 times daily).

The doses of some drugs may need to be adjusted if their effects are altered by concomitant use with other drugs, or in patients with hepatic or renal impairment (see Minimising Drug Interactions, and Prescribing for Patients with Hepatic or Renal Impairment).

Doses for specific patient groups (e.g. the elderly) may be included if they are different to the standard dose. Doses for children can be identified by the terms NEONATE, INFANT, and CHILD, and will vary according to their age or body-weight.

Conversions for imperial to metric measures can be found in the glossy pages at the back of the BNF.

Selecting a suitable preparation

Patients should be prescribed a preparation that complements their daily routine, and that provides the right dose of drug for the right indication and route of administration.

In the BNF, preparations usually follow immediately after the monograph for the drug which is their main ingredient. The preparation record (see fig. 1) provides information on the type of formulation (e.g. tablet), the amount of active drug in a solid dosage form, and the concentration of active drug in a liquid dosage form. The legal status is shown for prescription only medicines and controlled drugs; any exception to the legal status is shown by a Note immediately after the preparation record or a footnote. If a proprietary preparation has a distinct colour, coating, scoring, or flavour, this is shown in the preparation record. If a proprietary preparation includes excipients usually specified in the BNF (see p. 2), these are shown in the *Excipients* statement, and if it contains clinically significant quantities of electrolytes, these are usually shown in the *Electrolytes* statement.

Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as 'sugar-free' in the BNF. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked 'sugar-free' since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where a drug has several preparations, those of a similar type may be grouped together under a heading (e.g. 'Modified-release' for theophylline preparations, p. 181). Where there is good evidence to show that the preparations for a particular drug are not interchangeable, this is stated in a Note either in the Dose section of the monograph or by the group of preparations affected. When the dose of a drug varies according to different formulations of that drug, the right dose should be prescribed for the preparation selected.

In the case of compound preparations, the prescribing information of all constituents should be taken into account for prescribing.

Writing prescriptions

Guidance is provided on writing prescriptions that will help to reduce medication errors, see p. 5. Prescription requirements for controlled drugs are also specified on p. 8.

Administering drugs

If a drug can be given parenterally or by more than one route, the Dose section in the monograph or preparation record provides basic information on the route of administration. Further information on administration may be found in the monograph or preparation record, often as a Note or Counselling advice. If a class of drugs (e.g. topical corticosteroids, p. 708) share the same administration advice, this may be presented in the prescribing notes.

Appendix 6 (p. 892) provides practical information on the preparation of intravenous drug infusions, including compatibility of drugs with standard intravenous infusion fluids, method of dilution or reconstitution, and administration rates.

Advising patients

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (see Taking Medicines to Best Effect, p. 1). Taking the time to explain to the patient (and carers) the rationale and the potential adverse effects of treatment may improve adherence. For some medicines there is a special need for counselling (e.g. appropriate posture during administration of doxycycline); this is shown in *Counselling* statements, usually in the Cautions or Dose section of a monograph, or within a preparation record if it is specific to that preparation.

Patients should be advised if treatment is likely to affect their ability to drive or operate machinery.

Cautionary and advisory labels that pharmacists are recommended to add when dispensing are included in the preparation record (see fig. 1). Details of these labels can be found in Appendix 9 (p. 957); a list of products and their labels is included in alphabetical order of the non-proprietary and proprietary drug names.

Monitoring drug treatment

Patients should be monitored to ensure they are achieving the expected benefits from drug treatment without any unwanted side-effects. The prescribing notes or the Cautions in the drug monograph specify any special monitoring requirements. Further information on monitoring the plasma concentration of drugs with a narrow therapeutic index can be found as a Note under the Dose section of the drug monograph.

Identifying and reporting adverse drug reactions

Clinically relevant *Side-effects* for most drugs are included in the monographs. However, if a class of drugs (e.g. tetracyclines, p. 346) share the same side-effects, these are presented in the prescribing notes while those unique to a particular drug in that class are included in its individual drug monograph. Occa-

sionally, side-effects may be included within a preparation record if they are specific to that preparation or if the preparation is not accompanied by a monograph.

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness. The frequency of side-effects is described in fig. 1.

An exhaustive list of side-effects is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is generally not listed, unless the drug carries an increased risk of such reactions. The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

The prescribing notes in the BNF may highlight important safety concerns and differences between drugs in their ability to cause certain side-effects. Safety warnings issued by the Commission on Human Medicines (CHM) or Medicines and Healthcare products Regulatory Agency (MHRA) can also be found here or in the drug monographs.

Adverse Reactions to Drugs (p. 12) provides advice on preventing adverse drug reactions, and guidance on reporting adverse drug reactions to the MHRA. The black triangle symbol ▼ identifies those preparations in the BNF that are monitored intensively by the MHRA.

Finding significant changes in a new edition

The BNF is published in March and September each year and includes lists of changes in a new edition that are relevant to clinical practice:

- The print version includes an *Insert* that summarises the background to several key changes. A copy of the Insert can also be found at bnf.org in the section on Updates under 'What's new in BNF?';
- *Changes for this edition* (p. xvi), provides a list of significant changes, dose changes, classification changes, new names, and new preparations that have been incorporated into a new edition, as well as a list of preparations that have been discontinued since the last edition. For ease of identification, the margins of these pages are marked in blue;
- *Changes to the Dental Practitioners' Formulary* (p. 973), these are located at the end of the Dental List;
- *Changes to the Appendices*, drug entries that have been amended or introduced since the previous edition in Appendix 1 (Drug Interactions) or Appendix 9 (Cautionary and Advisory Labels for Dispensed Medicines) are underlined in the print versions;
- *E-newsletter*, the BNF & BNFC e-newsletter service is available free of charge. It alerts healthcare professionals to details of significant changes in the clinical content of these publications and to the way that this information is delivered. Newsletters also review clinical case studies and provide tips on using these publications effectively. To sign up for e-newsletters go to bnf.org/newsletter. To visit the e-newsletter archive, go to bnf.org/bnf/extra/current/450066.htm
- *BNF Update*, an e-learning programme developed in collaboration with the Centre for Pharmacy Postgraduate Education (CPPE), enables pharmacists to identify and assess how significant changes in the BNF affect their clinical practice. Separate modules for primary and secondary care can be found at www.cppe.ac.uk.

So many changes are made to each new edition of the BNF, that not all of them can be accommodated in the Insert and the Changes section. We encourage healthcare professionals to review regularly the prescribing information on drugs that they encounter frequently.

Nutrition

Appendix 7 (p. 903) includes tables of ACBS-approved enteral feeds and nutritional supplements based on their energy and protein content. There are separate tables for specialised formulae for specific clinical conditions. Classified sections on foods for special diets and nutritional supplements for metabolic diseases are also included.

Wound dressings

A table on wound dressings in Appendix 8 (p. 935) allows an appropriate dressing to be selected based on the appearance and condition of the wound. Further information about the dressing can be found by following the cross-reference to the relevant classified section in the Appendix. In section (A8.2) advanced wound contact dressings have been classified in order of increasing absorbency.

Unlicensed medicines

The BNF includes unlicensed use of medicines when the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience. When the BNF recommends an unlicensed medicine or the 'off-label' use of a licensed medicine, this is shown in the appropriate place by '[unlicensed]'.

Prices in the BNF

Basic **net prices** are given in the BNF to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective prescribing must, however, take into account other factors (such as dose frequency and duration of treatment) that affect the total cost. The use of more expensive drugs is justified if it will result in better treatment of the patient, or a reduction of the length of an illness, or the time spent in hospital. Prices have generally been calculated from the net cost used in pricing NHS prescriptions in October 2010. Prices generally reflect whole dispensing packs; prices for injections are stated per ampoule, vial, or syringe. The price for an extemporaneously prepared preparation has been omitted where the net cost of the ingredients used to make it would give a misleadingly low impression of the final price. In Appendix 8 prices stated are per dressing or bandage.

BNF prices are not suitable for quoting to patients seeking private prescriptions or contemplating over-

the-counter purchases because they do not take into account VAT, professional fees, and other overheads.

A fuller explanation of costs to the NHS may be obtained from the Drug Tariff. Separate drug tariffs are applicable to England and Wales, Scotland, and Northern Ireland; prices in the different tariffs may vary.

Extra resources on the BNF website

While the BNF website (bnf.org) hosts the digital content of the BNF proper, it also provides additional resources such as *Frequently Asked Questions* and online calculators.

BNF prescribing practice for medical students

This online revision aid, produced in collaboration with Onexamination, provides clinical case studies to help medical students improve their knowledge of safe and effective prescribing while using the BNF. Further details about this module can be found at bnf.org/bnf/extra/current/450048.htm

Using other sources for medicines information

The BNF is designed as a digest for rapid reference. Less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. *BNF for Children* should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services (see inside front cover).

Changes for this edition

Significant changes

The BNF is revised twice yearly and numerous changes are made between issues. All copies of BNF No. 60 (September 2010) should therefore be withdrawn and replaced by BNF No. 61 (March 2011). Significant changes have been made in the following sections for BNF No. 61:

Bowel cleansing preparations, section 1.6.5

Atrial fibrillation and atrial flutter, section 2.3.1

Dronedarone [NICE guidance], section 2.3.2

Hypertension in pregnancy, section 2.5

Hypertensive crises [title 'Accelerated or very severe hypertension' amended to 'Hypertensive crises' and advice updated], section 2.5

Sitaxentan (*Thelin®*) [to be withdrawn from the market due to hepatotoxicity], section 2.5.1

Heart failure, section 2.5.5

Management of stroke [new prescribing notes on the management of transient ischaemic attack, ischaemic stroke, and intracerebral haemorrhage], section 2.9

Clopidogrel and modified-release dipyridamole [NICE guidance], section 2.9

Familial hypercholesterolaemia, section 2.12

Formoterol dose in children [MHRA/CHM advice], section 3.1.1.1

Fentanyl [counselling for the use of patches], section 4.7.2

Epilepsy in pregnancy, section 4.8.1

Alcohol dependence, section 4.10.1

Nicotine dependence, section 4.10.2

Opioid dependence, section 4.10.3

Missed maintenance doses in opioid dependence, section 4.10.3

Summary of antibacterial therapy [advice reformatted], section 5.1, Table 1

Meningitis, section 5.1, Table 1

Urinary-tract infections [culture and sensitivity testing], section 5.1.13

Treatment of fungal infections: aspergillosis, section 5.2

Treatment of fungal infections: invasive or disseminated candidiasis, section 5.2

Indinavir [application of 'less suitable for prescribing' symbol], section 5.3.1

Saquinavir [changes to cautions and contra-indications], section 5.3.1

Peginterferon alfa, interferon alfa, and ribavirin for chronic hepatitis C [NICE guidance], section 5.3.3

Palivizumab [updated advice], section 5.3.5

Prophylaxis against malaria [recommendations for Morocco and Turkmenistan removed], section 5.4.1

Rosiglitazone [marketing authorisation suspended], section 6.1.2.3

Liraglutide for the treatment of type 2 diabetes mellitus [NICE guidance], section 6.1.2.3

Diabetic ketoacidosis, section 6.1.3

Treatment of hypoglycaemia, section 6.1.4

Denosumab for the prevention of osteoporotic fractures in postmenopausal women [NICE guidance], section 6.6.2

Recurrent vulvovaginal candidiasis [updated treatment regimens], section 7.2.2

Combined hormonal contraceptive interactions, section 7.3.1

Combined oral contraceptives [preparations tabulated], section 7.3.1

Imatinib for the adjuvant treatment of gastro-intestinal stromal tumours [NICE guidance], section 8.1.5

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours [NICE guidance], section 8.1.5

Trastuzumab for the treatment of HER2-positive metastatic gastric cancer [NICE guidance], section 8.1.5

Bevacizumab and sunitinib: risk of osteonecrosis of the jaw [MHRA/CHM advice], section 8.1.5

Caution when dispensing mycophenolate mofetil [new brand available], section 8.2.1

Rapamune® tablets [0.5 mg tablet not bioequivalent to other strengths], section 8.2.2

Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura [NICE guidance], section 9.1.4

G6PD deficiency [rasburicase and risk of haemolysis], section 9.1.5

Calcium gluconate injection [MHRA advice], section 9.5.1

Drugs unsafe for use in acute porphyrias, section 9.8.2

Etanercept, infliximab, and adalimumab for psoriatic arthritis [NICE guidance], section 10.1.3

Adalimumab, etanercept, infliximab, rituximab, and abatacept for rheumatoid arthritis after the failure of a TNF inhibitor [NICE guidance], section 10.1.3

Tocilizumab for rheumatoid arthritis [NICE guidance], section 10.1.3

Distigmine [removal of monograph for use in myasthenia gravis], section 10.2.1

Aqueous cream [skin reactions when used as a leave-on emollient], section 13.2.1

Immunisation schedule, section 14.1

Haemophilus type B conjugate vaccine in complement deficiency, section 14.4

Influenza vaccines, section 14.4

Meningococcal vaccines in complement deficiency, section 14.4

Adult advanced life support algorithm [Resuscitation Council (UK) updated algorithm 2010], inside back cover

Dose changes

Changes in dose statements introduced into BNF No. 61:

Aciclovir [herpes simplex treatment and suppression], p. 393

AmBisome®, p. 378

Atazanavir [paediatric dose], p. 386

Benzylpenicillin, p. 333

Bisacodyl, p. 69

Cefadroxil, p. 341

Cervarix®, p. 757

Cetirizine [dose in renal impairment], p. 192

Cetirizine [paediatric dose], p. 192

Co-amoxiclav [intravenous dose], p. 337

Cyproterone acetate [prevention of flare with initial gonadorelin analogue therapy], p. 573

Daptomycin [dose in renal impairment], p. 357

Ethosuximide [paediatric dose], p. 283

Famciclovir, p. 394

Fersamal®, p. 578

Fluoxetine [obsessive compulsive disorder], p. 241

Foradil® [dose for children under 12 years], p. 177

Fulvestrant, p. 570

Galantamine [dose in hepatic impairment], p. 318

Hyoscine butylbromide [by continuous infusion device for bowel colic and excessive respiratory secretions], p. 23

Hyoscine hydrobromide [by subcutaneous injection for excessive respiratory secretions], p. 21

Infliximab [severe active Crohn's disease], p. 66

Ipratropium [dose frequency for severe acute asthma in adults], p. 171 and p. 173

Itraconazole [histoplasmosis], p. 375

Melatonin, p. 212

Meropenem, p. 346

Methoxy polyethylene glycol-epoetin beta, p. 586

Metronidazole, p. 367

Pabrinex® [Wernicke's encephalopathy], p. 616

Pancuronium, p. 789

Pantoprazole, p. 57

Phenytoin sodium, p. 297

Prednisolone [maximum dose in paediatric acute asthma], p. 171 and p. 173

Primidone [essential tremor], p. 288

Remifentanil [analgesia and sedation in ventilated, intensive-care patients], p. 787

Salofalk® tablets, p. 62

Saquinavir, p. 389

Selenium sulphide [pityriasis versicolor text], p. 736

Sodium valproate [epilepsy], p. 291

Suxamethonium [by intravenous injection], p. 790

Temazepam [premedication], p. 785

Thiamine [mild deficiency], p. 616

Vagifem®, p. 491

Valaciclovir, p. 394

Xylometazoline [nasal spray], p. 692

Classification changes

Classification changes have been made in the following sections for BNF No. 61:

Section 2.1.2 Phosphodiesterase type-3 inhibitors [title change]

Section 3.3.3 Phosphodiesterase type-4 inhibitors [new sub-section]

Section 4.7.1 Non-opioid analgesics and compound analgesic preparations [title change]

Section 4.10.1 Alcohol dependence [new section]

Section 4.10.2 Nicotine dependence [new section]

Section 4.10.3 Opioid dependence [new section]

Section 4.10.3 Opioid substitution therapy [new sub-section]

Section 4.10.3 Adjunctive therapy and symptomatic treatment [new sub-section]

Section 4.10.3 Opioid-receptor antagonists [new sub-section]

Section 10.3 Drugs for the relief of soft-tissue inflammation and topical pain relief [title change]

Section 10.3.2 Rubefacients, topical NSAIDs, capsaicin, and poultices [title change]

Section 15.1.4.1 Anxiolytics [title change]

New names

Name changes introduced into BNF No. 61:

Hydrocortisone mucoadhesive buccal tablets [formerly *Corlan®*], p. 694

Laxido® Orange [formerly *Laxido®*], p. 71

Oilatum® Junior bath additive [formerly *Oilatum® Junior emollient bath additive*], p. 704

Deleted preparations

Preparations listed below have been discontinued during the compilation of BNF No. 61, or are still available but are not considered suiatable for inclusion by the Joint Formulary Committee (see footnote).

Actinac®

Andropatch®

Avandamet®

Avandia®

Baxan®

Clonidine injection[1]

Dexedrine®

Digitoxin[1]

Dimercaprol[1]

Flixotide® Diskhaler

Imuderm®

1. Not considered suitable for inclusion by the Joint Formulary Committee

Lidocaine 5% ointment
Linola® Gamma
Loceryl® cream
Magnapen® syrup
Mixtard® 30
Modalim®
Modisal LA®
Neosporin®
Norvir® capsules
Octagam®
Polytar AF®
Premarin® vaginal cream
Premique® Cycle
Protirelin
Regaine for Men Regular Strength®
Rosiglitazone
Select-A-Jet® Dopamine
Staril®
Zinc sulphate eye drops
Zoleptil®
Zotepine

New preparations included in this edition

Preparations included in the relevant sections of BNF No. 61:

Adoport® [tacrolimus], p. 558
Aquamol®, p. 702
Arzip® [mycophenolate mofetil], p. 555
Bocouture® [botulinum toxin type A], p. 309
Calcichew-D³® 500 mg/400 unit caplets [calcium carbonate with colecalciferol], p. 619
Capimune® [ciclosporin], p. 557
Catacrom® [sodium cromoglycate], p. 673
Clinitas Gel® [carbomers], p. 680
Cyanokit® [hydroxocobalamin], p. 39
Daxas® [roflumilast], p. 191
Dermatonics Heel Balm®, p. 703
Dovobet® gel [betametasone with calcipotriol], p. 717
Dovonex® ointment [calcipotriol], p. 717
Genotropin GoQuick® [somatropin], p. 465
Glusartel® [glucosamine sulphate], p. 657
Gynoxin® [fenticonazole], p. 493
Humulin I KwikPen® [isophane insulin], p. 424
Humulin M3 KwikPen® [biphasic isophane insulin], p. 426
Hyabak® [sodium hyaluronate], p. 681
Hylo-Care® [sodium hyaluronate], p. 681
Insuman Comb 25 SoloStar® [biphasic isophane insulin], p. 426
Levact® [bendamustine], p. 524
Lodotra® [prednisone], p. 448
Lumecare® Long Lasting Tear Gel [carbomers], p. 680
Lumecare® Preservative Free Tear Drops [hypromellose], p. 680
Marol® [tramadol m/r], p. 272
Miphtel® [acetylcholine chloride], p. 682
Monofer® [iron isomaltoside 1000], p. 579
Moxivig® [moxifloxacin], p. 668
Neokay® [phytomenadione], p. 621
Nexplanon® [etonorgestrel], p. 502
Nivestim® [filgrastim], p. 592
NuTRIflex® Omega plus, p. 605
NuTRIflex® Omega special, p. 605
Onbrez Breezhaler® [indacaterol], p. 177
Ozurdex® [dexamethasone], p. 671
PecFent® [fentanyl], p. 266
Rebif® (*Rebidose®*) injection [interferon beta-1a], p. 562
Renvela® [sevelamar carbonate], p. 613
Sativex® [*Cannabis sativa* extract], p. 661
Simponi® [golimumab], p. 653
Tears Naturale® Single Dose [hypromellose], p. 680
Tevagrastim® [filgrastim], p. 593
Tobravisc® [tobramycin], p. 669
Tracutil®, p. 607
Vimovo® [naproxen with esomeprazole], p. 639
Votrient® [pazopanib], p. 548
VPRIV® [velaglucerase alfa], p. 624
Zutectra® [hepatitis B-specific immunoglobulin], p. 771

Guidance on prescribing

General guidance

Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered (for further details see Prescribing in Pregnancy, p. 19).

It is important to discuss treatment options carefully with the patient to ensure that the patient is content to take the medicine as prescribed (see also Taking Medicines to Best Effect, below). In particular, the patient should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, the patient should be advised of this.

Taking medicines to best effect Difficulties in adherence to drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived adverse effects;
- patients' perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear;
- physical difficulty in taking medicines (e.g. swallowing the medicine, handling small tablets, or opening medicine containers);
- unattractive formulation (e.g. unpleasant taste);
- complicated regimen.

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them ('concordance'). The prescriber should be sensitive to religious, cultural, and personal beliefs that can affect a patient's acceptance of medicines.

Taking the time to explain to the patient (and relatives) the rationale and the potential adverse effects of treatment may improve adherence. Reinforcement and elaboration of the physician's instructions by the pharmacist and other members of the healthcare team also helps. Advising the patient of the possibility of alternative treatments may encourage the patient to seek advice rather than merely abandon unacceptable treatment.

Simplifying the drug regimen may help; the need for frequent administration may reduce adherence, although there appears to be little difference in adherence between once-daily and twice-daily administration. Combination products reduce the number of drugs taken but at the expense of the ability to titrate individual doses.

Biosimilar medicines A biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference medicine) in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

Biosimilar medicines have black triangle status (▼, see p. 12) at the time of initial marketing. It is important to report suspected adverse reactions to biosimilar medicines using the Yellow Card Scheme (p. 12). For biosimilar medicines, adverse reaction reports should clearly state the brand name of the suspected medicine.

Complementary and alternative medicine An increasing amount of information on complementary and alternative medicine is becoming available. The scope of the BNF is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John's wort—see Appendix 1). Further information on herbal medicines is available at www.mhra.gov.uk.

Abbreviation of titles In general, titles of drugs and preparations should be written *in full*. Unofficial abbreviations should not be used as they may be misinterpreted.

Non-proprietary titles Where non-proprietary ('generic') titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where there is a demonstrable difference in clinical effect between each manufacturer's version of the formulation, making it important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should **not** be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations.

Titles used as headings for monographs may be used freely in the United Kingdom but in other countries may be subject to restriction.

Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia, or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Medicines Act (Section 65).

Proprietary titles Names followed by the symbol® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

Marketing authorisation and BNF advice In general the *doses, indications, cautions, contra-indications,* and *side-effects* in the BNF reflect those in the manufacturers' data sheets or Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). The BNF does not generally include proprietary medicines that are not supported by a valid Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, the BNF reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisations. Unlicensed products can be obtained from 'special-order' manufacturers or specialist importing companies, see p. 988.

Where an unlicensed drug is included in the BNF, this is indicated in square brackets after the entry. When the BNF suggests a use (or route) that is outside the licensed indication of a product ('off-label' use), this too is indicated. Unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults.

Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

Oral syringes An **oral syringe** is supplied when oral liquid medicines are prescribed in doses other than multiples of 5 mL. The oral syringe is marked in 0.5-mL divisions from 1 to 5 mL to measure doses of less than 5 mL (other sizes of oral syringe may also be available). It is provided with an adaptor and an instruction leaflet. The *5-mL spoon* is used for doses of 5 mL (or multiples thereof).

To avoid inadvertent intravenous administration of oral liquid medicines, only an appropriate **oral** or **enteral syringe** should be used to measure an oral liquid medicine (if a medicine spoon or graduated measure cannot be used); these syringes should **not** be compatible with intravenous or other parenteral devices. Oral or enteral syringes should be clearly labelled 'Oral' or 'Enteral' in a large font size; it is the healthcare practitioner's responsibility to label the syringe with this information if the manufacturer has not done so.

Strengths and quantities The strength or quantity to be contained in capsules, lozenges, tablets, etc. should be stated by the prescriber. In particular, strengths of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).

If a pharmacist receives an incomplete prescription for a systemically administered preparation and considers it would not be appropriate for the patient to return to the doctor, the following procedures will apply[1]:

(a) an attempt must always be made to contact the prescriber to ascertain the intention;

(b) if the attempt is successful the pharmacist must, where practicable, subsequently arrange for details of quantity, strength where applicable, and dosage to be inserted by the prescriber on the incomplete form;

(c) where, although the prescriber has been contacted, it has not proved possible to obtain the written intention regarding an incomplete prescription, the pharmacist may endorse the form 'p.c.' (prescriber contacted) and add details of the quantity and strength where applicable of the preparation supplied, and of the dose indicated. The endorsement should be initialled and dated by the pharmacist;

(d) where the prescriber cannot be contacted and the pharmacist has sufficient information to make a professional judgement the preparation may be dispensed. If the quantity is missing the pharmacist may supply sufficient to complete up to 5 days' treatment; except that where a combination pack (i.e. a proprietary pack containing more than one medicinal product) or oral contraceptive is prescribed by name only, the smallest pack shall be dispensed. In all cases the prescription must be endorsed 'p.n.c.' (prescriber not contacted), the quantity, the dose, and the strength (where applicable) of the preparation supplied must be indicated, and the endorsement must be initialled and dated;

(e) if the pharmacist has any doubt about exercising discretion, an incomplete prescription must be referred back to the prescriber.

Excipients Branded oral liquid preparations that do not contain *fructose*, *glucose*, or *sucrose* are described as 'sugar-free' in the BNF. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked 'sugar-free' since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where information on the presence of *aspartame*, *gluten*, *sulphites*, *tartrazine*, *arachis (peanut) oil* or *sesame oil* is available, this is indicated in the BNF against the relevant preparation.

Information is provided on *selected excipients* in skin preparations (section 13.1.3), in vaccines (section 14.1), and on *selected preservatives* and *excipients* in eye drops and injections.

The presence of *benzyl alcohol* and *polyoxyl castor oil* (polyethoxylated castor oil) in injections is indicated in the BNF. Benzyl alcohol has been associated with a fatal

1. These recommendations are acceptable for **prescription-only medicines** (℞). For items marked CD see also Controlled Drugs and Drug Dependence, p. 8.

toxic syndrome in preterm neonates, and therefore, parenteral preparations containing the preservative should not be used in neonates. Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions.

The presence of *propylene glycol* in oral or parenteral medicines is indicated in the BNF; it can cause adverse effects if its elimination is impaired, e.g. in renal failure, in neonates and young children, and in slow metabolisers of the substance. It may interact with disulfiram and metronidazole.

The *lactose* content in most medicines is too small to cause problems in most lactose-intolerant patients. However in severe lactose intolerance, the lactose content should be determined before prescribing. The amount of lactose varies according to manufacturer, product, formulation, and strength.

In the absence of information on excipients in the BNF and in the product literature (available at www.emc.medicines.org.uk), contact the manufacturer (see Index of Manufacturers) if it is essential to check details.

Extemporaneous preparation A product should be dispensed extemporaneously only when no product with a marketing authorisation is available.

The BP direction that a preparation must be *freshly prepared* indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be *recently prepared* indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25° C.

The term **water** used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation (Water for injections, section 9.2.2).

Drugs and driving Prescribers and other healthcare professionals should advise patients if treatment is likely to affect their ability to perform skilled tasks (e.g. driving). This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient's fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk.

Patents In the BNF, certain drugs have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

Health and safety When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Substances such as corticosteroids, some antimicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

Safety in the home Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable *child-resistant container* unless:

- the medicine is in an original pack or patient pack such as to make this inadvisable;
- the patient will have difficulty in opening a child-resistant container;
- a specific request is made that the product shall not be dispensed in a child-resistant container;
- no suitable child-resistant container exists for a particular liquid preparation.

All patients should be advised to dispose of *unwanted medicines* by returning them to a supplier for destruction.

Name of medicine The name of the medicine should appear on the label unless the prescriber indicates otherwise.

(a) The strength is also stated on the label in the case of tablets, capsules, and similar preparations that are available in different strengths.

(b) If it is the wish of the prescriber that a description such as 'The Sedative Tablets' should appear on the label, the prescriber should write the desired description on the prescription form.

(c) The arrangement will extend to approved names, proprietary names or titles given in the BP, BPC, BNF, DPF, or NPF.

(d) The name written on the label is that used by the prescriber on the prescription.

(e) When a prescription is written other than on an NHS prescription form the name of the prescribed preparation will be stated on the label of the dispensed medicine unless the prescriber indicates otherwise.

(f) The Council of the Royal Pharmaceutical Society advises that the labels of dispensed medicines should indicate the total quantity of the product dispensed in the container to which the label refers. This requirement applies equally to solid, liquid, internal, and external preparations. If a product is dispensed in more than one container, the reference should be to the amount in each container.

Non-proprietary names of **compound preparations** which appear in the BNF are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients.
Prescribers should avoid creating their own compound names for the purposes of generic prescribing; such names do not have an approved definition and can be misinterpreted.
Special care should be taken to avoid errors when prescribing compound preparations; in particular the hyphen in the prefix 'co-' should be retained.
Special care should also be taken to avoid creating generic names for **modified-release** preparations where the use of these names could lead to confusion between formulations with different lengths of action.

EEA and Swiss prescriptions Pharmacists can dispense prescriptions issued by doctors and dentists from the European Economic Area (EEA) or Switzerland (except prescriptions for controlled drugs in Schedules 1 to 5 or for drugs without a UK marketing authorisation). Prescriptions should be written in ink or otherwise so as to be indelible, should be dated, should state the name of the patient, should state the address of the prescriber, should contain particulars indicating whether the prescriber is a doctor or dentist, and should be signed by the prescriber.

Security and validity of prescriptions The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions.

In particular, prescription forms should:

- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

Patient group direction (PGD) In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine by certain classes of healthcare professionals; the Direction is signed by a doctor (or dentist) and by a pharmacist. Further information on Patient Group Directions is available in Health Service Circular HSC 2000/026 (England), HDL (2001) 7 (Scotland), and WHC (2000) 116 (Wales) and at www.nelm.nhs.uk/en/Communities/NeLM/PGDs.

NICE and Scottish Medicines Consortium Advice issued by the National Institute for Health and Clinical Excellence (NICE) is included in the BNF when relevant. The BNF also includes advice issued by the Scottish Medicines Consortium (SMC) when a medicine is restricted or not recommended for use within NHS Scotland. If advice within a NICE Single Technology Appraisal differs from SMC advice, the Scottish Executive expects NHS Boards within NHS Scotland to comply with the SMC advice. Details of the advice together with updates can be obtained from www.nice.org.uk and from www.scottishmedicines.org.uk.

Prescription writing

Shared care
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Prescriptions[1] should be written legibly in ink or otherwise so as to be indelible[2], should be dated, should state the name and address of the patient, and should be signed in ink by the prescriber[3]. The age and the date of birth of the patient should preferably be stated, and it is a legal requirement in the case of prescription-only medicines to state the age for children under 12 years.

The following should be noted:

(a) The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg.
Quantities of 1 gram or more should be written as 1 g etc.
Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g.
Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg.
When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL.
Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.

(b) 'Micrograms' and 'nanograms' should **not** be abbreviated. Similarly 'units' should **not** be abbreviated.

(c) The term 'millilitre' (ml or mL)[4] is used in medicine and pharmacy, and cubic centimetre, c.c., or cm^3 should not be used.

(d) Dose and dose frequency should be stated; in the case of preparations to be taken 'as required' a **minimum dose interval** should be specified.
When doses other than multiples of 5 mL are prescribed for *oral liquid preparations* the dose-volume will be provided by means of an **oral syringe**, see p. 2 (except for preparations intended to be measured with a pipette).
Suitable quantities:

Elixirs, Linctuses, and Paediatric Mixtures (5-mL dose), 50, 100, or 150 mL

Adult Mixtures (10-mL dose), 200 or 300 mL

Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer's pack)

Eye Lotions, Gargles, and Mouthwashes, 200 mL

(e) For suitable quantities of dermatological preparations, see section 13.1.2.

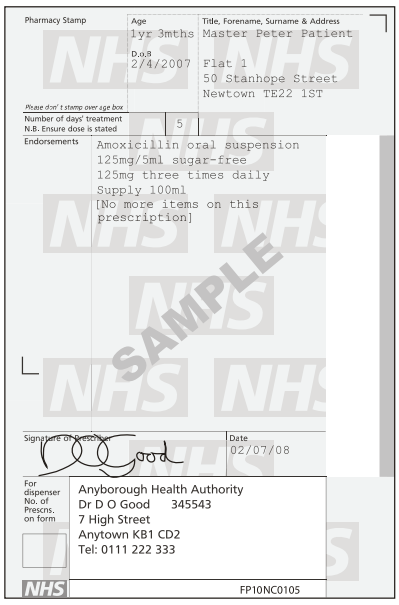
(f) The names of drugs and preparations should be written clearly and **not** abbreviated, using approved titles **only** (see also advice in box on p. 3 to **avoid** creating generic titles for modified-release preparations).

(g) The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated.
When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.

(h) Although directions should preferably be in **English without abbreviation**, it is recognised that some Latin abbreviations are used (for details see Inside Back Cover).

(i) Medical and dental practitioners may prescribe unlicensed medicines (i.e. those without marketing authorisation) or withdrawn medicines. The prescriber should inform the patient or the patient's carer that the product does not have a marketing authorisation.

For a sample prescription, see below.



1. These recommendations are acceptable for **prescription-only medicines** (PoM). For items marked CD see also Controlled Drugs and Drug Dependence, p. 8.
2. It is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink.
3. Computer-generated facsimile signatures do not meet the legal requirement.
4. The use of capital 'L' in mL is a printing convention throughout the BNF; both 'mL' and 'ml' are recognised SI abbreviations.

Prescribing by dental surgeons Until new prescribing arrangements are in place for NHS prescriptions, dental surgeons should use form FP10D (GP14 in Scotland, WP10D in Wales) to prescribe only those items listed in the Dental Practitioners' Formulary. The Act and Regulations do not set any limitations upon the number and variety of substances which the dental surgeon may administer to patients in the surgery or may order by private prescription—provided the relevant legal requirements are observed the dental surgeon may use or order whatever is required for the clinical situation. There is no statutory requirement for the dental surgeon to communicate with a patient's medical practitioner when prescribing for dental use. There are, however, occasions when this would be in the patient's interest and such communication is to be encouraged. For legal requirements relating to prescriptions for Controlled Drugs, see p. 8.

Computer-issued prescriptions

For computer-issued prescriptions the following advice, based on the recommendations of the Joint GP Information Technology Committee, should also be noted:

1. The computer must print out the date, the patient's surname, one forename, other initials, and address, and may also print out the patient's title and date of birth. The age of children under 12 years and of adults over 60 years must be printed in the box available; the age of children under 5 years should be printed in years and months. A facility may also exist to print out the age of patients between 12 and 60 years.
2. The doctor's name must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor's surgery address, reference number, and Primary Care Trust (PCT[1]) are also necessary. In addition, the surgery telephone number should be printed.
3. When prescriptions are to be signed by general practitioner registrars, assistants, locums, or deputising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal.
4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and to ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checks are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.
5. The dictionary may contain information on the usual doses, formulations, and pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.
6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112). It must also be possible to prescribe by indicating the length of treatment required, see (h) above.
7. The BNF recommendations should be followed as in (a), (b), (c), (d), and (e) above.
8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. For instructions such as 'as directed' and 'when required', the maximum daily dose should normally be specified.
9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.
10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should be in line with any warnings or advice in the BNF; numerical codes should not be used.
11. A mechanism (such as printing a series of non-specific characters) should be incorporated to cancel out unused space, or wording such as 'no more items on this prescription' may be added after the last item. Otherwise the doctor should delete the space manually.
12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.
13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations must be made in the doctor's own handwriting and countersigned; computer records should be updated to fully reflect any alteration. Prescriptions for drugs used for contraceptive purposes (but which are not promoted as contraceptives) may need to be marked in handwriting with the symbol ♀ (or endorsed in another way to indicate that the item is prescribed for contraceptive purposes).
14. Prescriptions for controlled drugs can be printed from the computer, but the prescriber's signature must be handwritten[2].
15. The strip of paper on the side of the FP10SS[3] may be used for various purposes but care should be taken to avoid including confidential information. It may be advisable for the patient's name to appear at the top, but this should be preceded by 'confidential'.
16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.
17. Prescription forms that are reprinted or issued as a duplicate should be labelled clearly as such.

1. Health Board in Scotland, Local Health Board in Wales.
2. See Controlled Drugs and Drug Dependence p. 8; the prescriber may use a date stamp.
3. GP10SS in Scotland, WP10SS in Wales.

Emergency supply of medicines

Emergency supply requested by member of the public

Pharmacists are sometimes called upon by members of the public to make an emergency supply of medicines. The Prescription Only Medicines (Human Use) Order 1997 allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

(a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:

  (i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;

  (ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed for the person requesting it;

  (iii) as to the dose that it would be appropriate for the person to take;

(b) that no greater quantity shall be supplied than will provide 5 days' treatment of phenobarbital, phenobarbital sodium, or Controlled Drugs in Schedules 4 or 5,[1] or 30 days' treatment for other prescription-only medicines, except when the prescription-only medicine is:

  (i) insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;

  (ii) an oral contraceptive when a full cycle may be supplied;

  (iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;

(c) that an entry shall be made by the pharmacist in the prescription book stating:

  (i) the date of supply;

  (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;

  (iii) the name and address of the patient;

  (iv) the nature of the emergency;

(d) that the container or package must be labelled to show:

  (i) the date of supply;

  (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;

  (iii) the name of the patient;

  (iv) the name and address of the pharmacy;

  (v) the words 'Emergency supply';

  (vi) the words 'Keep out of the reach of children' (or similar warning);

(e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available).[1]

1. Doctors or dentists from the European Economic Area and Switzerland, or their patients, cannot request an emergency supply of Controlled Drugs, or drugs that do not have a UK marketing authorisation.

Emergency supply requested by prescriber

Emergency supply of a prescription-only medicine may also be made at the request of a doctor, a dentist, a supplementary prescriber, a community practitioner nurse prescriber, a nurse, pharmacist, or optometrist independent prescriber, or a doctor or dentist from the European Economic Area or Switzerland, provided:

(a) that the pharmacist is satisfied that the prescriber by reason of some emergency is unable to furnish a prescription immediately;

(b) that the prescriber has undertaken to furnish a prescription within 72 hours;

(c) that the medicine is supplied in accordance with the directions of the prescriber requesting it;

(d) that the medicine is not a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available);[1]

(e) that an entry shall be made in the prescription book stating:

  (i) the date of supply;

  (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;

  (iii) the name and address of the practitioner requesting the emergency supply;

  (iv) the name and address of the patient;

  (v) the date on the prescription;

  (vi) when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society's guidelines

1. The pharmacist should consider the medical consequences of *not* supplying a medicine in an emergency.
2. If the pharmacist is unable to make an emergency supply of a medicine the pharmacist should advise the patient how to obtain essential medical care.

For conditions that apply to supplies made at the request of a patient see *Medicines, Ethics and Practice*, No. 34, London Pharmaceutical Press, 2010 (and subsequent editions).

Controlled Drugs and drug dependence

The Misuse of Drugs Act, 1971 prohibits certain activities in relation to 'Controlled Drugs', in particular their manufacture, supply, and possession. The penalties applicable to offences involving the different drugs are graded broadly according to the *harmfulness attributable to a drug when it is misused* and for this purpose the drugs are defined in the following three classes:

Class A includes: alfentanil, cocaine, diamorphine (heroin), dipipanone, lysergide (LSD), methadone, methylenedioxymethamfetamine (MDMA, 'ecstasy'), morphine, opium, pethidine, phencyclidine, remifentanil, and class B substances when prepared for injection

Class B includes: oral ampfetamines, barbiturates, cannabis, cannabis resin, codeine, ethylmorphine, glutethimide, nabilone, pentazocine, phenmetrazine, and pholcodine

Class C includes: certain drugs related to the amfetamines such as benzfetamine and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradrol, most benzodiazepines, zolpidem, androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin

The Misuse of Drugs Regulations 2001 define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

Schedule 1 includes drugs such as cannabis and lysergide which are not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.

Schedule 2 includes drugs such as diamorphine (heroin), morphine, nabilone, remifentanil, pethidine, secobarbital, glutethimide, amfetamine, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secobarbital), the need to keep registers, etc. (unless exempted in Schedule 5).

Schedule 3 includes the barbiturates (except secobarbital, now Schedule 2), buprenorphine, diethylpropion, mazindol, meprobamate, midazolam, pentazocine, phentermine, and temazepam. They are subject to the special prescription requirements (except for temazepam) and to the safe custody requirements (except for any 5,5 disubstituted barbituric acid (e.g. phenobarbital), mazindol, meprobamate, midazolam, pentazocine, phentermine, or any stereoisomeric form or salts of the above). Records in registers do not need to be kept (although there are requirements for the retention of invoices for 2 years).

Schedule 4 includes in Part I benzodiazepines (except temazepam and midazolam, which are in Schedule 3) and zolpidem, which are subject to minimal control. Part II includes androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

Schedule 5 includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

Prescriptions Preparations in Schedules 2 and 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are identified throughout the BNF by the symbol CD (Controlled Drug). The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance, p. 9).

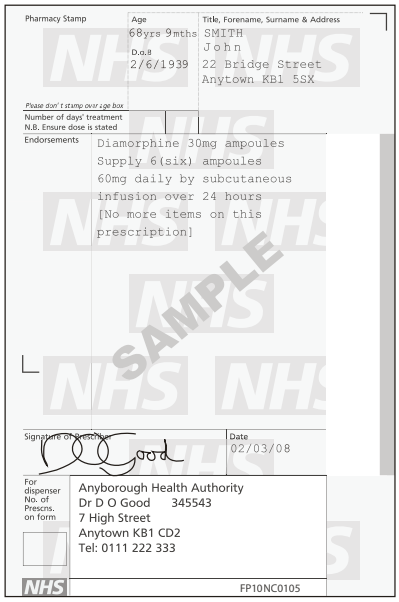
Prescription requirements

Prescriptions for Controlled Drugs that are subject to prescription requirements[1] must be indelible,[2] and must be *signed* by the prescriber, *be dated*, and specify the prescriber's *address*. The prescription must always state:

- the name and address of the patient;
- in the case of a preparation, the form[3] and where appropriate the strength[4] of the preparation;
- either the total quantity (in both words and figures) of the preparation,[5] or the number (in both words and figures) of dosage units, as appropriate, to be supplied; in any other case, the total quantity (in both words and figures) of the Controlled Drug to be supplied;
- the dose;[6]
- the words 'for dental treatment only' if issued by a dentist.

A pharmacist is **not** allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist. Failure to comply with the regulations concerning the writing of prescriptions will result in inconvenience to patients and delay in supplying the necessary medicine. A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon.[7]

1. All preparations in Schedules 2 and 3, except temazepam.
2. A machine-written prescription is acceptable. The prescriber's signature must be handwritten.
3. The dosage form (e.g. tablets) must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name (e.g. *MST Continus*) or whether only one form is available.
4. When more than one strength of a preparation exists the strength required must be specified.
5. The Home Office has advised that quantities of liquid preparations, such as methadone oral solution, should be written in millilitres.
6. The instruction 'one as directed' constitutes a dose but 'as directed' does not.
7. The prescriber may forward-date the prescription; the start date may also be specified in the body of the prescription.



Instalments and 'repeats' A prescription may order a Controlled Drug to be dispensed by instalments; the amount of instalments and the intervals to be observed must be specified.[1]

Instalment prescriptions must be dispensed in accordance with the directions in the prescription. However, the Home Office has approved specific wording which may be included in an instalment prescription, to cover certain situations; for example, if a pharmacy is closed on the day when an instalment is due. For details, see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available) or see *Drug Misuse and Dependence: UK Guidelines on Clinical Management* (2007), available at www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf.

Prescriptions ordering 'repeats' on the same form are **not** permitted for Controlled Drugs in Schedules 2 or 3.

Private prescriptions Private prescriptions for Controlled Drugs in Schedules 2 and 3 must be written on specially designated forms provided by Primary Care Trusts in England, Health Boards in Scotland, Local Health Boards in Wales, or the Northern Ireland Central Services Agency; in addition, prescriptions must specify the *prescriber's identification number*. Prescriptions to be supplied by a pharmacist in hospital are exempt from the requirements for private prescriptions.

1. A total of 14 days' treatment by instalment of any drug listed in Schedule 2 of the Misuse of Drugs Regulations, buprenorphine, and diazepam may be prescribed in England. In *England*, forms FP10(MDA) (blue) and FP10H(MDA) (blue) should be used. In *Scotland*, forms GP10 (peach), HBP (blue), or HBPA (pink) should be used. In *Wales* a total of 14 days' treatment by instalment of any drug listed in Schedules 2–5 of the Misuse of Drugs Regulations may be prescribed. In Wales, form WP10(MDA) or form WP10HP(AD) should be used.

Department of Health guidance Guidance (June 2006) issued by the Department of Health in England on prescribing and dispensing of Controlled Drugs requires:

- in general, prescriptions for Controlled Drugs in Schedules 2, 3, and 4 to be limited to a supply of up to 30 days' treatment; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient's notes;
- the patient's identifier to be shown on NHS and private prescriptions for Controlled Drugs in Schedules 2 and 3.

Further information is available at www.dh.gov.uk. For a sample prescription, see above

Dependence and misuse The most serious drugs of addiction are **cocaine**, **diamorphine** (heroin), **morphine**, and the **synthetic opioids**. For arrangements for prescribing of diamorphine, dipipanone, or cocaine for addicts, see p. 11.

Despite marked reduction in the prescribing of **amfetamines**, there is concern that abuse of illicit amfetamine and related compounds is widespread.

Benzodiazepines are commonly misused. However, the misuse of **barbiturates** is now uncommon, in line with declining medicinal use and consequent availability.

Cannabis (Indian hemp) has no approved medicinal use and cannot be prescribed by doctors. Its use is illegal but widespread. Cannabis is a mild hallucinogen seldom accompanied by a desire to increase the dose; withdrawal symptoms are unusual. **Lysergide** (lysergic acid diethylamide, LSD) is a much more potent hallucinogen; its use can lead to severe psychotic states which can be life-threatening.

There are concerns over increases in the availability and misuse of other drugs with variously combined hallucinogenic, anaesthetic, or sedative properties. These include ketamine and gamma-hydroxybutyrate (sodium oxybate, GHB).

Supervised consumption Individuals prescribed opioid substitution therapy (section 4.10.3) can take their daily dose under the supervision of a doctor, nurse, or pharmacist during the dose stabilisation phase (usually the first 3 months of treatment), after a relapse or period of instability, or if there is a significant increase in the dose of methadone. Supervised consumption should continue (in accordance with local protocols) until the prescriber is confident that the patient is compliant with their treatment.

Prescribing drugs likely to cause dependence or misuse The prescriber has three main responsibilities:

- To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious.
- To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more

likely. This tendency is seen especially with hypnotics and anxiolytics (for CSM advice see section 4.1). The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.

- To avoid being used as an unwitting source of supply for addicts. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctor. Doctors should also remember that their own patients may be attempting to collect prescriptions from other prescribers, especially in hospitals. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring.

The stealing and misuse of prescription forms could be minimised by the following precautions:

- do not leave unattended if called away from the consulting room or at reception desks; do not leave in a car where they may be visible; when not in use, keep in a locked drawer within the surgery and at home;
- draw a diagonal line across the blank part of the form under the prescription;
- write the quantity in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs (see Prescriptions, above);
- alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;
- if prescriptions are left for collection they should be left in a safe place in a sealed envelope.

Travelling abroad Prescribed drugs listed in Schedule 4 Part II (CD Anab) and Schedule 5 of the Misuse of Drugs Regulations 2001 are not subject to export or import licensing. However, patients intending to travel abroad for more than 3 months carrying any amount of drugs listed in Schedules 2, 3, or 4 Part I (CD Benz) will require a personal export/import licence. Further details can be obtained at www.homeoffice.gov.uk/drugs/licensing/personal, or from the Home Office by contacting licensing_enquiry.aadu@homeoffice.gsi.gov.uk (in cases of emergency, telephone (020) 7035 0484).

Applications must be supported by a covering letter from the prescriber and should give details of:

- the patient's name and address;
- the quantities of drugs to be carried;
- the strength and form in which the drugs will be dispensed;
- the country or countries of destination;
- the dates of travel to and from the United Kingdom.

Applications for licences should be sent to the Home Office, Drugs Licensing, Peel Building, 2 Marsham Street, London, SW1P 4DF. Alternatively, completed application forms can be emailed to licensing_enquiry.aadu@homeoffice.gsi.gov.uk with a scanned copy of the covering letter from the prescriber. A minimum of two weeks should be allowed for processing the application.

Patients travelling for less than 3 months do not require a personal export/import licence for carrying Controlled Drugs, but are advised to carry a letter from the prescribing doctor. Those travelling for more than 3 months are advised to make arrangements to have their medication prescribed by a practitioner in the country they are visiting.

Doctors who want to take Controlled Drugs abroad while accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who want to take Controlled Drugs abroad solely in case a family emergency should arise.

Personal export/import licences do not have any legal status outside the UK and are issued only to comply with the Misuse of Drugs Act and to facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it is necessary to approach that country's consulate in the UK.

Notification of drug misusers

Doctors should report cases of drug misuse to their regional or national drug misuse database or centre—see below for contact telephone numbers. The National Drugs Treatment Monitoring System (NDTMS) was introduced in England in April 2001; regional (NDTMS) centres replace the Regional Drug Misuse Databases. A similar system has been introduced in Wales.

Notification to regional (NDTMS) or national centre should be made when a patient starts treatment for drug misuse. All types of problem drug misuse should be reported including opioid, benzodiazepine, and CNS stimulant.

The regional (NDTMS) or national centres are now the only national and local source of epidemiological data on people presenting with problem drug misuse; they provide valuable information to those working with drug misusers and those planning services for them. The databases cannot, however be used as a check on multiple prescribing for drug addicts because the data are anonymised.

Enquiries about the regional (NDTMS) or national centres (including information on how to submit data) can be made to one of the centres listed below:

ENGLAND

Eastern
Tel: (01223) 767904
Fax: (01223) 330 345

South East
Tel: (01865) 334734
Fax: (01865) 334 964

London
Tel: (020) 7972 1986
Fax: (020) 7972 1998

North West
Tel: (0151) 231 4533
Fax: (0151) 231 4515

North East
Tel: (0191) 334 0372
Fax: (0191) 334 0391

Yorkshire and the Humber
Tel: (0113) 341 2923
Fax: (0113) 341 3082

South Western
Tel: (0117) 970 6474 ext 311
Fax: (0117) 970 7021

East Midlands
Tel: (0115) 971 2745
Fax: (0115) 971 2404

West Midlands
Tel: (0121) 415 8556
Fax: (0121) 414 8197

SCOTLAND

Tel: (0131) 551 8715
Fax: (0131) 551 1392

WALES

Tel: (029) 2050 3343
Fax: (029) 2050 2330

In **Northern Ireland**, the Misuse of Drugs (Notification of and Supply to Addicts) (Northern Ireland) Regulations 1973 require doctors to send particulars of persons whom they consider to be addicted to certain controlled drugs to the Chief Medical Officer of the Department of Health and Social Services. The Northern Ireland contacts are:

Medical contact:

Dr Ian McMaster
C3 Castle Buildings
Belfast, BT4 3FQ
Tel: (028) 9052 2421
Fax: (028) 9052 0718
ian.mcmaster@dhsspsni.gov.uk

Administrative contact:

Public Health Information & Research Branch
Annex 2
Castle Building
Belfast, BT4 3SQ
Tel: (028) 9052 2520

Public Health Information & Research Branch also maintains the Northern Ireland Drug Misuse Database (NIDMD) which collects detailed information on those presenting for treatment, on drugs misused and injecting behaviour; participation is not a statutory requirement.

Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts

The Misuse of Drugs (Supply to Addicts) Regulations 1997 require that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe, administer, or supply diamorphine, dipipanone (*Diconal®*), or cocaine in the treatment of drug addiction; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered.

General practitioners and other doctors do not require a special licence for prescribing diamorphine, dipipanone, and cocaine for patients (including addicts) for *relieving pain* from organic disease or injury.

For guidance on prescription writing, see p. 8.

Adverse reactions to drugs

Any drug may produce unwanted or unexpected adverse reactions. Rapid detection and recording of adverse drug reactions is of vital importance so that unrecognised hazards are identified promptly and appropriate regulatory action is taken to ensure that medicines are used safely. Healthcare professionals and coroners (see also Self-reporting below) are urged to report suspected adverse drug reactions directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.yellowcard.gov.uk. Alternatively, prepaid Yellow Cards for reporting are available from the address below and are also bound in this book (inside back cover).

Send Yellow Cards to:

FREEPOST YELLOW CARD
(No other address details required)
Tel: 0800 731 6789

Suspected adverse drug reactions to *any* therapeutic agent should be reported, including drugs *(self-medication* as well as those *prescribed)*, blood products, vaccines, radiographic contrast media, complementary and herbal products.

A 24-hour Freefone service is available to all parts of the UK for advice and information on suspected adverse drug reactions; contact the National Yellow Card Information Service at the MHRA on 0800 731 6789. Outside office hours a telephone-answering machine will take messages.

The following Yellow Card Centres can be contacted for further information:

Yellow Card Centre
Northwest
Freepost SW2991
70 Pembroke Place
Liverpool L69 3GF
Tel: (0151) 794 8122

Yellow Card Centre Wales
Freepost SW2991
University Hospital of Wales
Cardiff CF4 1ZZ
Tel: (029) 2074 4181

Yellow Card Centre
Northern & Yorkshire
Freepost SW2991
Wolfson Unit
Claremont Place
Newcastle upon Tyne NE2 4HH
Tel: (0191) 260 6181

Yellow Card Centre West Midlands
Freepost SW2991
City Hospital
Birmingham B18 7QH
Tel: (0121) 507 5672

Yellow Card Centre Scotland
Freepost NAT3271
CARDS, Royal Infirmary of Edinburgh
Edinburgh EH16 4SA
Tel: (0131) 242 2919

The MHRA's database facilitates the monitoring of adverse drug reactions.

More detailed information on reporting and a list of products currently under intensive monitoring can be found on the MHRA website: www.mhra.gov.uk.

Drug Safety Update is a monthly newsletter from the MHRA and the Commission on Human Medicines (CHM); it is available at www.mhra.gov.uk/drugsafetyupdate.

Self-reporting Patients and their carers can also report suspected adverse drug reactions to the MHRA. Reports can be submitted directly to the MHRA through the Yellow Card Scheme using the electronic form at www.yellowcard.gov.uk, by telephone on 0808 100 3352, or by downloading the Yellow Card form from www.mhra.gov.uk. Alternatively, patient Yellow Cards are available from pharmacies and GP surgeries. Information for patients about the Yellow Card Scheme is available in other languages at www.yellowcard.gov.uk.

Prescription-event monitoring In addition to the MHRA's Yellow Card Scheme, an independent scheme monitors the safety of new medicines using a different approach. The Drug Safety Research Unit identifies patients who have been prescribed selected new medicines and collects data on clinical events in these patients. The data are submitted on a voluntary basis by general practitioners on green forms. More information about the scheme and the Unit's educational material is available from www.dsru.org.

Newer drugs and vaccines Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice.

The black triangle symbol (▼) identifies newly licensed medicines that are monitored intensively by the MHRA. Such medicines include new active substances, biosimilar medicines, medicines that have been licensed for administration by a new route or drug delivery system, or for significant new indications which may alter the established risks and benefits of that drug, or that contain a new combination of active substances. There is no standard time for which products retain a black triangle; safety data are usually reviewed after 2 years.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. For medicines showing the black triangle symbol, the MHRA asks that **all** suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised, or if other drugs have been given at the same time.

Established drugs and vaccines Healthcare professionals and coroners are asked to report **all** serious suspected reactions to established drugs (including over-the-counter, herbal, and unlicensed medicines and medicines used off-label) and vaccines. Serious reactions include those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable comparison with other drugs of a similar class. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

For established drugs there is no need to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants or constipation with opioids.

Adverse reactions to medical devices Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at: www.mhra.gov.uk.

Side-effects in the BNF The BNF includes clinically relevant side-effects for most drugs; an exhaustive list is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Where causality has not been established, side-effects in the manufacturers' literature may be omitted from the BNF.

Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is not generally listed, unless the drug carries an increased risk of such reactions. The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness.

In the product literature the frequency of side-effects is generally described as follows:

Very common	greater than 1 in 10
Common	1 in 100 to 1 in 10
Uncommon ['less commonly' in BNF]	1 in 1000 to 1 in 100
Rare	1 in 10 000 to 1 in 1000
Very rare	less than 1 in 10 000

Special problems

Delayed drug effects Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported directly to the MHRA through the Yellow Card Scheme.

The elderly Particular vigilance is required to identify adverse reactions in the elderly.

Congenital abnormalities When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

Children Particular vigilance is required to identify and report adverse reactions in children, including those resulting from the unlicensed use of medicines; **all** suspected reactions should be reported directly to the MHRA through the Yellow Card Scheme (see also Adverse Drug Reactions in Children, p. 15).

Prevention of adverse reactions

Adverse reactions may be prevented as follows:

- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the patient had previous reactions;
- ask if the patient is already taking other drugs *including self-medication drugs, health supplements, complementary and alternative therapies*; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism, notably of isoniazid and the tricyclic antidepressants;
- prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions;
- whenever possible use a familiar drug; with a new drug, be particularly alert for adverse reactions or unexpected events;
- warn the patient if serious adverse reactions are liable to occur.

Oral side-effects of drugs

Drug-induced disorders of the mouth may be due to a local action on the mouth or to a systemic effect manifested by oral changes. In the latter case urgent referral to the patient's medical practitioner may be necessary.

Oral mucosa

Medicaments left in contact with or applied directly to the oral mucosa can lead to inflammation or ulceration; the possibility of allergy should also be borne in mind.

Aspirin tablets allowed to dissolve in the sulcus for the treatment of toothache can lead to a white patch followed by ulceration.

Flavouring agents, particularly **essential oils**, may sensitise the skin, but mucosal swelling is not usually prominent.

The oral mucosa is particularly vulnerable to ulceration in patients treated with cytotoxic drugs, e.g. **methotrexate**. Other drugs capable of causing oral ulceration include **captopril** (and other ACE inhibitors), **gold**, **nicorandil**, **NSAIDs**, **pancreatin**, **penicillamine**, **proguanil**, and **protease inhibitors**.

Erythema multiforme or Stevens-Johnson syndrome may follow the use of a wide range of drugs including **antibacterials**, **antiretrovirals**, **sulfonamide derivatives**, and **anticonvulsants**; the oral mucosa may be extensively ulcerated, with characteristic target lesions on the skin. Oral lesions of toxic epidermal necrolysis have been reported with a similar range of drugs.

Lichenoid eruptions are associated with **ACE inhibitors**, **NSAIDs**, **methyldopa**, **chloroquine**, **oral antidiabetics**, **thiazide diuretics**, and **gold**.

Candidiasis can complicate treatment with **antibacterials** and **immunosuppressants** and is an occasional side-effect of **corticosteroid inhalers**, see also p. 185.

Teeth and Jaw

Brown staining of the teeth frequently follows the use of **chlorhexidine** mouthwash, spray or gel, but can readily be removed by polishing. **Iron** salts in liquid form can stain the enamel black. Superficial staining has been reported rarely with **co-amoxiclav** suspension.

Intrinsic staining of the teeth is most commonly caused by **tetracyclines**. They will affect the teeth if given at any time from about the fourth month *in utero* until the age of twelve years; they are contra-indicated during pregnancy, in breast-feeding women, and in children under 12 years. All tetracyclines can cause permanent, unsightly staining in children, the colour varying from yellow to grey.

Excessive ingestion of **fluoride** leads to *dental fluorosis* with mottling of the enamel and areas of hypoplasia or pitting; fluoride supplements occasionally cause mild mottling (white patches) if the dose is too large for the child's age (taking into account the fluoride content of the local drinking water and of toothpaste).

The risk of *osteonecrosis of the jaw* is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease. All patients receiving bisphosphonates for cancer should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment. However, urgent bisphosphonate treatment should not be delayed, and a dental check-up should be carried out as soon as possible in these patients. All other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health, see also MHRA/CHM advice (Bisphosphonates: osteonecrosis of the jaw), p. 472. For cancer patients taking bevacizumab or sunitinib, see also MHRA/CHM advice (Bevacizumab and sunitinib: risk of osteonecrosis of the jaw), p. 537.

Periodontium

Gingival overgrowth (gingival hyperplasia) is a side-effect of **phenytoin** and sometimes of **ciclosporin** or of **nifedipine** (and some other calcium-channel blockers).

Thrombocytopenia may be drug related and may cause bleeding at the gingival margins, which may be spontaneous or may follow mild trauma (such as toothbrushing).

Salivary glands

The most common effect that drugs have on the salivary glands is to *reduce flow* (xerostomia). Patients with a persistently dry mouth may have poor oral hygiene; they are at an increased risk of dental caries and oral infections (particularly candidiasis). Many drugs have been implicated in xerostomia, particularly **antimuscarinics** (anticholinergics), **antidepressants** (including tricyclic antidepressants, and selective serotonin re-uptake inhibitors), **alpha-blockers**, **antihistamines**, **antipsychotics**, **baclofen**, **bupropion**, **clonidine**, **5HT$_1$ agonists**, **opioids**, and **tizanidine**. Excessive use of **diuretics** can also result in xerostomia.

Some drugs (e.g. clozapine, neostigmine) can *increase saliva production* but this is rarely a problem unless the patient has associated difficulty in swallowing.

Pain in the salivary glands has been reported with some **antihypertensives** (e.g. clonidine, methyldopa) and with **vinca alkaloids**.

Swelling of the salivary glands can occur with **iodides**, **antithyroid drugs**, **phenothiazines**, **ritodrine**, and **sulfonamides**.

Taste

There can be *decreased* taste acuity or *alteration* in taste sensation. Drugs implicated include **amiodarone**, **calcitonin**, **captopril** (and other ACE inhibitors), **carbimazole**, **clarithromycin**, **gold**, **griseofulvin**, **lithium salts**, **metformin**, **metronidazole**, **penicillamine**, **phenindione**, **propafenone**, **protease inhibitors**, **terbinafine**, and **zopiclone**.

Defective medicines

During the manufacture or distribution of a medicine an error or accident may occur whereby the finished product does not conform to its specification. While such a defect may impair the therapeutic effect of the product and could adversely affect the health of a patient, it should **not** be confused with an Adverse Drug Reaction where the product conforms to its specification.

The Defective Medicines Report Centre assists with the investigation of problems arising from licensed medicinal products thought to be defective and co-ordinates any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road
London, SW1W 9SZ
Tel: (020) 3080 6588
info@mhra.gsi.gov.uk

Prescribing for children

For detailed advice on medicines used for children, consult *BNF for Children*

Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care. At this age, the risk of toxicity is increased by reduced drug clearance and differing target organ sensitivity.

Whenever possible, intramuscular injections should be **avoided** in children because they are painful.

Where possible, medicines for children should be prescribed within the terms of the marketing authorisation (product licence). However, many children may require medicines not specifically licensed for paediatric use.

Although medicines cannot be promoted outside the limits of the licence, the Medicines Act does not prohibit the use of unlicensed medicines. It is recognised that the informed use of unlicensed medicines or of licensed medicines for unlicensed applications ('off-label' use) is often necessary in paediatric practice.

Adverse drug reactions in children The reporting of **all** suspected adverse drug reactions, no matter how minor, in children under 18 years is **strongly encouraged** through the Yellow Card Scheme (see p. 12) even if the intensive monitoring symbol (▼) has been removed. This is because experience in children may still be limited.

The identification and reporting of adverse reactions to drugs in children is particularly important because:

- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs are not extensively tested in children;
- many drugs are not specifically licensed for use in children and are used 'off-label';
- suitable formulations may not be available to allow precise dosing in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

Prescription writing Prescriptions should be written according to the guidelines in Prescription Writing (p. 5) Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for **all** prescriptions for children.

It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, they may contain sugar which encourages dental decay. Sugar-free medicines are preferred for long-term treatment.

Many children are able to swallow tablets or capsules and may prefer a solid dose form; involving the child and parents in choosing the formulation is helpful.

When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL an **oral syringe** will be supplied (for details, see p. 2).

Parents should be advised not to add any medicines to the infant's feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents.

Parents must be warned to keep **all** medicines out of reach of children, see Safety in the Home, p. 3.

Rare paediatric conditions

Information on substances such as *biotin* and *sodium benzoate* used in rare metabolic conditions is included in *BNF for Children*; further information can be obtained from:

Alder Hey Children's Hospital
Drug Information Centre
Liverpool L12 2AP
Tel: (0151) 252 5381

Great Ormond Street Hospital for Children
Pharmacy
Great Ormond St
London WC1N 3JH
Tel: (020) 7405 9200

Dosage in children

Children's doses in the BNF are stated in the individual drug entries as far as possible, except where paediatric use is not recommended, information is not available, or there are special hazards.

Doses are generally based on body-weight (in kilograms) or the following age ranges:

first month (neonate)

up to 1 year (infant)

1–5 years

6–12 years

Unless the age is specified, the term 'child' in the BNF includes persons aged 12 years and younger.

Dose calculation Many children's doses are standardised by **weight** (and therefore require multiplying by the body-weight in kilograms to determine the child's dose); occasionally, the doses have been standardised by **body surface area** (in m^2). These methods should be used rather than attempting to calculate a child's dose on the basis of doses used in adults.

For most drugs the adult maximum dose should not be exceeded. For example if the dose is stated as 8 mg/kg (max. 300 mg), a child weighing 10 kg should receive 80 mg but a child weighing 40 kg should receive 300 mg (rather than 320 mg).

Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from

an ideal weight, related to height and age (see inside back cover).

Body surface area (BSA) estimates are sometimes preferable to body-weight for calculation of paediatric doses since many physiological phenomena correlate better with body surface area. Body surface area can be estimated from weight. For more information, refer to *BNF for Children*.

Where the dose for children is not stated, prescribers should consult *BNF for Children* or seek advice from a medicines information centre.

Dose frequency Antibacterials are generally given at regular intervals throughout the day. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the child's bedtime.

Where new or potentially toxic drugs are used, the manufacturers' recommended doses should be carefully followed.

Prescribing in hepatic impairment

Liver disease may alter the response to drugs in several ways as indicated below, and drug prescribing should be kept to a minimum in all patients with severe liver disease. The main problems occur in patients with jaundice, ascites, or evidence of encephalopathy.

Impaired drug metabolism Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large and liver disease has to be severe before important changes in drug metabolism occur. Routine liver-function tests are a poor guide to the capacity of the liver to metabolise drugs, and in the individual patient it is not possible to predict the extent to which the metabolism of a particular drug may be impaired.

A few drugs, e.g. rifampicin and fusidic acid, are excreted in the bile unchanged and can accumulate in patients with intrahepatic or extrahepatic obstructive jaundice.

Hypoproteinaemia The hypoalbuminaemia in severe liver disease is associated with reduced protein binding and increased toxicity of some highly protein-bound drugs such as phenytoin and prednisolone.

Reduced clotting Reduced hepatic synthesis of blood-clotting factors, indicated by a prolonged prothrombin time, increases the sensitivity to oral anticoagulants such as warfarin and phenindione.

Hepatic encephalopathy In severe liver disease many drugs can further impair cerebral function and may precipitate hepatic encephalopathy. These include all sedative drugs, opioid analgesics, those diuretics that produce hypokalaemia, and drugs that cause constipation.

Fluid overload Oedema and ascites in chronic liver disease can be exacerbated by drugs that give rise to fluid retention, e.g. NSAIDs and corticosteroids.

Hepatotoxic drugs Hepatotoxicity is either dose-related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function, and some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. These drugs should be avoided or used very carefully in patients with liver disease.

Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

Prescribing in renal impairment

The use of drugs in patients with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs.

Principles of dose adjustment in renal impairment

The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity.

For many drugs with only minor or no dose-related side-effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient.

For more toxic drugs with a small safety margin or patients at extremes of weight, dose regimens based on creatinine clearance (see below for details) should be used. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma-drug concentration.

Renal function declines with age; many elderly patients have renal impairment but, because of reduced muscle mass, this may not be indicated by a raised serum creatinine. It is wise to assume at least mild impairment of renal function when prescribing for the elderly.

The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose for a patient with normal renal function.

Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced.

Dose recommendations are based on the severity of renal impairment.

Renal function is measured either in terms of estimated **glomerular filtration rate** (eGFR) calculated from a formula derived from the Modification of Diet in Renal Disease study ('MDRD formula' that uses serum creatinine, age, sex, and race (for Afro-Caribbean patients)) or it can be expressed as **creatinine clearance** (best derived from a 24-hour urine collection but often calculated from the Cockcroft and Gault formula (CG).

Cockcroft and Gault formula

$$\text{Estimated Creatinine Clearance in mL/minute} = \frac{(140 - \text{Age}) \times \text{Weight} \times \text{Constant}}{\text{Serum creatinine}}$$

Age in years
Weight in kilograms; use ideal body-weight
Serum creatinine in micromol/litre
Constant = 1.23 for men; 1.04 for women

The serum-creatinine concentration is sometimes used instead as a measure of renal function but it is only a **rough guide** to drug dosing.

Important

Renal function in adults is increasingly being reported on the basis of estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m^2 and derived from the Modification of Diet in Renal Disease (MDRD) formula. However, published information on the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance as a surrogate for glomerular filtration rate (GFR).

The information on dosage adjustment in the BNF is expressed in terms of eGFR, rather than creatinine clearance, for most drugs (see exceptions below: Toxic Drugs and Patients at Extremes of Weight). Although the two measures of renal function are not interchangeable, in practice, for most drugs and for most patients (over 18 years) of average build and height, eGFR (MDRD 'formula') can be used to determine dosage adjustments in place of creatinine clearance. An individual's absolute glomerular filtration rate can be calculated from the eGFR as follows: $GFR_{Absolute}$ = eGFR × (individual's body surface area/1.73)

Toxic drugs For potentially toxic drugs with a small safety margin, creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages in addition to plasma-drug concentration and clinical response.

Patients at extremes of weight In patients at both extremes of weight (BMI of less than 18.5 kg/m^2 or greater than 30 kg/m^2) the absolute glomerular filtration rate or creatinine clearance (calculated from the Cockcroft and Gault formula) should be used to adjust drug dosages.

In the BNF, values for eGFR, creatinine clearance (for toxic drugs), or another measure of renal function are included where possible. However, where such values are not available, the BNF reflects the terms used in the published information.

Chronic kidney disease in adults: UK guidelines for identification, management and referral (March 2006) define renal function as follows:

Degree of impairment	eGFR mL/minute/1.73 m^2
Normal - Stage 1	More than 90 (with other evidence of kidney damage)
Mild - Stage 2	60–89 (with other evidence of kidney damage)
Moderate[1] - Stage 3	30–59
Severe - Stage 4	15–29
Established renal failure - Stage 5	Less than 15

1. NICE clinical guideline 73 (September 2008)—Chronic kidney disease: Stage 3A eGFR 45–59, Stage 3B eGFR 30–44

Dialysis

For prescribing in patients on continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis, consult specialist literature.

Drug prescribing should be kept to the minimum in all patients with severe renal disease.

If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing **any** drug which requires dose modification.

Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Prescribing in pregnancy

Drugs can have harmful effects on the embryo or fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of *childbearing age* or for men *trying* to *father* a child.

During the *first trimester* drugs can produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy.

During the *second* and *third trimesters* drugs can affect the growth or functional development of the fetus, or they can have toxic effects on fetal tissues.

Drugs given shortly before term or during labour can have adverse effects on labour or on the neonate after delivery.

Not all the damaging effects of intrauterine exposure to drugs are obvious at birth, some may only manifest later in life. Such late-onset effects include malignancy, e.g. adenocarcinoma of the vagina after puberty in females exposed to diethylstilbestrol in the womb, and adverse effects on intellectual, social, and functional development.

The BNF identifies drugs which:

- may have harmful effects in pregnancy and indicates the trimester of risk
- are not known to be harmful in pregnancy

The information is based on human data, but information from *animal* studies has been included for some drugs when its omission might be misleading.

Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF.

Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used.
Few drugs have been shown conclusively to be teratogenic in humans, but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available when there is a known risk of certain defects.
Absence of information does not imply safety.
It should be noted that the BNF provides independent advice and may not always agree with the product literature.
Information on drugs and pregnancy is also available from the UK Teratology Information Service.
Tel: 0844 892 0909 (08:30–17:00 Monday to Friday)
Fax: (0191) 260 6193
Outside of these hours, urgent enquiries only www.uktis.org

Prescribing in breast-feeding

Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds.

Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:

- the amount of drug or active metabolite of the drug delivered to the infant (dependent on the pharmacokinetic characteristics of the drug in the mother);
- the efficiency of absorption, distribution, and elimination of the drug by the infant (infant pharmacokinetics);
- the nature of the effect of the drug on the infant (pharmacodynamic properties of the drug in the infant).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernible effect on the infant. This applies particularly to drugs that are poorly absorbed and need to be given parenterally. However, there is a theoretical possibility that a small amount of drug present in breast milk can induce a hypersensitivity reaction.

A clinical effect can occur in the infant if a pharmacologically significant quantity of the drug is present in milk. For some drugs (e.g. fluvastatin), the ratio between the concentration in milk and that in maternal plasma may be high enough to expose the infant to adverse effects. Some infants, such as those born prematurely or who have jaundice, are at a slightly higher risk of toxicity.

Some drugs inhibit the infant's sucking reflex (e.g. phenobarbital) while others can affect lactation (e.g. bromocriptine).

The BNF identifies drugs:

- that should be used with caution or are contra-indicated in breast-feeding;
- that can be given to the mother during breast-feeding because they are present in milk in amounts which are too small to be harmful to the infant;
- that might be present in milk in significant amount but are not known to be harmful.

Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast-feeding, absence of information does not imply safety.

Prescribing in palliative care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems, is paramount to provide the best quality of life for patients and their families. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team.

Specialist palliative care is available in most areas as day hospice care, home-care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams.

Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish.

Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, support can be provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

Drug treatment The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain

Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

Paracetamol (p. 259) or a **NSAID** (section 10.1.1) given regularly will often make the use of opioid analgesics unnecessary. A NSAID may also control the pain of *bone secondaries*; if necessary, flurbiprofen or indometacin can be given rectally. Radiotherapy, bisphosphonates (section 6.6.2), and radioactive isotopes of **strontium** (*Metastron*®) available from GE Healthcare) may also be useful for pain due to bone metastases.

An opioid analgesic (section 4.7.2) such as **codeine** (p. 264), alone or in combination with a non-opioid analgesic at adequate dosage, may be helpful in the control of moderate pain if non-opioid analgesics alone are not sufficient. Alternatively, **tramadol** (p. 271) can be considered for moderate pain. If these preparations do not control the pain, **morphine** (p. 268) is the most useful opioid analgesic. Alternatives to morphine, including **hydromorphone** (p. 267), **methadone** (p. 267), **oxycodone** (p. 269), and transdermal **fentanyl** (see below and p. 265) are best initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Equivalent single doses of opioid analgesics

These equivalences are intended **only** as an approximate guide; patients should be carefully monitored after **any** change in medication and dose titration may be required

Analgesic	Dose
Morphine salts (oral)	10 mg
Diamorphine hydrochloride (intramuscular)	3 mg
Hydromorphone hydrochloride	1.3 mg
Oxycodone (oral)	5 mg

Oral route Morphine (p. 268) is given *by mouth* as an oral solution or as standard ('immediate release') tablets regularly every 4 hours, the initial dose depending largely on the patient's previous treatment. A dose of 5–10 mg is enough to replace a weaker analgesic (such as paracetamol), but 10–20 mg or more is required to replace a strong one (comparable to morphine itself). If the first dose of morphine is no more effective than the previous analgesic, the next dose should be increased by 30–50%, the aim being to choose the lowest dose that prevents pain. The dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics (such as NSAIDs) should also be considered. Although morphine in a dose of 5–20 mg is usually adequate there should be no hesitation in increasing it stepwise according to response to 100 mg or occasionally up to 500 mg or higher if necessary. It may be possible to omit the overnight dose if double the usual dose is given at bedtime.

When the pain is controlled and the patient's 24-hour morphine requirement is established, the daily dose can be given as a *modified-release preparation* in a single dose or in two divided doses.

Preparations suitable for twice-daily administration include *Morphgesic*® *SR* tablets (p. 268), *MST Continus*® tablets or suspension (p. 269), and *Zomorph*® capsules (p. 269). *MXL*® capsules (p. 269) allow administration of the total daily morphine requirement as a single dose.

The starting dose of modified-release morphine preparations designed for twice daily administration is usually 10–20 mg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as co-codamol) the starting dose is usually 20–30 mg every 12 hours. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

The effective dose of modified-release preparations can alternatively be determined by giving the oral solution of morphine every 4 hours in increasing doses until the pain has been controlled, and then transferring the patient to the same total 24-hour dose of morphine given as the modified-release preparation (divided into two portions for 12-hourly administration). The first dose of the modified-release preparation is given with, or within 4 hours of, the last dose of the oral solution. The patient should be monitored closely for treatment efficacy and side-effects.

If pain occurs between regular doses of morphine ('breakthrough pain'), an additional dose ('rescue dose') should be given. An additional dose should also

be given 30 minutes before an activity that causes pain (e.g. wound dressing). Morphine, as oral solution or standard formulation tablets, should be prescribed for breakthrough pain. The standard dose of a strong opioid for breakthrough pain is usually one-tenth to one-sixth of the regular 24 hour total daily dose, repeated every 4 hours if necessary (review pain management if analgesic required more frequently). Each patient should be assessed on an individual basis. Fentanyl lozenges are also licensed for breakthrough pain.

Oxycodone (p. 269) can be used in patients who require an opioid but cannot tolerate morphine. If the patient is already receiving an opioid, oxycodone should be started at a dose equivalent to the current analgesic (see Equivalent Single Doses of Opioid Analgesics table, p. 20).

Levomepromazine (p. 220) is licensed to treat pain in palliative care, and may be of benefit in some patients. It should be reserved for use in conjunction with strong opioid analgesics in distressed patients with severe pain unresponsive to other measures.

Parenteral route If the patient becomes unable to swallow, the equivalent intramuscular dose of morphine is half the oral solution dose; in the case of the modified-release tablets it is half the total 24-hour dose (which is then divided into 6 portions to be given every 4 hours). **Diamorphine** (p. 264) is preferred for injection because, being more soluble, it can be given in a smaller volume. The equivalent intramuscular (or subcutaneous) dose is approximately a third of the oral dose of morphine. *Subcutaneous infusion* of diamorphine via continuous infusion device can be useful (for details, see p. 23).

If the patient can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of diamorphine. See table of approximate equivalent doses of morphine and diamorphine, p. 24.

Rectal route **Morphine** (p. 269) is also available for *rectal administration* as suppositories; alternatively **oxycodone** (p. 269) suppositories can be obtained on special order.

Transdermal route Transdermal preparations of fentanyl and buprenorphine are available (section 4.7.2); they are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations (see under Fentanyl, p. 265) because inappropriate use has caused fatalities.

The following 24-hour doses of morphine **by mouth** are considered to be approximately equivalent to the fentanyl patches shown:

- Morphine salt 45 mg daily ≡ fentanyl '12' patch
- Morphine salt 90 mg daily ≡ fentanyl '25' patch
- Morphine salt 180 mg daily ≡ fentanyl '50' patch
- Morphine salt 270 mg daily ≡ fentanyl '75' patch
- Morphine salt 360 mg daily ≡ fentanyl '100' patch

Morphine (as oral solution or standard formulation tablets) is given for breakthrough pain.

Gastro-intestinal pain The pain of *bowel colic* may be reduced by loperamide 2–4 mg 4 times daily. Hyoscine hydrobromide (section 4.6) may also be helpful, given sublingually at a dose of 300 micrograms 3 times daily as *Kwells*® tablets. For the dose by subcutaneous infusion, see p. 23).

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (section 1.1.1) and a prokinetic such as domperidone 10 mg 3 times daily before meals.

Muscle spasm The pain of muscle spasm can be helped by a muscle relaxant such as diazepam 5–10 mg daily or baclofen 5–10 mg 3 times daily.

Neuropathic pain Patients with neuropathic pain (section 4.7.3) may benefit from a trial of a tricyclic antidepressant for several weeks. An anticonvulsant may be added or substituted if pain persists; gabapentin and pregabalin (both section 4.8.1) are licensed for neuropathic pain. Ketamine is sometimes used under specialist supervision for neuropathic pain that responds poorly to opioid analgesics.

Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone 8 mg daily, which reduces oedema around the tumour, thus reducing compression.

Nerve blocks can be considered when pain is localised to a specific area. **Transcutaneous electrical nerve stimulation** (TENS) may also help.

Miscellaneous conditions

Unlicensed indications or routes
Several recommendations in this section involve unlicensed indications or routes.

Anorexia Anorexia may be helped by prednisolone 15–30 mg daily or dexamethasone 2–4 mg daily.

Bowel colic and excessive respiratory secretions
Bowel colic and excessive respiratory secretions may be reduced by a subcutaneous injection of hyoscine hydrobromide 400 micrograms, hyoscine butylbromide 20 mg, or glycopyrronium 200 micrograms. These antimuscarinics are generally given every 4 hours when required, but hourly use is occasionally necessary, particularly in excessive respiratory secretions. If symptoms persist, they can be given regularly via a continuous infusion device, see p. 23. Care is required to avoid the discomfort of dry mouth.

Capillary bleeding Capillary bleeding can be treated with tranexamic acid (section 2.11) by mouth; treatment is usually discontinued one week after the bleeding has stopped, or, if necessary, it can be continued at a reduced dose. Alternatively, gauze soaked in tranexamic acid 100 mg/mL or adrenaline (epinephrine) solution 1 mg/mL (1 in 1000) can be applied to the affected area.

Vitamin K may be useful for the treatment and prevention of bleeding associated with prolonged clotting in liver disease. In severe chronic cholestasis, absorption of vitamin K may be impaired; either parenteral or water-soluble oral vitamin K should be considered (section 9.6.6).

Constipation Constipation is a very common cause of distress and is almost invariable after administration of an opioid analgesic. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer) or lactulose solution with a senna preparation should be used (section 1.6.2 and section 1.6.3). Methylnaltrexone (section 1.6.6) is licensed for the treatment of opioid-induced constipation.

Convulsions Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin or carbamazepine (section 4.8.1) should be considered. When oral medication is no longer possible, diazepam as suppositories 10–20 mg every 4 to 8 hours, or phenobarbital by injection 50–200 mg twice daily is continued as prophylaxis. For the use of midazolam by subcutaneous infusion using a continuous infusion device, see below.

Dry mouth Dry mouth may be relieved by good mouth care and measures such as chewing sugar-free gum, sucking ice or pineapple chunks, or the use of artificial saliva (section 12.3.5); dry mouth associated with candidiasis can be treated by oral preparations of nystatin or miconazole (section 12.3.2); alternatively, fluconazole can be given by mouth (section 5.2.1). Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiemetics; if possible, an alternative preparation should be considered.

Dysphagia A corticosteroid such as dexamethasone 8 mg daily may help, temporarily, if there is an obstruction due to tumour. See also Dry Mouth, above.

Dyspnoea Breathlessness at rest may be relieved by regular oral morphine in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam 5–10 mg daily may be helpful for dyspnoea associated with anxiety. A corticosteroid, such as dexamethasone 4–8 mg daily, may also be helpful if there is bronchospasm or partial obstruction.

Fungating tumours Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole (section 5.1.11) is often required to reduce malodour but topical metronidazole (section 13.10.1.2) is also used.

Hiccup Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent (section 1.1.1). If this fails, metoclopramide 10 mg every 6 to 8 hours by mouth or by subcutaneous or intramuscular injection can be added; if this also fails, baclofen 5 mg twice daily, or nifedipine 10 mg three times daily, or chlorpromazine (section 4.2.1) can be tried.

Hypercalcaemia see section 9.5.1.2

Insomnia Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam (section 4.1.1), may be useful.

Intractable cough Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine in an initial dose of 5 mg every 4 hours. Methadone linctus should be avoided because it has a long duration of action and tends to accumulate.

Nausea and vomiting Nausea and vomiting are common in patients with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic (section 4.6) is started.

Nausea and vomiting may occur with opioid therapy particularly in the initial stages but can be prevented by giving an antiemetic such as haloperidol or metoclopramide. An antiemetic is usually necessary only for the first 4 or 5 days and therefore combined preparations containing an opioid with an antiemetic are not recommended because they lead to unnecessary antiemetic therapy (and associated side-effects when used long-term).

Metoclopramide has a prokinetic action and is used in a dose of 10 mg 3 times daily by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not be used concurrently.

Haloperidol is used by mouth in an initial dose of 1.5 mg once or twice daily (can be increased if necessary to 5–10 mg daily in divided doses) for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure).

Cyclizine is given in a dose of 50 mg up to 3 times daily by mouth. It is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness.

Antiemetic therapy should be reviewed every 24 hours; it may be necessary to substitute the antiemetic or to add another one.

Levomepromazine can be used if first-line antiemetics are inadequate; it is given by mouth in a dose of 6–50 mg daily (6-mg tablets available from 'special-order' manufacturers or specialist importing companies, see p. 988) in 1–2 divided doses. For the dose by subcutaneous infusion, see p. 23. Dexamethasone 8–16 mg daily by mouth can be used as an adjunct.

For the administration of antiemetics by subcutaneous infusion using a continuous infusion device, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy, see section 8.1.

Pruritus Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients (section 13.2.1). In the case of obstructive jaundice, further measures include administration of colestyramine (section 1.9.2).

Raised intracranial pressure Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone 16 mg daily for 4 to 5 days, subsequently reduced to 4–6 mg daily if possible; dexamethasone should be given before 6 p.m. to reduce the risk of insomnia.

Restlessness and confusion Restlessness and confusion may require treatment with haloperidol 1–3 mg by mouth every 8 hours. Levomepromazine is also used occasionally for restlessness. For the dose by subcutaneous infusion using a continuous infusion device, see p. 23.

Continuous infusion devices

Although drugs can usually be administered *by mouth* to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. Repeated administration of *intramuscular injections* can be difficult in a cachectic patient. This has led to the use of portable continuous infusion devices, such as syringe drivers, to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Syringe driver rate settings

Staff using syringe drivers should be **adequately trained** and different rate settings should be **clearly identified** and **differentiated**; incorrect use of syringe drivers is a common cause of medication errors.

Indications for the **parenteral route** are:

- the patient is unable to take medicines by mouth owing to *nausea and vomiting, dysphagia, severe weakness,* or *coma;*
- there is *malignant bowel obstruction* in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- occasionally when the patient *does not wish* to take regular medication by mouth.

Bowel colic and excessive respiratory secretions Hyoscine hydrobromide effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a *subcutaneous infusion dose* of 1.2–2.4 mg/24 hours.

Hyoscine butylbromide is used for bowel colic and for excessive respiratory secretions, and is less sedative than hyoscine hydrobromide. Hyoscine butylbromide is given in a *subcutaneous infusion dose* of 60–300 mg/24 hours for bowel colic and 20–120 mg/24 hours for excessive respiratory secretions (**important:** these doses of *hyoscine butylbromide* must not be confused with the much lower dose of *hyoscine hydrobromide*, above).

Glycopyrronium 0.6–1.2 mg/24 hours by subcutaneous infusion may also be used.

Convulsions If a patient has previously been receiving an antiepileptic drug *or* has a primary or secondary cerebral tumour *or* is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam is the benzodiazepine antiepileptic of choice for *continuous subcutaneous infusion*, and it is given initially in a dose of 20–40 mg/24 hours.

Nausea and vomiting Haloperidol is given in a *subcutaneous infusion dose* of 2.5–10 mg/24 hours.

Levomepromazine is given in a *subcutaneous infusion dose* of 5–25 mg/24 hours but sedation can limit the dose.

Cyclizine is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below); it is given in a *subcutaneous infusion dose* of 150 mg/24 hours.

Metoclopramide can cause skin reactions; it is given in a *subcutaneous infusion dose* of 30–100 mg/24 hours.

Octreotide (section 8.3.4.3), which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion in a dose of 250–500 micrograms/24 hours to reduce intestinal secretions and to reduce vomiting due to bowel obstruction. Doses of 750 micrograms/24 hours, and occasionally higher, are sometimes required.

Pain control Diamorphine is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table on p. 24 shows approximate equivalent doses of morphine and diamorphine.

Restlessness and confusion Haloperidol has little sedative effect; it is given in a *subcutaneous infusion dose* of 5–15 mg/24 hours.

Levomepromazine has a sedative effect; it is given in a *subcutaneous infusion dose* of 12.5–200 mg/24 hours.

Midazolam is a sedative and an antiepileptic that may be used in addition to an antipsychotic drug in a very restless patient; it is given in a *subcutaneous infusion dose* of 20–100 mg/24 hours.

Mixing and compatibility The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine, prochlorperazine, and diazepam are **contra-indicated** as they cause skin reactions at the injection site; to a lesser extent cyclizine and levomepromazine also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9%) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either *water for injections* or *physiological saline* (sodium chloride 0.9%) is a suitable diluent—above that strength only *water for injections* is used (to avoid precipitation).

The following can be mixed with *diamorphine*:

Cyclizine[1]	Hyoscine hydrobromide
Dexamethasone[2]	Levomepromazine
Haloperidol[3]	Metoclopramide[4]
Hyoscine butylbromide	Midazolam

1. Cyclizine may precipitate at concentrations above 10 mg/mL *or* in the presence of sodium chloride 0.9% *or* as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
2. Special care is needed to avoid precipitation of dexamethasone when preparing it.
3. Mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
4. Under some conditions infusions containing metoclopramide become discoloured; such solutions should be discarded.

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.

Problems encountered with syringe drivers The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs *too quickly* check the rate setting and the calculation;
- if the subcutaneous infusion runs *too slowly* check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an *injection site reaction* make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

Equivalent doses of morphine sulphate and diamorphine hydrochloride given over 24 hours

These equivalences are *approximate only* and should be adjusted according to response

MORPHINE		PARENTERAL DIAMORPHINE
Oral morphine sulphate	Subcutaneous infusion of morphine sulphate	Subcutaneous infusion of diamorphine hydrochloride
over 24 hours	**over 24 hours**	**over 24 hours**
30 mg	15 mg	10 mg
60 mg	30 mg	20 mg
90 mg	45 mg	30 mg
120 mg	60 mg	40 mg
180 mg	90 mg	60 mg
240 mg	120 mg	80 mg
360 mg	180 mg	120 mg
480 mg	240 mg	160 mg
600 mg	300 mg	200 mg
780 mg	390 mg	260 mg
960 mg	480 mg	320 mg
1200 mg	600 mg	400 mg

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).
To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.

Prescribing for the elderly

Old people, especially the very old, require special care and consideration from prescribers. *Medicines for Older People*, a component document of the National Service Framework for Older People,[1] describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

Appropriate prescribing Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance (see Taking medicines to best effect under General guidance). The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients' medicines should be reviewed regularly and medicines which are not of benefit should be stopped.

Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and lightheadedness when associated with social stress as in widowhood, loneliness, and family dispersal.

In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help them, such as anticoagulants or antiplatelet drugs for atrial fibrillation, antihypertensives, statins, and drugs for osteoporosis.

Form of medicine Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and whilst in an upright position to avoid the possibility of oesophageal ulceration. It can be helpful to discuss with the patient the possibility of taking the drug as a liquid if available.

Manifestations of ageing In the very old, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. In addition, age-related muscle weakness and difficulty in maintaining balance should not be confused with neurological disease. Disorders such as lightheadedness not associated with postural or postprandial hypotension are unlikely to be helped by drugs.

Sensitivity The nervous system of elderly patients is more sensitive to many commonly used drugs, such as

1. Department of Health. National Service Framework for Older People. London: Department of Health, March 2001.

opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as antihypertensives and NSAIDs.

Pharmacokinetics

Pharmacokinetic changes can markedly increase the tissue concentration of a drug in the elderly, especially in debilitated patients.

The most important effect of age is reduced renal clearance. Many aged patients thus *excrete drugs slowly*, and are *highly susceptible to nephrotoxic drugs*. Acute illness can lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin) can rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory-tract infection. The hepatic metabolism of lipid soluble drugs is reduced in elderly patients because there is a reduction in liver volume. This is important for drugs with a narrow therapeutic window.

Adverse reactions

Adverse reactions often present in the elderly in a vague and non-specific fashion. *Confusion* is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are *constipation* (with antimuscarinics and many tranquillisers) and postural *hypotension* and *falls* (with diuretics and many psychotropics).

Hypnotics Many hypnotics with long half-lives have serious hangover effects, including drowsiness, unsteady gait, slurred speech, and confusion. Hypnotics with short half-lives should be used but they too can present problems (section 4.1.1). Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence. Benzodiazepines impair balance, which can result in falls.

Diuretics Diuretics are overprescribed in old age and should **not** be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs Bleeding associated with aspirin and other NSAIDs is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk.

Owing to the *increased susceptibility of the elderly* to the *side-effects of NSAIDs* the following recommendations are made:

- for *osteoarthritis, soft-tissue lesions*, and *back pain*, first try measures such as weight reduction (if obese), warmth, exercise, and use of a walking stick;
- for *osteoarthritis, soft-tissue lesions, back pain*, and *pain in rheumatoid arthritis*, paracetamol should be used first and can often provide adequate pain relief;
- alternatively, a low-dose NSAID (e.g. ibuprofen up to 1.2 g daily) may be given;
- for pain relief when either drug is inadequate, paracetamol in a full dose plus a low-dose NSAID may be given;
- if necessary, the NSAID dose can be increased or an opioid analgesic given with paracetamol;
- do not give two NSAIDs at the same time.

For advice on prophylaxis of NSAID-induced peptic ulcers if continued NSAID treatment is necessary, see section 1.3.

Other drugs Other drugs which commonly cause adverse reactions are *antiparkinsonian drugs, antihypertensives, psychotropics*, and *digoxin*. The usual maintenance dose of digoxin in very old patients is 125 micrograms daily (62.5 micrograms in those with renal disease); lower doses are often inadequate but toxicity is common in those given 250 micrograms daily.

Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. *co-trimoxazole, mianserin*) should be avoided unless there is no acceptable alternative.

The elderly generally require a lower maintenance dose of *warfarin* than younger adults; once again, the outcome of bleeding tends to be more serious.

Guidelines

Always consider whether a drug is indicated at all.

Limit range It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

Reduce dose Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. long-acting antidiabetic drugs such as glibenclamide) should be avoided altogether.

Review regularly Review repeat prescriptions regularly. In many patients it may be possible to stop some drugs, provided that clinical progress is monitored. It may be necessary to reduce the dose of some drugs as renal function declines.

Simplify regimens Elderly patients benefit from simple treatment regimens. Only drugs with a clear indication should be prescribed and whenever possible given once or twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

Explain clearly Write full instructions on every prescription (*including* repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like 'as directed'. Child-resistant containers may be unsuitable.

Repeats and disposal Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities.

If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.

Prescribing in dental practice

The following is a list of topics of particular relevance to dental surgeons.

Advice on the drug management of dental and oral conditions has been integrated into the BNF. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections of the BNF.

General guidance
- Prescribing by dental surgeons, p. 6
- Oral side-effects of drugs, p. 13
- Medical emergencies in dental practice, below
- Medical problems in dental practice, p. 28

Drug management of dental and oral conditions
- **Dental and orofacial pain,** p. 257
  - Neuropathic pain, p. 272
  - Non-opioid analgesics and compound analgesic preparations, p. 257
  - Opioid analgesics, p. 263
  - Non-steroidal anti-inflammatory drugs, p. 631
- **Oral infections**
  - Bacterial infections, p. 321
    - Phenoxymethylpenicillin, p. 333
    - Broad-spectrum penicillins (amoxicillin and ampicillin), p. 336
    - Cephalosporins (cefalexin and cefradine), p. 341
    - Tetracyclines, p. 347
    - Macrolides (clarithromycin, erythromycin and azithromycin), p. 352
    - Clindamycin, p. 354
    - Metronidazole, p. 367
    - Fusidic acid p. 735
  - Fungal infections, p. 695
    - Local treatment, p. 695
    - Systemic treatment, p. 373
  - Viral infections
    - Herpetic gingivostomatitis, local treatment, p. 696
    - Herpetic gingivostomatitis, systemic treatment, p. 392 and p. 696
    - Herpes labialis, p. 739
- **Anaesthetics, anxiolytics and hypnotics**
  - Anaesthesia, sedation, and resuscitation in dental practice, p. 776
  - Hypnotics, p. 208
  - Peri-operative anxiolytics, p. 783
  - Local anaesthesia, p. 794
- **Oral ulceration and inflammation,** p. 693
- **Mouthwashes, gargles and dentifrices,** p. 697
- **Dry mouth,** p. 698
- **Minerals**
  - Fluorides, p. 613
- **Aromatic inhalations,** p. 203
- **Nasal decongestants,** p. 691

Dental Practitioners' Formulary, p. 972

Changes to Dental Practitioners' Formulary, p. 973

Medical emergencies in dental practice

This section provides guidelines on the management of the more common medical emergencies which may arise in dental practice. Dental surgeons and their staff should be familiar with standard resuscitation procedures, but in all circumstances it is advisable to summon medical assistance as soon as possible. For an **algorithm** of the procedure for **cardiopulmonary resuscitation**, see inside back cover.

The drugs referred to in this section include:
Adrenaline Injection (Epinephrine Injection), adrenaline 1 in 1000, (adrenaline 1 mg/mL as acid tartrate), 1-mL amps
Aspirin Dispersible Tablets 300 mg
Glucagon Injection, glucagon (as hydrochloride), 1-unit vial (with solvent)
Glucose (for administration by mouth)
Glyceryl Trinitrate Spray
Midazolam Buccal Liquid, midazolam 10 mg/mL *or* Midazolam Injection, midazolam (as hydrochloride) 2 mg/mL, 5-mL amps, or 5 mg/mL, 2-mL amps
Oxygen
Salbutamol Aerosol Inhalation, salbutamol 100 micrograms/metered inhalation

Adrenal insufficiency

Adrenal insufficiency may follow prolonged therapy with corticosteroids and can persist for years after stopping. A patient with adrenal insufficiency may become hypotensive under the stress of a dental visit (important: see also p. 444 for details of corticosteroid cover before dental surgical procedures under general anaesthesia).

Management

- Lay the patient flat
- Give **oxygen** (see section 3.6)
- Transfer patient urgently to hospital

Anaphylaxis

A severe allergic reaction may follow oral or parenteral administration of a drug. Anaphylactic reactions in dentistry may follow the administration of a drug or contact with substances such as latex in surgical gloves. In general, the more rapid the onset of the reaction the more profound it tends to be. Symptoms may develop within minutes and rapid treatment is essential.

Anaphylactic reactions may also be associated with *additives* and *excipients* in foods and medicines (see Excipients, p. 2). Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergenic fats or oils (including those for topical application, particularly if they are intended for use in the mouth or for application to the nasal mucosa).

Symptoms and signs

- Paraesthesia, flushing, and swelling of face
- Generalised itching, especially of hands and feet
- Bronchospasm and laryngospasm (with wheezing and difficulty in breathing)
- Rapid weak pulse together with fall in blood pressure and pallor; finally cardiac arrest

Management

First-line treatment includes securing the airway, restoration of blood pressure (laying the patient flat and raising the feet, or in the recovery position if unconscious or nauseous and at risk of vomiting), and administration of **adrenaline** (epinephrine) injection (section 3.4.3). This is given **intramuscularly** in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) may be appropriate for *immediate self-administration*. The dose is repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function. **Oxygen** administration is also of primary importance (see section 3.6). Arrangements should be made to transfer the patient to hospital urgently.

For further details on the management of anaphylaxis including details of paediatric doses of adrenaline, see p. 197

Asthma

Patients with asthma may have an attack while at the dental surgery. Most attacks will respond to 2 puffs of the patient's short-acting beta$_2$ agonist inhaler such as **salbutamol** 100 micrograms/puff; further puffs are required if the patient does not respond rapidly. If the patient is unable to use the inhaler effectively, further puffs should be given through a large-volume spacer device (or, if not available, through a plastic or paper cup with a hole in the bottom for the inhaler mouthpiece). If the response remains unsatisfactory, or if further deterioration occurs, then the patient should be transferred urgently to hospital. Whilst awaiting transfer, **oxygen** (section 3.6) should be given with salbutamol 5 mg or terbutaline 10 mg by nebuliser; if a nebuliser is unavailable, then 2–10 puffs of salbutamol 100 micrograms/metered inhalation should be given (preferably by a large-volume spacer), and repeated every 10–20 minutes if necessary. If asthma is part of a more generalised anaphylactic reaction, an intramuscular injection of **adrenaline** (as detailed under Anaphylaxis above) should be given.

For a table describing the management of acute asthma, see p. 173

Patients with severe chronic asthma or whose asthma has deteriorated previously during a dental procedure may require an increase in their prophylactic medication before a dental procedure. This should be discussed with the patient's medical practitioner and may include increasing the dose of inhaled or oral corticosteroid.

Cardiac emergencies

If there is a history of *angina* the patient will probably carry **glyceryl trinitrate** spray or tablets (or isosorbide dinitrate tablets) and should be allowed to use them. Hospital admission is not necessary if symptoms are mild and resolve rapidly with the patient's own medication. See also Coronary Artery Disease on p. 29.

Arrhythmias may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also Pacemakers, p. 29.

The pain of *myocardial infarction* is similar to that of angina but generally more severe and more prolonged. For general advice see also Coronary Artery Disease on p. 29

Symptoms and signs of myocardial infarction

- Progressive onset of severe, crushing pain across front of chest; pain may radiate towards the shoulder and down arm, or into neck and jaw
- Skin becomes pale and clammy
- Nausea and vomiting are common
- Pulse may be weak and blood pressure may fall
- Breathlessness

Initial management of myocardial infarction

Call immediately for medical assistance and an ambulance, as appropriate.

Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. **Oxygen** may be administered (see section 3.6).

Sublingual glyceryl trinitrate may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug.

Reassure the patient as much as possible to relieve further anxiety. If available, aspirin in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see p. 156.

If the patient collapses and loses consciousness attempt standard resuscitation measures. For an **algorithm** of the procedure for **cardiopulmonary resuscitation**, see inside back cover.

Epileptic seizures

Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

Symptoms and signs

- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

Management

During a convulsion try to ensure that the patient is not at risk from injury but make no attempt to put anything in the mouth or between the teeth (in mistaken belief that this will protect the tongue). Give **oxygen** (section 3.6) to support respiration if necessary.

Do not attempt to restrain convulsive movements.

After convulsive movements have subsided place the patient in the coma (recovery) position and check the airway.

After the convulsion the patient may be confused ('post-ictal confusion') and may need reassurance and sympathy. The patient should not be sent home until fully recovered. Seek medical attention or transfer the patient to hospital if it was the first episode of epilepsy, or if the convulsion was atypical, prolonged (or repeated), or if injury occurred.

Medication should only be given if convulsive seizures are prolonged (convulsive movements lasting 5 minutes or longer) or repeated rapidly.

Either **midazolam** buccal liquid or midazolam injection solution can be given by the buccal route [unlicensed use] in a single dose of 10 mg. For further details on the management of status epilepticus, including details of paediatric doses of midazolam, see p. 296.

Focal seizures similarly need very little active management (in an automatism only a minimum amount of restraint should be applied to prevent injury). Again, the patient should be observed until post-ictal confusion has completely resolved.

Hypoglycaemia

Insulin-treated diabetic patients attending for dental treatment under local anaesthesia should inject insulin and eat meals as normal. If food is omitted the blood glucose will fall to an abnormally low level (hypoglycaemia). Patients can often recognise the symptoms themselves and this state responds to sugar in water or a few lumps of sugar. Children may not have such prominent changes but may appear unduly lethargic.

Symptoms and signs

- Shaking and trembling
- Sweating
- 'Pins and needles' in lips and tongue
- Hunger
- Palpitation
- Headache (occasionally)
- Double vision
- Difficulty in concentration
- Slurring of speech
- Confusion
- Change of behaviour; truculence
- Convulsions
- Unconsciousness

Management

Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of *Lucozade® Energy Original* 55 mL, *Coca-Cola®* 100 mL, *Ribena® Blackcurrant* 18 mL (to be diluted), 2 teaspoons sugar, and also from 3 sugar lumps[1]. If necessary this may be repeated in 10–15 minutes.

If glucose cannot be given by mouth, if it is ineffective, or if the hypoglycaemia causes unconsciousness, **glucagon** 1 mg (1 unit) should be given by intramuscular (or subcutaneous) injection; a child under 8 years or of body-weight under 25 kg should be given 500 micrograms. Once the patient regains consciousness oral glucose should be administered as above. If glucagon is ineffective or contra-indicated, the patient should be transferred urgently to hospital. The patient must also be admitted to hospital if hypoglycaemia is caused by an oral antidiabetic drug.

Syncope

Insufficient blood supply to the brain results in loss of consciousness. The commonest cause is a vasovagal attack or simple faint (syncope) due to emotional stress.

Symptoms and signs

- Patient feels faint
- Low blood pressure
- Pallor and sweating
- Yawning and slow pulse
- Nausea and vomiting
- Dilated pupils
- Muscular twitching

Management

- Lay the patient as flat as is reasonably comfortable and, in the absence of associated breathlessness, raise the legs to improve cerebral circulation
- Loosen any tight clothing around the neck
- Once consciousness is regained, give sugar in water or a cup of sweet tea

Other possible causes

Postural hypotension can be a consequence of rising abruptly or of standing upright for too long; antihypertensive drugs predispose to this. When rising, susceptible patients should take their time. Management is as for a vasovagal attack.

Under stressful circumstances, some patients hyperventilate. This gives rise to feelings of faintness but does not usually result in syncope. In most cases reassurance is all that is necessary; rebreathing from cupped hands or a bag may be helpful but calls for careful supervision.

Adrenal insufficiency or arrhythmias are other possible causes of syncope, see p. 26 and p. 29.

Medical problems in dental practice

Individuals presenting at the dental surgery may also suffer from an unrelated medical condition; this may require modification to the management of their dental condition. If the patient has systemic disease or is taking other medication, the matter may need to be discussed with the patient's general practitioner or hospital consultant.

For advice on adrenal insufficiency, anaphylaxis, asthma, cardiac emergencies, epileptic seizures, hypoglycaemia and syncope see under Medical Emergencies in Dental Practice.

1. Proprietary products of quick-acting carbohydrate (e.g. *GlucoGel®*, *Dextrogel®*, *Hypo-Fit®*) are available on prescription for the patient to keep to hand in case of hypoglycaemia

Allergy

Patients should be asked about any history of allergy; those with a history of atopic allergy (asthma, eczema, hay fever, etc.) are at special risk. Those with a history of a severe allergy or of anaphylactic reactions are at high risk—it is essential to confirm that they are not allergic to any medication, or to any dental materials or equipment (including latex gloves). See also Anaphylaxis on p. 26.

Arrhythmias

Patients, especially those who suffer from heart failure or who have sustained a myocardial infarction, may have irregular cardiac rhythm. Atrial fibrillation is a common arrhythmia even in patients with normal hearts and is of little concern except that dental surgeons should be aware that such patients may be receiving anticoagulant therapy. The patient's medical practitioner should be asked whether any special precautions are necessary. Premedication (e.g. with temazepam) may be useful in some instances for very anxious patients.

See also Cardiac emergencies, p. 27 and Dental Anaesthesia, p. 794.

Cardiac prostheses

For an account of the risk of infective endocarditis in patients with prosthetic heart valves, see Infective Endocarditis, below. For advice on patients receiving anticoagulants, see Thromboembolic disease, below.

Coronary artery disease

Patients are vulnerable for at least 4 weeks following a myocardial infarction or following any sudden increase in the symptoms of angina. It would be advisable to check with the patient's medical practitioner before commencing treatment. See also Cardiac Emergencies on p. 27.

Treatment with low-dose aspirin (75 mg daily), clopidogrel, or dipyridamole should not be stopped routinely nor should the dose be altered before dental procedures.

A Working Party of the British Society for Antimicrobial Chemotherapy has not recommended antibiotic prophylaxis for patients following coronary artery bypass surgery.

Cyanotic heart disease

Patients with cyanotic heart disease are at risk in the dental chair, particularly if they have pulmonary hypertension. In such patients a syncopal reaction increases the shunt away from the lungs, causing more hypoxia which worsens the syncopal reaction—a vicious circle that may prove fatal. The advice of the cardiologist should be sought on any patient with congenital cyanotic heart disease. Treatment in hospital is more appropriate for some patients with this condition.

Hypertension

Patients with hypertension are likely to be receiving antihypertensive drugs such as those described in section 2.5. Their blood pressure may fall dangerously low under general anaesthesia, see also under Dental Anaesthesia on p. 794.

Immunosuppression and indwelling intraperitoneal catheters

See Table 2, section 5.1

Infective endocarditis

While almost any dental procedure can cause bacteraemia, there is no clear association with the development of infective endocarditis. Routine daily activities such as tooth brushing also produce a bacteraemia and may present a greater risk of infective endocarditis than a single dental procedure.

Antibacterial prophylaxis and chlorhexidine mouthwash are **not** recommended for the prevention of endocarditis in patients undergoing dental procedures. Such prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Reduction of oral bacteraemia Patients at risk of endocarditis[1] should be advised to maintain the highest possible standards of oral hygiene in order to reduce the:

- need for dental extractions or other surgery;
- chances of severe bacteraemia if dental surgery is needed;
- possibility of 'spontaneous' bacteraemia.

Postoperative care Patients at risk of endocarditis[1] should be warned to report to the doctor or dental surgeon any unexplained illness that develops after dental treatment. Any infection in patients at risk of endocarditis[1] should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

Patients on anticoagulant therapy For general advice on dental surgery in patients receiving oral anticoagulant therapy see Thromboembolic Disease, below.

Joint prostheses

See Table 2, section 5.1

Pacemakers

Pacemakers prevent asystole or severe bradycardia. Some ultrasonic scalers, electronic apex locators, electro-analgesic devices, and electrocautery devices interfere with the normal function of pacemakers (including shielded pacemakers) and should not be used. The manufacturer's literature should be consulted whenever possible. If severe bradycardia occurs in a patient fitted with a pacemaker, electrical equipment should be switched off and the patient placed supine with the legs elevated. If the patient loses consciousness and the pulse remains slow or is absent, cardiopulmonary resuscitation (see inside back cover) may be needed. Call immediately for medical assistance and an ambulance, as appropriate.

1. Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis

A Working Party of the British Society for Antimicrobial Chemotherapy does not recommend antibacterial prophylaxis for patients with pacemakers.

Thromboembolic disease

Patients receiving a **heparin** or an oral anticoagulant such as **warfarin**, **acenocoumarol** (nicoumalone), **phenindione**, **dabigatran etexilate**, or **rivaroxaban** may be liable to excessive bleeding after extraction of teeth or other dental surgery. Often dental surgery can be delayed until the anticoagulant therapy has been completed.

For a patient requiring long-term therapy with warfarin, the patient's medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure. This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If possible, a single extraction should be done first; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding.

For a patient on long-term warfarin, the advice of the clinician responsible for the patient's anticoagulation should be sought if:

- the INR is unstable, or if the INR is greater than 4.0;
- the patient has thrombocytopenia, haemophilia, or other disorders of haemostasis, or suffers from liver impairment, alcoholism, or renal failure;
- the patient is receiving antiplatelet drugs, cytotoxic drugs or radiotherapy.

Intramuscular injections are *contra-indicated* in patients on anticoagulant therapy, and in those with any disorder of haemostasis.

A local anaesthetic containing a vasoconstrictor should be given by infiltration, or by intraligamentary or mental nerve injection if possible. If regional nerve blocks cannot be avoided the local anaesthetic should be given cautiously using an aspirating syringe.

Drugs which have potentially serious interactions with anticoagulants include aspirin and other NSAIDs, carbamazepine, imidazole and triazole antifungals (including miconazole), erythromycin, clarithromycin, and metronidazole; for details of these and other interactions with anticoagulants, see Appendix 1 (dabigatran etexilate, heparins, phenindione, rivaroxaban, and coumarins). Although studies have failed to demonstrate an interaction, common experience in anticoagulant clinics is that the INR can be altered following a course of an oral broad-spectrum antibiotic, such as ampicillin or amoxicillin.

Information on the treatment of patients who take anticoagulants is available at www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant

Liver disease

Liver disease may alter the response to drugs and drug prescribing should be kept to a minimum in patients with severe liver disease. Problems are likely mainly in patients with *jaundice*, *ascites*, or evidence of *encephalopathy*.

For guidance on prescribing for patients with hepatic impairment, see p. 17. Where care is needed when prescribing in hepatic impairment, this is indicated under the relevant drug in the BNF.

Renal impairment

The use of drugs in patients with reduced renal function can give rise to many problems. Many of these problems can be avoided by reducing the dose or by using alternative drugs.

Special care is required in renal transplantation and immunosuppressed patients; if necessary such patients should be referred to specialists.

For guidance on prescribing in patients with renal impairment, see p. 17. Where care is needed when prescribing in renal impairment, this is indicated under the relevant drug in the BNF.

Pregnancy

Drugs taken during pregnancy can be harmful to the fetus and should be prescribed only if the expected benefit to the mother is thought to be greater than the risk to the fetus; all drugs should be avoided if possible during the first trimester.

For guidance on prescribing in pregnancy, see p. 19. Where care is needed when prescribing in pregnancy, this is indicated under the relevant drug in the BNF.

Breast-feeding

Some drugs taken by the mother whilst breast-feeding can be transferred to the breast milk, and may affect the infant.

For guidance on prescribing in breast-feeding, see p. 19. Where care is needed when prescribing in breast-feeding, this is indicated under the relevant drug in the BNF.

Drugs and sport

UK Anti-Doping advises that athletes are personally responsible should a prohibited substance be detected in their body. An advice card listing examples of permitted and prohibited substances is available from:

UK Anti-Doping
Oceanic House
1a Cockspur Street
London SW1Y 5BG
Tel: (020) 7766 7350
information@ukad.org.uk
www.ukad.org.uk

A similar card detailing classes of drugs and doping methods prohibited in football is available from the Football Association. This contains information specific to the Football Association Doping Control Regulations including the Football Association's policy on social drugs. Further information is available at www.thefa.com.

General Medical Council's advice

Doctors who prescribe or collude in the provision of drugs or treatment with the intention of improperly enhancing an individual's performance in sport contravene the GMC's guidance, and such actions would usually raise a question of a doctor's continued registration. This does not preclude the provision of any care or treatment where the doctor's intention is to protect or improve the patient's health.

Emergency treatment of poisoning

These notes provide only an overview of the treatment of poisoning, and it is strongly recommended that either **TOXBASE** or the **UK National Poisons Information Service** (see below) be consulted when there is doubt about the degree of risk or about management.

Hospital admission Patients who have features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed action should also be admitted, even if they appear well. Delayed-action poisons include aspirin, iron, paracetamol, tricyclic antidepressants, and co-phenotrope (diphenoxylate with atropine, *Lomotil*®); the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

Further information and advice

TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the internet to registered users at www.toxbase.org (a backup site is available at www.toxbasebackup.org if the main site cannot be accessed). It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the **UK National Poisons Information Service** on the following number:
Tel: 0844 892 0111

Advice on laboratory analytical services can be obtained from TOXBASE or from the National Poisons Information Service.

Help with identifying capsules or tablets may be available from a regional medicines information centre (see inside front cover) or (out of hours) from the National Poisons Information Service.

General care

It is often impossible to establish with certainty the identity of the poison and the size of the dose. This is not usually important because only a few poisons (such as opioids, paracetamol, and iron) have specific antidotes; few patients require active removal of the poison. In most patients, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned individual and from carers or parents. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses and patients should be assessed carefully. Accidents may involve domestic and industrial products (the contents of which are not generally known). The **National Poisons Information Service** should be consulted when there is doubt about any aspect of suspected poisoning.

Respiration

Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such patients should be monitored in a critical care area.

Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants. A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by tilting down the head of the bed and administration of either sodium chloride intravenous infusion or a colloidal infusion. Vasoconstrictor sympathomimetics (section 2.7.2) are rarely required and their use may be discussed with the National Poisons Information Service.

Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea.

Hypertension, often transient, occurs less frequently than hypotension in poisoning; it may be associated with sympathomimetic drugs such as amfetamines, phencyclidine, and cocaine.

Heart

Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities, but ventricular arrhythmias that cause serious hypotension require treatment (section 2.3.1). If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the patient reaches hospital.

Body temperature

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hypothermia should be managed by prevention of further heat loss and appropriate rewarming as clinically indicated.

Hyperthermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with **tepid** water will promote evaporation. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome.

Both hypothermia and hyperthermia require **urgent** hospitalisation for assessment and supportive treatment.

Convulsions

Single short-lived convulsions do not require treatment. If convulsions are protracted or recur frequently, lorazepam 4 mg or diazepam (preferably as emulsion) 10 mg should be given by slow intravenous injection into a large vein (section 4.8.2). Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, diazepam can be administered as a rectal solution or midazolam [unlicensed use] can be given by the buccal route (section 4.8.2).

Removal and elimination

Prevention of absorption

Given by mouth, **activated charcoal** can bind many poisons in the gastro-intestinal system, thereby *reducing their absorption*. The **sooner** it is given the **more effective** it is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is particularly useful for the prevention of absorption of poisons that are toxic in small amounts, such as antidepressants.

For the use of charcoal in active elimination techniques, see below.

Active elimination techniques

Repeated doses of **activated charcoal** by mouth *enhance the elimination* of some drugs after they have been absorbed; repeated doses are given after overdosage with:

Carbamazepine

Dapsone

Phenobarbital

Quinine

Theophylline

The usual dose of activated charcoal in adults and children over 12 years of age is 50 g initially then 50 g every 4 hours. Vomiting should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be reduced and the frequency increased (e.g. 25 g every 2 hours *or* 12.5 g every hour) but this may compromise efficacy.

In children under 12 years of age, activated charcoal is given in a dose of 1 g/kg (max. 50 g) every 4 hours; the dose may be reduced and the frequency increased if not tolerated.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate;
- alkalinisation of the urine for salicylates.

Removal from the gastro-intestinal tract

Gastric lavage is rarely required; for substances that cannot be removed effectively by other means (e.g. iron), it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Gastric lavage is contra-indicated if a corrosive substance or a petroleum distillate has been ingested, but it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal, such as iron or lithium. Induction of *emesis* (e.g. with ipecacuanha) is **not** recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration.

Whole bowel irrigation (by means of a bowel cleansing preparation) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with iron and lithium salts, and if illicit drugs are carried in the gastro-intestinal tract ('body-packing'). However, it is not clear that the procedure improves outcome and advice should be sought from the National Poisons Information Service.

CHARCOAL, ACTIVATED

Indications reduction of absorption of poisons in the gastro-intestinal system; see also active elimination techniques, above

Cautions drowsy or comatose patient (risk of aspiration, ensure airway protected); reduced gastro-intestinal motility (risk of obstruction); **not** for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, and metal salts including iron and lithium salts

Side-effects black stools

Dose

- Reduction of absorption, ADULT and CHILD over 12 years, 50 g; CHILD under 12 years, 1 g/kg (max. 50 g)
- Active elimination, see notes above

Note Activated charcoal doses in BNF may differ from those in product literature. Suspension or reconstituted powder may be mixed with soft drinks (e.g. caffeine-free diet cola) or fruit juices to mask the taste

Actidose-Aqua® Advance (Alliance)

Oral suspension, activated charcoal 1.04 g/5 mL, net price 50-g pack (240 mL) = £8.69

Carbomix® (Beacon)
Powder, activated charcoal, net price 25-g pack = £8.50, 50-g pack = £11.90

Charcodote® (TEVA UK)
Oral suspension, activated charcoal 1 g/5 mL, net price 50-g pack = £11.88

Specific drugs

Alcohol

Acute intoxication with alcohol (ethanol) is common in adults but also occurs in children. The features include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Aspiration of vomit is a special hazard and hypoglycaemia may occur in children and some adults. Patients are managed supportively, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Analgesics (non-opioid)

Aspirin The main features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital, where plasma salicylate, pH, and electrolytes can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in the young and the elderly, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is less below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre), unless there is evidence of metabolic acidosis. Activated charcoal can be given within 1 hour of ingesting more than 125 mg/kg of aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5).

Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis.

NSAIDs Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent require treatment, see p. 33.

Overdosage with ibuprofen may cause nausea, vomiting, epigastric pain, and tinnitus, but more serious toxicity is very uncommon. Activated charcoal followed by symptomatic measures are indicated if more than 400 mg/kg has been ingested within the preceding hour.

Paracetamol

In cases of **intravenous paracetamol** poisoning contact the National Poisons Information Service for advice on risk assessment and management.

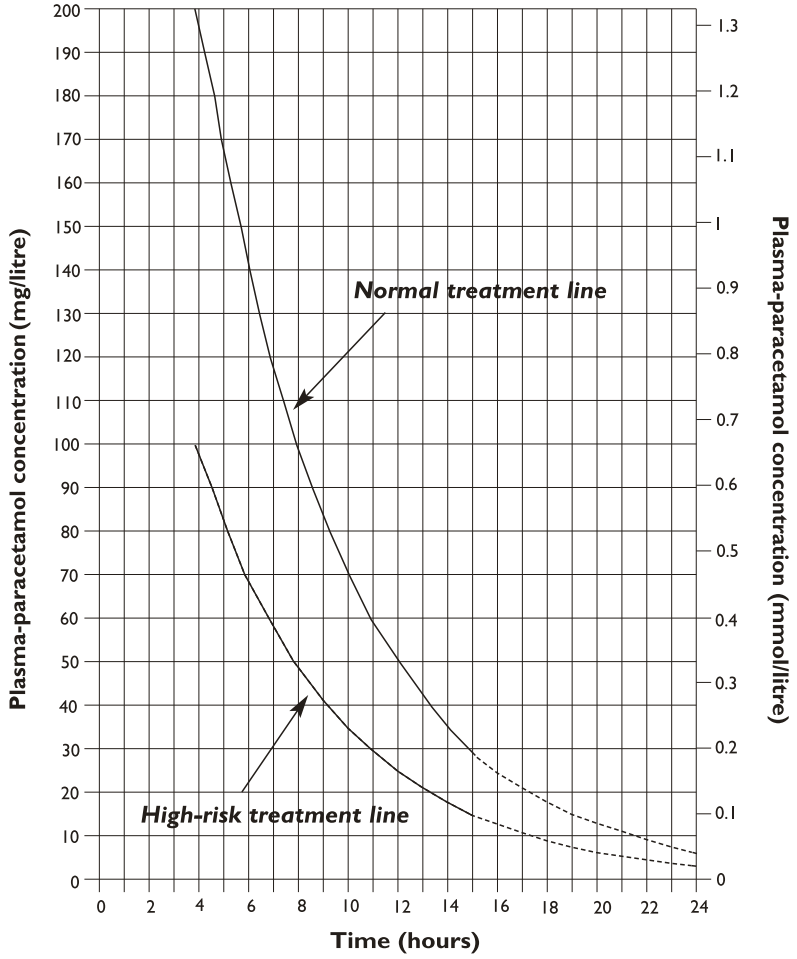
Single or repeated doses totalling as little as 10–15 g (20–30 tablets) or 150 mg/kg of paracetamol ingested within 24 hours may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Patients at *high-risk* of liver damage, including those taking enzyme-inducing drugs or who are malnourished (see p. 35), may develop liver toxicity with as little as 75 mg/kg of paracetamol (equivalent to approx. 5 g (10 tablets) in a 70-kg patient) taken within 24 hours. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tenderness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after ingestion and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

Therefore, despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently.

Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg or 12 g, **whichever is the smaller** (or in excess of 75 mg/kg for those considered to be at *high risk*, see below), is thought to have been ingested within the previous hour.

Acetylcysteine protects the liver if infused up to, and possibly beyond, 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after which effectiveness declines. In patients who present 8–36 hours after a potentially toxic ingestion, acetylcysteine treatment should commence immediately even if plasma-paracetamol concentrations are not yet available; if more than 24 hours have elapsed since ingestion advice should be sought from the National Poisons Information Service. Giving acetylcysteine by mouth [unlicensed route] is an alternative if intravenous access is not possible—contact the National Poisons Information Service for advice. In remote areas, **methionine** by mouth is an alternative only if acetylcysteine cannot be given promptly. Once the patient reaches hospital the need to continue treatment with the antidote will be assessed from the plasma-paracetamol concentration (related to the time from ingestion).

Patients at risk of liver damage and therefore requiring treatment can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line ('normal treatment line') joining plots of 200 mg/litre (1.32 mmol/litre) at 4 hours and 6.25 mg/litre (0.04 mmol/litre) at 24 hours (see p. 35). Those whose plasma-paracetamol concentration is above the *normal treatment line* are treated with acetylcysteine by intravenous infusion (or, if acetylcysteine is not available, with methionine by mouth, provided the overdose has been taken **within 10–12 hours** *and* the patient is not vomiting).



Patients whose plasma-paracetamol concentrations are above the **normal treatment line** should be treated with acetylcysteine by intravenous infusion (or, if acetylcysteine cannot be used, with methionine by mouth, provided the overdose has been taken **within 10–12 hours** and the patient is not vomiting).

Patients at *high-risk* of liver damage include those:

- taking liver enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, efavirenz, nevirapine, alcohol, St John's wort);
- who are malnourished (e.g. in anorexia or bulimia, cystic fibrosis, hepatitis C, in alcoholism, or those who are HIV-positive);
- who have not eaten for a few days.

These patients should be treated if their plasma-paracetamol concentration is above the **high-risk treatment line.**

The prognostic accuracy after 15 hours is uncertain but a plasma-paracetamol concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage.

Graph reproduced courtesy of University of Wales College of Medicine Therapeutics and Toxicology Centre

Patients at *high-risk* of liver damage include those:

- taking liver enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, efavirenz, nevirapine, alcohol and St John's wort);
- who are malnourished (e.g. in anorexia or bulimia, cystic fibrosis, hepatitis C, in alcoholism, or those who are HIV-positive);
- who have not eaten for a few days.

These patients can develop toxicity at **lower** plasma-paracetamol concentration and should be treated if the concentration is above the *high-risk treatment line* (which joins plots that are at 50% of the plasma-paracetamol concentrations of the normal treatment line).

The prognostic accuracy of plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage.

The plasma-paracetamol concentration may be difficult to interpret when paracetamol has been ingested over several hours. If there is doubt about timing or the need for treatment then the patient should be treated with an antidote.

ACETYLCYSTEINE

Indications paracetamol overdosage, see notes above

Cautions asthma (see side-effects below but do not delay acetylcysteine treatment)

Side-effects hypersensitivity-like reactions managed by reducing infusion rate or suspending until reaction settled (rash also managed by giving antihistamine; acute asthma managed by giving nebulised short-acting beta$_2$ agonist)—contact the National Poisons Information Service if reaction severe

Dose

- By intravenous infusion, ADULT and CHILD, initially 150 mg/kg (max. 16.5 g) over 15 minutes, then 50 mg/kg (max. 5.5 g) over 4 hours then 100 mg/kg (max. 11 g) over 16 hours

  Administration Dilute requisite dose in glucose intravenous infusion 5% as follows: ADULT and CHILD over 12 years, initially 200 mL given over 15 minutes, then 500 mL over 4 hours, then 1 litre over 16 hours; CHILD under 12 years, body-weight over 20 kg, initially 100 mL given over 15 minutes, then 250 mL over 4 hours, then 500 mL over 16 hours; CHILD body-weight under 20 kg, initially 3 mL/kg given over 15 minutes, then 7 mL/kg over 4 hours, then 14 mL/kg over 16 hours

  Note Manufacturer also recommends other infusion fluids, but glucose 5% is preferable

Acetylcysteine (Non-proprietary) PoM

Injection, acetylcysteine 200 mg/mL, net price 10-mL amp = £1.96

Parvolex® (UCB Pharma) PoM

Injection, acetylcysteine 200 mg/mL, net price 10-mL amp = £2.25

METHIONINE

Indications paracetamol overdosage, see notes above

Hepatic impairment may precipitate coma

Side-effects nausea, vomiting, drowsiness, irritability

Dose

- ADULT and CHILD over 6 years initially 2.5 g, followed by 3 further doses of 2.5 g every 4 hours, CHILD under 6 years initially 1 g, followed by 3 further doses of 1 g every 4 hours

Methionine (Pharma Nord)

Tablets, f/c, methionine 500 mg, net price 20-tab pack = £9.95

With paracetamol (co-methiamol)

Section 4.7.1

Analgesics (opioid)

Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. The specific antidote **naloxone** is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone. Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Naloxone reverses the opioid effects of dextropropoxyphene; the long duration of action of dextropropoxyphene calls for prolonged monitoring and further doses of naloxone may be required. Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with **sodium bicarbonate**, or **magnesium sulphate**, or both; arrhythmias may occur for up to 12 hours.

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

NALOXONE HYDROCHLORIDE

Indications overdosage with opioids; reversal of opioid-induced respiratory depression and reversal of neonatal respiratory depression resulting from opioid administration to mother during labour (section 15.1.7)

Cautions physical dependence on opioids; cardiac irritability; naloxone is short-acting, see notes above

Pregnancy section 15.1.7

Breast-feeding section 15.1.7

Dose

- By intravenous injection, 0.4–2 mg; if no response repeat at intervals of 2–3 minutes to a max. of 10 mg (then review diagnosis); further doses may be required if respiratory function deteriorates; CHILD 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg (then review diagnosis); further doses may be required if respiratory function deteriorates
- By subcutaneous *or* intramuscular injection, ADULT and CHILD dose as for intravenous injection but use only if intravenous route not feasible (onset of action slower)
- By continuous intravenous infusion using an infusion pump, rate adjusted according to response (initial rate may be set at 60% of initial intravenous injection dose (see above) and infused over 1 hour)

  Important Doses used in acute opioid overdosage may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use; see also section 15.1.7 for management of postoperative respiratory depression

[1] **Naloxone** (Non-proprietary) PoM

Injection, naloxone hydrochloride 20 micrograms/mL, net price 2-mL amp = £5.50; 400 micrograms/mL, 1-mL amp = £4.10; 1 mg/mL, 2-mL prefilled syringe = £8.36

[1] **Minijet® Naloxone** (UCB Pharma) PoM

Injection, naloxone hydrochloride 400 micrograms/mL, net price 1-mL disposable syringe = £20.40, 2-mL disposable syringe = £12.96, 5-mL disposable syringe = £12.68

1. PoM restriction does not apply where administration is for saving life in emergency

Antidepressants

Tricyclic and related antidepressants Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Assessment in hospital is strongly advised in case of poisoning by *tricyclic and related antidepressants* but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

Selective serotonin re-uptake inhibitors (SSRIs) Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

Management of SSRI poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or buccal midazolam [unlicensed use] (see p. 33). Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

Antimalarials

Overdosage with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

Beta-blockers

Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (sometimes of the torsade de pointes type). The effects of massive overdosage can vary from one beta-blocker to another; propranolol overdosage in particular may cause coma and convulsions.

Acute massive overdosage must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine is required to treat bradycardia (3 mg for an adult, 40 micrograms/kg (max. 3 mg) for a child). Cardiogenic shock unresponsive to atropine is probably best treated with an intravenous injection of glucagon 2–10 mg (CHILD 50–150 micrograms/kg, max. 10 mg) [unlicensed indication and dose] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion of 50 micrograms/kg/hour. If glucagon is not available, intravenous isoprenaline (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is an alternative. A cardiac pacemaker can be used to increase the heart rate.

Calcium-channel blockers

Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.

Activated charcoal should be considered if the patient presents within 1 hour of overdosage with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved. In patients with significant features of poisoning, calcium chloride or calcium gluconate (section 9.5.1.1) is given by injection; atropine is given to correct symptomatic bradycardia. In severe cases, an insulin and glucose infusion may be required in the management of hypotension and myocardial failure. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression—advice should be sought from the National Poisons Information Service.

Hypnotics and anxiolytics

Benzodiazepines Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma. Activated charcoal can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected. Benzodiazepines potentiate the effects of other central nervous system depressants taken concomitantly. Use of the benzodiazepine antagonist flumazenil [unlicensed indication] can be hazardous, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; it should be used on expert advice only and not as a diagnostic test in patients with a reduced level of consciousness.

Iron salts

Iron poisoning in childhood is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension and hepatocellular necrosis can occur later. Coma, shock, and metabolic acidosis indicate severe poisoning.

Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with **desferrioxamine**, which chelates iron. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine given to chelate absorbed iron in excess of the expected iron binding capacity. In **severe toxicity** intravenous desferrioxamine should be given *immediately* without waiting for the result of the serum-iron measurement.

DESFERRIOXAMINE MESILATE
(Deferoxamine Mesilate)

Indications iron poisoning; chronic iron overload (section 9.1.3)

Cautions section 9.1.3

Renal impairment section 9.1.3

Pregnancy section 9.1.3

Breast-feeding section 9.1.3

Side-effects section 9.1.3

Dose

- By continuous intravenous infusion, ADULT and CHILD up to 15 mg/kg/hour, reduced after 4–6 hours; max. 80 mg/kg in 24 hours (in severe cases, higher doses on advice from the National Poisons Information Service)

Preparations

Section 9.1.3

Lithium

Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug because of a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) owing to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes arising from the patient's depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic serum-lithium concentrations are within the range of 0.4–1 mmol/litre; concentrations in excess of 2 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage much higher serum-lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. Gastric lavage may be considered if it can be performed within 1 hour of ingesting significant quantities of lithium. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service, p. 32.

Phenothiazines and related drugs

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluoperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine (section 4.9.2) or diazepam (section 4.8.2, emulsion preferred).

Atypical antipsychotic drugs

Features of poisoning by atypical antipsychotic drugs (section 4.2.1) include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Activated charcoal can be given within 1 hour of ingesting a significant quantity of an atypical antipsychotic drug.

Stimulants

Amfetamines Amfetamines cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by diazepam or lorazepam; advice should be sought from the National Poisons Information Service (p. 32) on the management of hypertension. Later, tepid sponging, anticonvulsants, and artificial respiration may be needed.

Cocaine Cocaine stimulates the central nervous system, causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hypertonia, and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Initial treatment of cocaine poisoning involves intravenous administration of diazepam to control agitation and cooling measures for hyperthermia (see Body temperature, p. 33); hypertension and cardiac effects require specific treatment and expert advice should be sought.

Ecstasy Ecstasy (methylenedioxymethamfetamine, MDMA) may cause severe reactions, even at doses that were previously tolerated. The most serious effects are delirium, coma, convulsions, ventricular arrhythmias, hyperthermia, rhabdomyolysis, acute renal failure, acute hepatitis, disseminated intravascular coagulation, adult respiratory distress syndrome, hyperreflexia, hypotension and intracerebral haemorrhage; hyponatraemia has also been associated with ecstasy use.

Treatment of methylenedioxymethamfetamine poisoning is supportive, with diazepam to control severe agitation or persistent convulsions and close monitoring including ECG. Self-induced water intoxication should be considered in patients with ecstasy poisoning.

'Liquid ecstasy' is a term used for sodium oxybate (gamma-hydroxybutyrate, GHB), which is a sedative.

Theophylline

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repeated doses of activated charcoal can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques, p. 33). Ondansetron (section 4.6) may be effective for severe vomiting that is resistant to other antiemetics [unlicensed indication]. Hypokalaemia is corrected by intravenous infusion of potassium chloride and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring). Convulsions should be controlled by intravenous administration of lorazepam or diazepam (see Convulsions, p. 33). Sedation with diazepam may be necessary in agitated patients.

Provided the patient does **not** suffer from asthma, a short-acting beta-blocker (section 2.4) can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.

Other poisons

Consult either the National Poisons Information Service day and night or TOXBASE, see p. 32.

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Cyanides

Oxygen should be administered to patients with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. Dicobalt edetate is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning. **Dicobalt edetate** itself is toxic, associated with anaphylactoid reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of **sodium nitrite** followed by **sodium thiosulphate** is an alternative if dicobalt edetate is not available.

Hydroxocobalamin (*Cyanokit®*—no other preparation of hydroxocobalamin is suitable) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

DICOBALT EDETATE

Indications severe poisoning with cyanides

Cautions owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness; **not** to be used as a precautionary measure

Side-effects hypotension, tachycardia, and vomiting; anaphylactoid reactions including facial and laryngeal oedema and cardiac abnormalities

Dose

- By intravenous injection, ADULT 300 mg over 1 minute (5 minutes if condition less serious) followed immediately by 50 mL of glucose intravenous infusion 50%; if response inadequate a second dose of both may be given, but risk of cobalt toxicity; CHILD consult the National Poisons Information Service

[1] **Dicobalt Edetate** (Non-proprietary) PoM
Injection, dicobalt edetate 15 mg/mL, net price 20-mL (300-mg) amp = £13.75

HYDROXOCOBALAMIN

Indications see notes above

Side-effects gastro-intestinal disturbances, transient hypertension, peripheral oedema, dyspnoea, throat disorders, hot flush, dizziness, headache, restlessness, memory impairment, red coloration of urine, lymphocytopenia, eye disorders, pustular rashes, pruritus, reversible red coloration of skin and mucous membranes

Dose

- By intravenous infusion, ADULT 5 g over 15 minutes; a second dose of 5 g can be given over 15 minutes–2 hours depending on severity of poisoning and patient stability; CHILD 70 mg/kg (max. 5 g) over 15 minutes; a second dose of 70 mg/kg (max. 5 g) can be given over 15 minutes–2 hours depending on severity of poisoning and patient stability

Cyanokit® (Swedish Orphan) ▼ PoM
Intravenous infusion, powder for reconstitution, hydroxocobalamin, net price 2 × 2.5-g vials = £772.00
Note Deep red colour of hydroxocobalamin may interfere with laboratory tests (see Side-effects, above)

SODIUM NITRITE

Indications poisoning with cyanides (used in conjunction with sodium thiosulphate)

Side-effects flushing and headache due to vasodilatation

1. PoM restriction does not apply where administration is for saving life in emergency

Dose

- By intravenous injection over 5–20 minutes (as sodium nitrite injection 30 mg/mL), 300 mg; CHILD 4–10 mg/kg (max. 300 mg)

[1] **Sodium Nitrite** PoM

Injection, sodium nitrite 3% (30 mg/mL) in water for injections

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

SODIUM THIOSULPHATE

Indications in conjunction with sodium nitrite for cyanide poisoning

Dose

- By intravenous injection over 10 minutes (as sodium thiosulphate injection 500 mg/mL), 12.5 g; dose may be repeated in severe cyanide poisoning if dicobalt edetate not available; CHILD 400 mg/kg (max. 12.5 g); dose may be repeated in severe cyanide poisoning if dicobalt edetate not available

[1] **Sodium Thiosulphate** PoM

Injection, sodium thiosulphate 50% (500 mg/mL) in water for injections

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Ethylene glycol and methanol

Fomepizole (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, **ethanol** (by mouth or by intravenous infusion) can be used, but with caution. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

Heavy metals

Heavy metal antidotes include succimer (DMSA) [unlicensed], unithiol (DMPS) [unlicensed], sodium calcium edetate, and dimercaprol. Dimercaprol in the management of heavy metal poisoning has been superseded by other chelating agents. In all cases of heavy metal poisoning, the advice of the National Poisons Information Service should be sought.

SODIUM CALCIUM EDETATE

(Sodium Calciumedetate)

Indications lead poisoning

Renal impairment use with caution in mild impairment; avoid in moderate to severe impairment—contact the National Poisons Information Service for advice

Side-effects nausea, diarrhoea, abdominal pain, pain at site of injection, thrombophlebitis if given too rapidly, renal damage particularly in overdosage; hypotension, lacrimation, myalgia, nasal congestion, sneezing, malaise, thirst, fever, chills, headache, and zinc depletion also reported

Dose

- By intravenous infusion, ADULT and CHILD 40 mg/kg twice daily for up to 5 days; if necessary, a second course can be given at least 7 days after the first course, a third course can be given at least 7 days after the second course

Ledclair® (Durbin) PoM

Injection, sodium calcium edetate 200 mg/mL, net price 5-mL amp = £7.29

1. PoM restriction does not apply where administration is for saving life in emergency

Noxious gases

Carbon monoxide Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Immediate treatment of carbon monoxide poisoning is essential. The person should be moved to fresh air, the airway cleared, and high-flow **oxygen** 100% administered through a tight-fitting mask with an inflated face seal. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The patient should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema may occur in severe poisoning and is treated with an intravenous infusion of mannitol (section 2.2.5). Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the patient is pregnant or in cases of severe poisoning, such as if the patient is or has been unconscious, or has psychiatric or neurological features other than a headache, or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%.

Sulphur dioxide, chlorine, phosgene, ammonia
All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Patients are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

CS Spray

CS spray, which is used for riot control, irritates the eyes (hence 'tear gas') and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with

features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

Nerve agents

Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning (see below), but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits ('NAAS pods') containing **pralidoxime** can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

The **National Poisons Information Service** (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Pesticides

Organophosphorus insecticides Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. All are absorbed through the bronchi and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure.

Anxiety, restlessness, dizziness, headache, miosis, nausea, hypersalivation, vomiting, abdominal colic, diarrhoea, bradycardia, and sweating are common features of organophosphorus poisoning. Muscle weakness and fasciculation may develop and progress to generalised flaccid paralysis, including the ocular and respiratory muscles. Convulsions, coma, pulmonary oedema with copious bronchial secretions, hypoxia, and arrhythmias occur in severe cases. Hyperglycaemia and glycosuria without ketonuria may also be present.

Further absorption of the organophosphorus insecticide should be prevented by moving the patient to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. **Atropine** will reverse the muscarinic effects of acetylcholine and is given by intravenous injection in a dose of 2 mg (20 micrograms/kg (max. 2 mg) in a child) as atropine sulphate every 5 to 10 minutes (according to the severity of poisoning) until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

Pralidoxime chloride, a cholinesterase reactivator, is used as an adjunct to atropine in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is continued until the patient has not required atropine for 12 hours. Pralidoxime chloride can be obtained from designated centres, the names of which are held by the National Poisons Information Service (see p. 32).

PRALIDOXIME CHLORIDE

Indications adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent

Cautions myasthenia gravis

Contra-indications poisoning with carbamates or with organophosphorus compounds without anticholinesterase activity

Renal impairment use with caution

Side-effects drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness

Dose

- By intravenous infusion, ADULT and CHILD initially 30 mg/kg over 20 minutes, followed by 8 mg/kg/hour; usual max. 12 g in 24 hours

Note The loading dose may be administered by intravenous injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an intravenous infusion; pralidoxime chloride doses in BNF may differ from those in product literature

[1] **Pralidoxime chloride** PoM

Injection, powder for reconstitution, pralidoxime chloride 1 g/vial

Available as *Protopam®* (from designated centres for organophosphorus insecticide poisoning or from the National Blood Service (or Welsh Ambulance Services for Mid West and South East Wales)—see TOXBASE for list of designated centres)

1. PoM restriction does not apply where administration is for saving life in emergency

Snake bites and animal stings

Snake bites Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (*Vipera berus*). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure. Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.

Early anaphylactic symptoms should be treated with **adrenaline (epinephrine)** (section 3.4.3). Indications for antivenom treatment include *systemic envenoming*, especially hypotension (see above), ECG abnormalities, vomiting, haemostatic abnormalities, and marked local envenoming such that after bites on the hand or foot, swelling extends beyond the wrist or ankle within 4 hours of the bite. For both **adults** and **children**, the contents of one vial (10 mL) of **European viper venom antiserum** (available from Movianto) is given *by intravenous injection* over 10–15 minutes or *by intravenous infusion* over 30 minutes after diluting in sodium chloride intravenous infusion 0.9% (use 5 mL diluent/kg body-weight). The dose can be repeated after 1–2 hours if symptoms of *systemic envenoming* persist. However, for those patients who present with clinical features of *severe envenoming* (e.g. shock, ECG abnormalities, or local swelling that has advanced from the foot

to above the knee or from the hand to above the elbow within 2 hours of the bite), an initial dose of 2 vials (20 mL) of the antiserum is recommended; if symptoms of *systemic envenoming* persist contact the National Poisons Information Service. Adrenaline (epinephrine) injection must be immediately to hand for treatment of anaphylactic reactions to the antivenom (for the management of anaphylaxis, see section 3.4.3).

Antivenom is available for bites by certain foreign snakes and spiders, stings by scorpions and fish. For information on identification, management, and for supply in an emergency, telephone the National Poisons Information Service. Whenever possible the TOXBASE entry should be read, and relevant information collected, before telephoning the National Poisons Information Service (see p. 32).

Insect stings Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible. Anaphylactic reactions require immediate treatment with intramuscular **adrenaline** (**epinephrine**); self-administered intramuscular adrenaline (e.g. *EpiPen®*) is the best first-aid treatment for patients with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions. For the management of anaphylaxis, see section 3.4.3. A short course of an **oral antihistamine** or a **topical corticosteroid** may help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings (section 3.4.2).

Marine stings The severe pain of weeverfish (*Trachinus vipera*) and Portuguese man-o'-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45° C). People stung by jellyfish and Portuguese man-o'-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should **not** be applied because they can cause further discharge of stinging hairs. Ice packs will reduce pain and a slurry of baking soda (sodium bicarbonate), but not vinegar, may be useful for treating stings from UK species.

1 Gastro-intestinal system

1.1 Dyspepsia and gastro-oesophageal reflux disease 43
1.1.1 Antacids and simeticone 44
1.1.2 Compound alginates and proprietary indigestion preparations 46
1.2 Antispasmodics and other drugs altering gut motility 47
1.3 Antisecretory drugs and mucosal protectants 49
1.3.1 H_2-receptor antagonists 51
1.3.2 Selective antimuscarinics 53
1.3.3 Chelates and complexes 53
1.3.4 Prostaglandin analogues 54
1.3.5 Proton pump inhibitors 54
1.4 Acute diarrhoea 57
1.4.1 Adsorbents and bulk-forming drugs 58
1.4.2 Antimotility drugs 58
1.5 Chronic bowel disorders 59
1.5.1 Aminosalicylates 61
1.5.2 Corticosteroids 64
1.5.3 Drugs affecting the immune response 65
1.5.4 Food allergy 66
1.6 Laxatives 67
1.6.1 Bulk-forming laxatives 67
1.6.2 Stimulant laxatives 68
1.6.3 Faecal softeners 70
1.6.4 Osmotic laxatives 71
1.6.5 Bowel cleansing preparations 73
1.6.6 Peripheral opioid-receptor antagonists 74
1.6.7 $5HT_4$-receptor agonists 75
1.7 Local preparations for anal and rectal disorders 75
1.7.1 Soothing haemorrhoidal preparations 75
1.7.2 Compound haemorrhoidal preparations with corticosteroids 76
1.7.3 Rectal sclerosants 77
1.7.4 Management of anal fissures 77
1.8 Stoma care 77
1.9 Drugs affecting intestinal secretions 78
1.9.1 Drugs affecting biliary composition and flow 78
1.9.2 Bile acid sequestrants 78
1.9.3 Aprotinin 79
1.9.4 Pancreatin 79

This chapter also includes advice on the drug management of the following:

Clostridium difficile infection, p. 60
constipation, p. 67
Crohn's disease, p. 59
diverticular disease, p. 61
food allergy, p. 66
Helicobacter pylori infection, p. 49
irritable bowel syndrome, p. 61
NSAID-associated ulcers, p. 50
ulcerative colitis, p. 59

1.1 Dyspepsia and gastro-oesophageal reflux disease

1.1.1 Antacids and simeticone
1.1.2 Compound alginates and proprietary indigestion preparations

Dyspepsia

Dyspepsia covers upper abdominal pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration (section 1.3) and gastric cancer but most commonly it is of uncertain origin.

Urgent endoscopic investigation is required if dyspepsia is accompanied by 'alarm features' (e.g. bleeding, dysphagia, recurrent vomiting, or weight loss). Urgent investigation should also be considered for patients over 55 years with unexplained, recent-onset dyspepsia that has not responded to treatment.

Patients with dyspepsia should be advised about lifestyle changes (see Gastro-oesophageal reflux disease, below). Some medications may cause dyspepsia—these should be stopped, if possible. Antacids may provide some symptomatic relief.

If symptoms persist in *uninvestigated dyspepsia*, treatment involves a **proton pump inhibitor** (section 1.3.5) for 4 weeks. A proton pump inhibitor can be used intermittently to control symptoms long term. Patients with uninvestigated dyspepsia, who do not respond to an initial trial with a proton pump inhibitor, should be tested for *Helicobacter pylori* and given eradication therapy (section 1.3) if *H. pylori* is present. Alternatively, particularly in populations where *H. pylori* infection is more likely, the 'test and treat' strategy for *H. pylori* can be used before a trial with a proton pump inhibitor.

If *H. pylori* is present in patients with *functional (investigated, non-ulcer) dyspepsia*, eradication therapy should be provided. If symptoms persist, treatment with either a **proton pump inhibitor** (section 1.3.5) or a **histamine H_2-receptor antagonist** (section 1.3.1) can be given for 4 weeks. These antisecretory drugs can be used intermittently to control symptoms long term. However, most patients with functional dyspepsia do not benefit symptomatically from *H. pylori* eradication therapy or antisecretory drugs.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (including non-erosive gastro-oesophageal reflux and erosive oesophagitis) is associated with heartburn, acid regurgitation, and sometimes, difficulty in swallowing (dysphagia); oesophageal inflammation (oesophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-oesophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response. The extent of healing depends on the severity of the disease, the treatment chosen, and the duration of therapy.

Patients with gastro-oesophageal reflux disease should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation, and raising the head of the bed.

For *mild symptoms* of gastro-oesophageal reflux disease, initial management may include the use of **antacids** and **alginates**. Alginate-containing antacids can form a 'raft' that floats on the surface of the stomach contents to reduce reflux and protect the oesophageal mucosa. **Histamine H_2-receptor antagonists** (section 1.3.1) may relieve symptoms and permit reduction in antacid consumption. However, **proton pump inhibitors** (section 1.3.5) provide more effective relief of symptoms than H_2-receptor antagonists. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by giving treatment intermittently).

For *severe symptoms* of gastro-oesophageal reflux disease or for patients with a proven or severe pathology (e.g. *oesophagitis, oesophageal ulceration, oesophagopharyngeal reflux, Barrett's oesophagus*), initial management involves the use of a **proton pump inhibitor** (section 1.3.5); patients need to be reassessed if symptoms persist despite treatment for 4–6 weeks with a proton pump inhibitor. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by reducing the dose of the proton pump inhibitor or by giving it intermittently, or by substituting treatment with a histamine H_2-receptor antagonist). However, for endoscopically confirmed *erosive, ulcerative*, or *stricturing* disease, or *Barrett's oesophagus*, treatment with a proton pump inhibitor usually needs to be maintained at the minimum effective dose.

A prokinetic drug such as **metoclopramide** (section 4.6) may improve gastro-oesophageal sphincter function and accelerate gastric emptying.

Children Gastro-oesophageal reflux disease is common in infancy but most symptoms resolve without treatment between 12 and 18 months of age. In infants, mild or moderate reflux without complications can be managed initially by changing the frequency and volume of feed; a feed thickener or thickened formula feed can be used (with advice of a dietitian—see Appendix 7 for suitable products). If necessary, a suitable alginate-containing preparation can be used instead of thickened feeds. For older children, life-style changes similar to those for adults (see above) may be helpful followed if necessary by treatment with an alginate-containing preparation.

Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital; an H_2-receptor antagonist (section 1.3.1) may be needed to reduce acid secretion. If the oesophagitis is resistant to H_2-receptor blockade, the proton pump inhibitor omeprazole (section 1.3.5) can be tried.

1.1.1 Antacids and simeticone

Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in *ulcer dyspepsia* and in *non-erosive gastro-oesophageal reflux* (see also section 1.1); they are also sometimes used in functional (non-ulcer) dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, 4 or more times daily; additional doses may be required up to once an hour. Conventional doses e.g. 10 mL 3 or 4 times daily of liquid magnesium–aluminium antacids promote ulcer healing, but less well than antisecretory drugs (section 1.3); proof of a relationship between healing and neutralising capacity is lacking. Liquid preparations are more effective than tablet preparations.

Aluminium- and **magnesium-containing** antacids (e.g. aluminium hydroxide, and magnesium carbonate, hydroxide and trisilicate), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal.

The acid-neutralising capacity of preparations that contain more than one antacid may be the same as simpler preparations. Complexes such as **hydrotalcite** confer no special advantage.

Sodium bicarbonate should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. However, it retains a place in the management of urinary-tract disorders (section 7.4.3) and acidosis (section 9.2.1.3 and section 9.2.2). Sodium bicarbonate should be avoided in patients on salt-restricted diets.

Bismuth-containing antacids (unless chelates) are not recommended because absorbed bismuth can be neurotoxic, causing encephalopathy; they tend to be constipating. **Calcium-containing** antacids (section 1.1.2)

can induce rebound acid secretion: with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis, and can precipitate the milk-alkali syndrome.

Simeticone (activated dimeticone) is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care. **Alginates**, added as protectants, may be useful in gastro-oesophageal reflux disease (section 1.1 and section 1.1.2). The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

See also section 1.3 for drugs used in the treatment of peptic ulceration.

Hepatic impairment In patients with fluid retention, avoid antacids containing large amounts of sodium. Avoid antacids that cause constipation because this can precipitate coma. Avoid antacids containing magnesium salts in hepatic coma if there is a risk of renal failure.

Renal impairment In patients with fluid retention, avoid antacids containing large amounts of sodium. There is a risk of accumulation and aluminium toxicity with antacids containing aluminium salts. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics). Antacids containing magnesium salts should be avoided or used at a reduced dose because there is an increased risk of toxicity.

Interactions Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may also damage enteric coatings designed to prevent dissolution in the stomach. See also **Appendix 1** (antacids, calcium salts).

Low Na^+
The words 'low Na^+' added after some preparations indicate a sodium content of less than 1 mmol per tablet or 10-mL dose.

Aluminium- and magnesium-containing antacids

ALUMINIUM HYDROXIDE

Indications dyspepsia; hyperphosphataemia (section 9.5.2.2)
Cautions see notes above; **interactions:** Appendix 1 (antacids)
Contra-indications hypophosphataemia; neonates and infants
Hepatic impairment see notes above
Renal impairment see notes above
Side-effects see notes above

Aluminium-only preparations

Alu-Cap® (Meda)
Capsules, green/red, dried aluminium hydroxide 475 mg (low Na^+). Net price 120-cap pack = £3.75
Dose antacid, 1 capsule 4 times daily and at bedtime; CHILD not recommended for antacid therapy

Co-magaldrox

Co-magaldrox is a mixture of aluminium hydroxide and magnesium hydroxide; the proportions are expressed in the form *x*/*y* where *x* and *y* are the strengths in milligrams per unit dose of magnesium hydroxide and aluminium hydroxide respectively

Maalox® (Sanofi-Aventis)
Suspension, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na^+)). Net price 500 mL = £2.79
Dose ADULT and CHILD over 14 years, 10–20 mL 20–60 minutes after meals and at bedtime or when required

Mucogel® (Chemidex)
Suspension, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na^+)). Net price 500 mL = £1.71
Dose ADULT and CHILD over 12 years, 10–20 mL 3 times daily, 20–60 minutes after meals, and at bedtime or when required

MAGNESIUM CARBONATE

Indications dyspepsia
Cautions see notes above; **interactions:** Appendix 1 (antacids)
Contra-indications hypophosphataemia
Hepatic impairment see notes above
Renal impairment see notes above; magnesium carbonate mixture has a high sodium content
Side-effects diarrhoea; belching due to liberated carbon dioxide

Aromatic Magnesium Carbonate Mixture, BP (Aromatic Magnesium Carbonate Oral Suspension)
Oral suspension, light magnesium carbonate 3%, sodium bicarbonate 5%, in a suitable vehicle containing aromatic cardamom tincture. Contains about 6 mmol Na^+/10 mL. Net price 200 mL = 66p
Dose 10 mL 3 times daily in water
For **preparations** also containing aluminium, see above and section 1.1.2.

MAGNESIUM TRISILICATE

Indications dyspepsia
Cautions see under Magnesium Carbonate
Contra-indications see under Magnesium Carbonate
Hepatic impairment see notes above
Renal impairment see notes above; magnesium trisilicate mixture has a high sodium content
Side-effects diarrhoea, belching due to liberated carbon dioxide; silica-based renal stones reported on long-term treatment

Magnesium Trisilicate Tablets, Compound, BP
Tablets, magnesium trisilicate 250 mg, dried aluminium hydroxide 120 mg
Dose 1–2 tablets chewed when required

Magnesium Trisilicate Mixture, BP (Magnesium Trisilicate Oral Suspension)
Oral suspension, 5% each of magnesium trisilicate, light magnesium carbonate, and sodium bicarbonate in a suitable vehicle with a peppermint flavour. Contains about 6 mmol Na^+/10 mL
Dose 10–20 mL in water 3 times daily or as required; CHILD 5–12 years, 5–10 mL in water 3 times daily or as required
For **preparations** also containing aluminium, see above and section 1.1.2.

Aluminium-magnesium complexes

HYDROTALCITE

Aluminium magnesium carbonate hydroxide hydrate

Indications dyspepsia

Cautions see notes above; **interactions**: Appendix 1 (antacids)

Hepatic impairment see notes above

Renal impairment see notes above

Side-effects see notes above

◢With simeticone

Altacite Plus® see below

Antacid preparations containing simeticone

Altacite Plus® (Peckforton)

Suspension, sugar-free, co-simalcite 125/500 (simeticone 125 mg, hydrotalcite 500 mg)/5 mL (low Na^+). Net price 500 mL = £2.79

Dose 10 mL between meals and at bedtime when required; CHILD 8–12 years 5 mL between meals and at bedtime when required

Asilone® (Thornton & Ross)

Suspension, sugar-free, dried aluminium hydroxide 420 mg, simeticone 135 mg, light magnesium oxide 70 mg/5 mL (low Na^+). Net price 500 mL = £1.95

Dose ADULT and CHILD over 12 years, 5–10 mL after meals and at bedtime or when required up to 4 times daily

Maalox Plus® (Sanofi-Aventis)

Suspension, sugar-free, dried aluminium hydroxide 220 mg, simeticone 25 mg, magnesium hydroxide 195 mg/5 mL (low Na^+). Net price 500 mL = £2.79

Dose 5–10 mL 4 times daily (after meals and at bedtime) or when required; CHILD under 12 years see *BNF for Children*

Simeticone alone

Simeticone (activated dimeticone) is an antifoaming agent. It is licensed for infantile colic but evidence of benefit is uncertain.

Dentinox® (DDD) ◢

Colic drops (= emulsion), simeticone 21 mg/2.5-mL dose. Net price 100 mL = £1.73

Dose colic or wind pains, NEONATE and INFANT 2.5 mL with or after each feed (max. 6 doses in 24 hours); may be added to bottle feed

Note The brand name *Dentinox®* is also used for other preparations including teething gel

Infacol® (Forest) ◢

Liquid, sugar-free, simeticone 40 mg/mL (low Na^+). Net price 50 mL = £2.26. Counselling, use of dropper

Dose colic or wind pains, NEONATE and INFANT 0.5–1 mL before feeds

1.1.2 Compound alginates and proprietary indigestion preparations

Alginate taken in combination with an antacid increases the viscosity of stomach contents and can protect the oesophageal mucosa from acid reflux. Some alginate-containing preparations form a viscous gel ('raft') that floats on the surface of the stomach contents, thereby reducing symptoms of reflux.

Antacids may damage enteric coatings designed to prevent dissolution in the stomach. For **interactions**, see Appendix 1 (antacids, calcium salts).

Alginate raft-forming oral suspensions

The following preparations contain sodium alginate, sodium bicarbonate, and calcium carbonate in a suitable flavoured vehicle, and conform to the specification for Alginate Raft-forming Oral Suspension, BP.

Acidex® (Pinewood)

Liquid, sugar-free, sodium alginate 250 mg, sodium bicarbonate 133.5 mg, calcium carbonate 80 mg/5 mL. Contains about 3 mmol Na^+/5 mL. Net price 500 mL (aniseed- or peppermint-flavour) = £2.30

Dose 10–20 mL after meals and at bedtime; CHILD 6–12 years 5–10 mL after meals and at bedtime

Peptac® (IVAX)

Suspension, sugar-free, sodium bicarbonate 133.5 mg, sodium alginate 250 mg, calcium carbonate 80 mg/5 mL. Contains 3.1 mmol Na^+/5 mL. Net price 500 mL (aniseed- or peppermint-flavoured) = £2.16

Dose 10–20 mL after meals and at bedtime; CHILD 6–12 years 5–10 mL after meals and at bedtime

Other compound alginate preparations

Gastrocote® (Actavis)

Tablets, alginic acid 200 mg, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium bicarbonate 70 mg. Contains about 1 mmol Na^+/tablet. Net price 100-tab pack = £3.51

Cautions diabetes mellitus (high sugar content)

Dose ADULT and CHILD over 6 years, 1–2 tablets chewed 4 times daily (after meals and at bedtime)

Liquid, sugar-free, peach-coloured, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium alginate 220 mg, sodium bicarbonate 70 mg/5 mL. Contains 2.13 mmol Na^+/5 mL. Net price 500 mL = £2.67

Dose 5–15 mL 4 times daily (after meals and at bedtime); CHILD 6–12 years, 5–10 mL 4 times daily (after meals and at bedtime)

Gaviscon® Advance (Reckitt Benckiser)

Tablets, sugar-free, sodium alginate 500 mg, potassium bicarbonate 100 mg. Contains 2.25 mmol Na^+, 1 mmol K^+/tablet. Net price 60-tab pack (peppermint-flavoured) = £3.07

Excipients include aspartame (section 9.4.1)

Dose ADULT and CHILD over 12 years, 1–2 tablets to be chewed after meals and at bedtime; CHILD 6–12 years, 1 tablet to be chewed after meals and at bedtime (under medical advice only)

Suspension, sugar-free, aniseed- or peppermint flavour, sodium alginate 500 mg, potassium bicarbonate

100 mg/5 mL. Contains 2.3 mmol Na^+, 1 mmol K^+/5 mL, net price 250 mL = £2.56, 500 mL = £5.12

Dose ADULT and CHILD over 12 years, 5–10 mL after meals and at bedtime; CHILD 2–12 years, 2.5–5 mL after meals and at bedtime (under medical advice only)

Gaviscon Infant® (Reckitt Benckiser)

Oral powder, sugar-free, sodium alginate 225 mg, magnesium alginate 87.5 mg, with colloidal silica and mannitol/dose. Contains 0.92 mmol Na^+/dose. Net price 30 doses = £2.46

Dose INFANT body-weight under 4.5 kg, 1 'dose' mixed with feeds (or water in breast-fed infants) when required (max. 6 times in 24 hours); body-weight over 4.5 kg, 2 'doses' mixed with feeds (or water in breast-fed infants) when required (max. 6 times in 24 hours); CHILD 2 'doses' in water after each meal (max. 6 times in 24 hours)

Note Not to be used in preterm neonates, or where excessive water loss likely (e.g. fever, diarrhoea, vomiting, high room temperature), or if intestinal obstruction. Not to be used with other preparations containing thickening agents

Important Each half of the dual-sachet is identified as 'one dose'. To avoid errors prescribe with directions in terms of 'dose'

Topal® (Fabre)

Tablets, alginic acid 200 mg, dried aluminium hydroxide 30 mg, light magnesium carbonate 40 mg with lactose 220 mg, sucrose 880 mg, sodium bicarbonate 40 mg (low Na^+). Net price 42-tab pack = £1.67

Cautions diabetes mellitus (high sugar content)

Dose ADULT and CHILD over 12 years, 1–3 tablets chewed 4 times daily (after meals and at bedtime)

1.2 Antispasmodics and other drugs altering gut motility

Drugs in this section include antimuscarinic compounds and drugs believed to be direct relaxants of intestinal smooth muscle. The smooth muscle relaxant properties of antimuscarinic and other antispasmodic drugs may be useful in *irritable bowel syndrome* and in *diverticular disease*.

The dopamine-receptor antagonists metoclopramide and domperidone (section 4.6) stimulate transit in the gut.

Antimuscarinics

Antimuscarinics (formerly termed 'anticholinergics') reduce intestinal motility. They are used for the management of *irritable bowel syndrome* and *diverticular disease*. However, their value has not been established and response varies. Other indications for antimuscarinic drugs include arrhythmias (section 2.3.1), asthma and airways disease (section 3.1.2), motion sickness (section 4.6), parkinsonism (section 4.9.2), urinary incontinence (section 7.4.2), mydriasis and cycloplegia (section 11.5), premedication (section 15.1.3) and as an antidote to organophosphorus poisoning (p. 41).

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines **atropine sulphate** and **dicycloverine hydrochloride** and the quaternary ammonium compounds **propantheline bromide** and **hyoscine butylbromide**. The quaternary ammonium compounds are less lipid soluble than atropine and are less likely to cross the blood–brain barrier; they are also less well absorbed from the gastro-intestinal tract.

Dicycloverine hydrochloride has a much less marked antimuscarinic action than atropine and may also have some direct action on smooth muscle. Hyoscine butylbromide is advocated as a gastro-intestinal antispasmodic, but it is poorly absorbed; the injection is useful in endoscopy and radiology. Atropine and the belladonna alkaloids are outmoded treatments, any clinical virtues being outweighed by atropinic side-effects.

Cautions Antimuscarinics should be used with caution in Down's syndrome, in children and in the elderly; they should also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, autonomic neuropathy, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, and in individuals susceptible to angle-closure glaucoma. **Interactions:** Appendix 1 (antimuscarinics).

Contra-indications Antimuscarinics are contra-indicated in myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases—section 10.2.1), paralytic ileus, pyloric stenosis, toxic megacolon, and prostatic enlargement.

Side-effects Side-effects of antimuscarinics include constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Side-effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting, and giddiness; very rarely, angle-closure glaucoma may occur.

ATROPINE SULPHATE

Indications symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm; mydriasis and cycloplegia (section 11.5); premedication (section 15.1.3); see also notes above

Cautions see notes above

Contra-indications see notes above

Pregnancy not known to be harmful; manufacturer advises caution

Breast-feeding small amount present in milk—manufacturer advises caution

Side-effects see notes above

Dose

- 0.6–1.2 mg at night

Atropine (Non-proprietary) PoM

Tablets, atropine sulphate 600 micrograms. Net price 28-tab pack = £17.59

DICYCLOVERINE HYDROCHLORIDE
(Dicyclomine hydrochloride)

Indications symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

Cautions see notes above

Contra-indications see notes above; also infants under 6 months

Pregnancy not known to be harmful; manufacturer advises use only if essential

Breast-feeding avoid—present in milk; apnoea reported in infant

Side-effects see notes above

Dose

- 10–20 mg 3 times daily; INFANT 6–24 months 5–10 mg 3–4 times daily, 15 minutes before feeds; CHILD 2–12 years 10 mg 3 times daily

Merbentyl® (Sanofi-Aventis) PoM

Tablets, dicycloverine hydrochloride 10 mg, net price 100-tab pack = £4.84; 20 mg (*Merbentyl 20®*), 84-tab pack = £8.14

Syrup, dicycloverine hydrochloride 10 mg/5 mL, net price 120 mL = £1.77

Note Dicycloverine hydrochloride can be sold to the public provided that max. single dose is 10 mg and max. daily dose is 60 mg

Compound preparations

Kolanticon® (Peckforton)

Gel, sugar-free, dicycloverine hydrochloride 2.5 mg, dried aluminium hydroxide 200 mg, light magnesium oxide 100 mg, simeticone 20 mg/5 mL, net price 200 mL = £2.21, 500 mL = £3.35

Dose ADULT and CHILD over 12 years, 10–20 mL every 4 hours when required

HYOSCINE BUTYLBROMIDE

Indications symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm; bowel colic and excessive respiratory secretions (see Prescribing in Palliative Care, p. 23)

Cautions see notes above

Contra-indications see notes above

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount too small to be harmful

Side-effects see notes above

Dose

- By mouth (but poorly absorbed, see notes above), smooth muscle spasm, 20 mg 4 times daily; CHILD 6–12 years, 10 mg 3 times daily

  Irritable bowel syndrome, 10 mg 3 times daily, increased if required up to 20 mg 4 times daily
- By intramuscular *or* slow intravenous injection, acute spasm and spasm in diagnostic procedures, 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 100 mg daily; CHILD 2–18 years see *BNF for Children*

Buscopan® (Boehringer Ingelheim) PoM

Tablets, coated, hyoscine butylbromide 10 mg, net price 56-tab pack = £2.25

Note Hyoscine butylbromide tablets can be sold to the public for medically confirmed irritable bowel syndrome, provided single dose does not exceed 20 mg, daily dose does not exceed 80 mg, and pack does not contain a total of more than 240 mg

Injection, hyoscine butylbromide 20 mg/mL, net price 1-mL amp = 22p

PROPANTHELINE BROMIDE

Indications symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm; urinary frequency (section 7.4.2); gustatory sweating (section 6.1.5)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid unless essential

Breast-feeding may suppress lactation

Side-effects see notes above

Dose

- ADULT and CHILD over 12 years, 15 mg 3 times daily at least 1 hour before meals and 30 mg at night, max. 120 mg daily

Pro-Banthine® (Archimedes) PoM

Tablets, pink, s/c, propantheline bromide 15 mg, net price 112-tab pack = £14.40. Label: 23

Other antispasmodics

Alverine, **mebeverine**, and **peppermint oil** are believed to be direct relaxants of intestinal smooth muscle and may relieve pain in *irritable bowel syndrome* and *diverticular disease*. They have no serious adverse effects but, like all antispasmodics, should be avoided in paralytic ileus. Peppermint oil occasionally causes heartburn.

ALVERINE CITRATE

Indications adjunct in gastro-intestinal disorders characterised by smooth muscle spasm; dysmenorrhoea

Contra-indications paralytic ileus

Pregnancy use with caution

Breast-feeding manufacturer advises avoid—limited information available

Side-effects nausea; headache, dizziness; pruritus, rash; hepatitis also reported

Dose

- ADULT and CHILD over 12 years, 60–120 mg 1–3 times daily

Spasmonal® (Norgine)

Capsules, alverine citrate 60 mg (blue/grey), net price 100-cap pack = £9.47; 120 mg (*Spasmonal® Forte*, blue/grey), 60-cap pack = £10.94

MEBEVERINE HYDROCHLORIDE

Indications adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

Cautions avoid in acute porphyria (section 9.8.2.)

Contra-indications paralytic ileus

Pregnancy not known to be harmful; manufacturers advise caution

Side-effects allergic reactions (including rash, urticaria, angioedema) reported

Dose

- ADULT and CHILD over 10 years 135–150 mg 3 times daily preferably 20 minutes before meals; CHILD under 10 years see *BNF for Children*

[1] **Mebeverine Hydrochloride** (Non-proprietary) PoM

Tablets, mebeverine hydrochloride 135 mg, net price 100-tab pack = £4.21

Oral suspension, mebeverine hydrochloride (as mebeverine embonate) 50 mg/5 mL, net price 300 mL = £137.00

1. Mebeverine hydrochloride can be sold to the public for symptomatic relief of irritable bowel syndrome provided that max. single dose is 135 mg and max. daily dose is 405 mg; for uses other than symptomatic relief of irritable bowel syndrome provided that max. single dose is 100 mg and max. daily dose is 300 mg

Colofac® (Solvay) PoM

Tablets, s/c, mebeverine hydrochloride 135 mg, net price 100-tab pack = £7.52

Modified release

Colofac® MR (Solvay) PoM

Capsules, m/r, mebeverine hydrochloride 200 mg, net price 60-cap pack = £6.67. Label: 25

Dose irritable bowel syndrome, 1 capsule twice daily preferably 20 minutes before meals; CHILD 12–18 years see *BNF for Children*

Compound preparations

[1] **Fybogel® Mebeverine** (Reckitt Benckiser) PoM

Granules, buff, effervescent, ispaghula husk 3.5 g, mebeverine hydrochloride 135 mg/sachet, net price 10 sachets = £2.50. Label: 13, 22, counselling, see below

Excipients include aspartame (section 9.4.1)
Electrolytes K^+ 2.5 mmol/sachet

Dose irritable bowel syndrome, ADULT and CHILD over 12 years, 1 sachet in water, morning and evening 30 minutes before food; an additional sachet may also be taken before the midday meal if necessary

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

1. 10-sachet pack can be sold to the public

PEPPERMINT OIL

Indications relief of abdominal colic and distension, particularly in irritable bowel syndrome

Cautions sensitivity to menthol

Pregnancy not known to be harmful

Breast-feeding significant levels of menthol in breast milk unlikely

Side-effects heartburn, perianal irritation; rarely, allergic reactions (including rash, headache, bradycardia, muscle tremor, ataxia)

Local irritation Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus

Dose

- See preparations

Colpermin® (McNeil)

Capsules, m/r, e/c, light blue/dark blue, blue band, peppermint oil 0.2 mL. Net price 100-cap pack = £12.05. Label: 5, 22, 25

Excipients include arachis (peanut) oil

Dose ADULT and CHILD over 15 years, 1–2 capsules, swallowed whole with water, 3 times daily for up to 3 months if necessary

Mintec® (Almirall)

Capsules, e/c, green/ivory, peppermint oil 0.2 mL. Net price 84-cap pack = £7.04. Label: 5, 22, 25

Dose ADULT over 18 years, 1–2 capsules swallowed whole with water, 3 times daily before meals for up to 2–3 months if necessary

Motility stimulants

Metoclopramide and **domperidone** (section 4.6) are dopamine receptor antagonists which stimulate gastric emptying and small intestinal transit, and enhance the strength of oesophageal sphincter contraction. They are used in some patients with *functional dyspepsia* that has not responded to a proton pump inhibitor or a H_2-receptor antagonist. Metoclopramide is also used to speed the transit of barium during intestinal follow-through examination, and as accessory treatment for *gastro-oesophageal reflux disease*. For the management of gastroparesis in patients with diabetes, see section 6.1.5. Metoclopramide and domperidone are useful in non-specific and in cytotoxic-induced nausea and vomiting. Metoclopramide and occasionally domperidone can cause acute dystonic reactions, particularly in young women and children—for further details of this and other side-effects, see section 4.6.

1.3 Antisecretory drugs and mucosal protectants

1.3.1 H_2-receptor antagonists
1.3.2 Selective antimuscarinics
1.3.3 Chelates and complexes
1.3.4 Prostaglandin analogues
1.3.5 Proton pump inhibitors

Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma.

Healing can be promoted by general measures, stopping smoking and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by *Helicobacter pylori*.

The management of *H. pylori* infection and of NSAID-associated ulcers is discussed below.

Helicobacter pylori infection

Eradication of *Helicobacter pylori* reduces recurrence of gastric and duodenal ulcers and the risk of rebleeding. It also causes regression of most localised gastric mucosa-associated lymphoid-tissue (MALT) lymphomas. The presence of *H. pylori* should be confirmed before starting eradication treatment. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*; reinfection is rare. Antibiotic-associated colitis is an uncommon risk.

For initial treatment, a one-week triple-therapy regimen that comprises a proton pump inhibitor, clarithromycin,

Recommended regimens for *Helicobacter pylori* eradication in adults

Acid suppressant	Antibacterial			Price for 7-day course
	Amoxicillin	Clarithromycin	Metronidazole	
Esomeprazole 20 mg twice daily	1 g twice daily	500 mg twice daily	—	£15.10
	—	250 mg twice daily	400 mg twice daily	£13.32
Lansoprazole 30 mg twice daily	1 g twice daily	500 mg twice daily	—	£6.97
	1 g twice daily	—	400 mg twice daily	£3.77
	—	250 mg twice daily	400 mg twice daily	£5.19
Omeprazole 20 mg twice daily	1 g twice daily	500 mg twice daily	—	£6.81
	500 mg 3 times daily	—	400 mg 3 times daily	£3.62
	—	250 mg twice daily	400 mg twice daily	£5.03
Pantoprazole 40 mg twice daily	1 g twice daily	500 mg twice daily	—	£7.26
	—	250 mg twice daily	400 mg twice daily	£5.48
Rabeprazole 20 mg twice daily	1 g twice daily	500 mg twice daily	—	£15.63
	—	250 mg twice daily	400 mg twice daily	£13.85

and *either* amoxicillin *or* metronidazole can be used. However, if a patient has been treated with metronidazole for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin is preferred for initial therapy. If a patient has been treated with a macrolide for other infections, a regimen containing a proton pump inhibitor, amoxicillin and metronidazole is preferred for initial therapy. These regimens eradicate *H. pylori* in about 85% of cases. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H_2-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation, then antisecretory treatment is continued for a further 3 weeks. Treatment failure usually indicates antibacterial resistance or poor compliance. Resistance to amoxicillin is rare. However, resistance to clarithromycin and metronidazole is common and can develop during treatment.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial are licensed, but produce low rates of *H. pylori* eradication and are **not** recommended.

Tinidazole is also used occasionally for *H. pylori* eradication as an alternative to metronidazole; tinidazole should be combined with antisecretory drugs and other antibacterials.

A two-week regimen comprising a proton pump inhibitor (e.g. omeprazole 20 mg twice daily) *plus* tripotassium dicitratobismuthate 120 mg four times daily, *plus* tetracycline 500 mg four times daily, *plus* metronidazole 400–500 mg three times daily can be used for eradication failure. Alternatively, the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

For the role of *H. pylori* eradication therapy in patients starting or taking a NSAID, see NSAID-associated Ulcers, below. For *H. pylori* eradication in patients with dyspepsia, see also section 1.1.

Test for *Helicobacter pylori*

^{13}C-Urea breath test kits are available for the diagnosis of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of ^{13}C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific ^{13}C-urea breath test kit for children is available (*Helicobacter Test INFAI for children of the age 3–11*®). However, the appropriateness of testing for *H. pylori* infection in children has not been established.

diabact UBT® (MDE) PoM
Tablets, ^{13}C-urea 50 mg, net price 1 kit (including 1 tablet, 4 breath-sample containers, straws) = £21.25 (analysis included), 10-kit pack (hosp. only) = £74.50 (analysis not included)

Helicobacter Test INFAI® (Infai) PoM
Oral powder, ^{13}C-urea 75 mg, net price 1 kit (including 4 breath-sample containers, straws) = £19.20 (spectrometric analysis included), 1 kit (including 2 breath bags) = £14.20 (spectroscopic analysis not included), 50-test set = £855.00 (spectrometric analysis included); 45 mg (*Helicobacter Test INFAI for children of the age 3–11*®), 1 kit (including 4 breath-sample containers, straws) = £19.20 (spectrometric analysis included)

Pylobactell® (Torbet) PoM
Soluble tablets, ^{13}C-urea 100 mg, net price 1 kit (including 6 breath-sample containers, 30-mL mixing and administration vial, straws) = £20.75 (analysis included)

NSAID-associated ulcers

Gastro-intestinal bleeding and ulceration can occur with NSAID use (section 10.1.1). The risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs (see CSM advice, p. 632). Whenever possible, the NSAID should be **withdrawn** if an ulcer occurs.

Patients at high risk of developing gastro-intestinal complications with a NSAID include those aged over 65 years, those with a history of peptic ulcer disease or serious gastro-intestinal complication, those taking other medicines that increase the risk of gastro-intestinal side-effects, or those with serious co-morbidity. In those at risk of ulceration, a proton pump inhibitor can be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; a H_2-receptor antagonist such as ranitidine given at twice the usual dose or misoprostol are alternatives. Colic and diarrhoea may limit the dose of misoprostol. A combination of a cyclo-oxygenase-2 selective inhibitor with a proton pump inhibitor may be more appropriate for those with a history of upper gastro-intestinal bleeding or 3 or more risk factors for gastro-intestinal ulceration, but see NSAIDs and Cardiovascular Events, p. 631.

NSAID use and *H. pylori* infection are independent risk factors for gastro-intestinal bleeding and ulceration. In patients already taking a NSAID, eradication of *H. pylori* is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in patients with dyspepsia or a history of gastric or duodenal ulcer, who are *H. pylori* positive, and who are about to start long-term treatment with a non-selective NSAID, eradication of *H. pylori* may reduce the overall risk of ulceration.

If the *NSAID can be discontinued* in a patient who has developed an ulcer, a proton pump inhibitor usually produces the most rapid healing; alternatively, the ulcer can be treated with a H_2-receptor antagonist or misoprostol.

If *treatment with a non-selective NSAID needs to continue*, the following options are suitable:

- Treat ulcer with a proton pump inhibitor and on healing continue the proton pump inhibitor (dose not normally reduced because asymptomatic ulcer recurrence may occur);
- Treat ulcer with a proton pump inhibitor and on healing switch to misoprostol for maintenance therapy (colic and diarrhoea may limit the dose of misoprostol);
- Treat ulcer with a proton pump inhibitor and switch non-selective NSAID to a cyclo-oxygenase-2 selective inhibitor, but see NSAIDs and Cardiovascular Events, p. 631; on healing, continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

If *treatment with a cyclo-oxygenase-2 selective inhibitor needs to continue*, treat ulcer with a proton pump inhibitor; on healing continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

1.3.1 H_2-receptor antagonists

Histamine H_2-receptor antagonists heal *gastric and duodenal ulcers* by reducing gastric acid output as a result of histamine H_2-receptor blockade; they are also used to relieve symptoms of *gastro-oesophageal reflux disease* (section 1.1). H_2-receptor antagonists should not normally be used for *Zollinger-Ellison syndrome* because proton pump inhibitors (section 1.3.5) are more effective.

Maintenance treatment with low doses for the prevention of peptic ulcer disease has largely been replaced in *Helicobacter pylori* positive patients by eradication regimens (section 1.3).

H_2-receptor antagonists are used for the treatment of *functional dyspepsia* (section 1.1). H_2-receptor antagonists may be used for the treatment of *uninvestigated dyspepsia* in patients without alarm features.

H_2-receptor antagonist therapy can promote healing of *NSAID-associated ulcers* (particularly duodenal) (section 1.3).

Treatment with a H_2-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from *gastroduodenal erosions in hepatic coma*, and possibly in other conditions requiring intensive care. H_2-receptor antagonists also reduce the risk of *acid aspiration* in obstetric patients at delivery (Mendelson's syndrome).

Cautions H_2-receptor antagonists might mask symptoms of gastric cancer; particular care is required in patients presenting with 'alarm features' (see p. 43), in such cases gastric malignancy should be ruled out before treatment.

Side-effects Side-effects of the H_2-receptor antagonists include diarrhoea, headache, and dizziness. Rash (including erythema multiforme and toxic epidermal necrolysis) occurs less frequently. Other side-effects reported rarely or very rarely include hepatitis, cholestatic jaundice, bradycardia, psychiatric reactions (including confusion, depression, and hallucinations) particularly in the elderly or the very ill, blood disorders (including leucopenia, thrombocytopenia, and pancytopenia), arthralgia, and myalgia. Gynaecomastia and impotence occur occasionally with cimetidine and there are isolated reports with the other H_2-receptor antagonists.

Interactions Cimetidine retards oxidative hepatic drug metabolism by binding to microsomal cytochrome P450. It should be avoided in patients stabilised on warfarin, phenytoin, and theophylline (or aminophylline), but other interactions (see **Appendix 1**) may be of less clinical relevance. Famotidine, nizatidine, and ranitidine do not share the drug metabolism inhibitory properties of cimetidine.

CIMETIDINE

Indications benign gastric and duodenal ulceration, stomal ulcer, reflux oesophagitis, other conditions where gastric acid reduction is beneficial (see notes above and section 1.9.4)

Cautions see notes above; **interactions:** Appendix 1 (histamine H_2-antagonists) and notes above

Hepatic impairment increased risk of confusion; reduce dose

Renal impairment reduce dose; 200 mg 4 times daily if eGFR 30–50 mL/minute/1.73 m^2; 200 mg 3 times daily if eGFR 15–30 mL/minute/1.73 m^2; 200 mg twice daily if eGFR less than 15 mL/minute/1.73 m^2; occasional risk of confusion

Pregnancy manufacturer advises avoid unless essential

Breast-feeding significant amount present in milk—not known to be harmful but manufacturer advises avoid

Side-effects see notes above; also malaise; *less commonly* tachycardia; *rarely* interstitial nephritis; *very rarely* pancreatitis, galactorrhoea, vasculitis, alopecia

Dose

- 400 mg twice daily (with breakfast and at night) *or* 800 mg at night (benign gastric and duodenal ulceration) for at least 4 weeks (6 weeks in gastric ulceration, 8 weeks in NSAID-associated ulceration); when necessary the dose may be increased to 400 mg 4 times daily; INFANT under 1 year 20 mg/kg daily in divided doses has been used; CHILD 1–12 years, 25–30 mg/kg daily in divided doses; max. 400 mg 4 times daily

  Maintenance, 400 mg at night *or* 400 mg morning and night
- Reflux oesophagitis, 400 mg 4 times daily for 4–8 weeks
- Prophylaxis of stress ulceration, 200–400 mg every 4–6 hours
- Gastric acid reduction (prophylaxis of acid aspiration; do not use syrup), obstetrics 400 mg at start of labour, then up to 400 mg every 4 hours if required (max. 2.4 g daily); surgical procedures 400 mg 90–120 minutes before induction of general anaesthesia
- Short-bowel syndrome, 400 mg twice daily (with breakfast and at bedtime) adjusted according to response
- To reduce degradation of pancreatic enzyme supplements, 0.8–1.6 g daily in 4 divided doses 1–1½ hours before meals

[1] **Cimetidine** (Non-proprietary) PoM

Tablets, cimetidine 200 mg, net price 60-tab pack = £9.08; 400 mg, 60-tab pack = £7.61; 800 mg, 30-tab pack = £22.86

Oral solution, cimetidine 200 mg/5 mL, net price 300 mL = £14.56

Excipients may include propylene glycol (see Excipients, p. 2)

1. Cimetidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks' supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity (max. single dose 200 mg, max. daily dose 800 mg), and for the prophylactic management of nocturnal heartburn (single night-time dose 100 mg)

Tagamet® (Chemidex) PoM

Tablets, all green, f/c, cimetidine 200 mg, net price 120-tab pack = £19.58; 400 mg, 60-tab pack = £22.62; 800 mg, 30-tab pack = £22.62

Syrup, orange, cimetidine 200 mg/5 mL. Net price 600 mL = £28.49

Excipients include propylene glycol 10%, (see Excipients, p. 2)

FAMOTIDINE

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (histamine H_2-antagonists) and notes above

Renal impairment use normal dose every 36–48 hours or use half normal dose if eGFR less than 50 mL/minute/1.73 m^2; seizures reported very rarely

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding present in milk—not known to be harmful but manufacturer advises avoid

Side-effects see notes above; also constipation; *less commonly* dry mouth, nausea, vomiting, flatulence, taste disorders, anorexia, fatigue; *very rarely* chest tightness, interstitial pneumonia, seizures, paraesthesia

Dose

- Benign gastric and duodenal ulceration, treatment, 40 mg at night for 4–8 weeks; maintenance (duodenal ulceration), 20 mg at night
- Reflux oesophagitis, 20–40 mg twice daily for 6–12 weeks; maintenance, 20 mg twice daily
- CHILD not recommended

[1] **Famotidine** (Non-proprietary) PoM

Tablets, famotidine 20 mg, net price 28-tab pack = £4.47; 40 mg, 28-tab pack = £5.64

1. Famotidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks' supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink including when they cause sleep disturbance (max. single dose 10 mg, max. daily dose 20 mg)

Pepcid® (MSD) PoM

Tablets, f/c, famotidine 20 mg (beige), net price 28-tab pack = £13.37; 40 mg (brown), 28-tab pack = £25.40

NIZATIDINE

Indications see under Dose

Cautions see notes above; also avoid rapid intravenous injection (risk of arrhythmias and postural hypotension); **interactions:** Appendix 1 (histamine H_2-antagonists) and notes above

Hepatic impairment manufacturer advises caution

Renal impairment use half normal dose if eGFR 20–50 mL/minute/1.73 m^2; use one-quarter normal dose if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless essential

Breast-feeding amount too small to be harmful

Side-effects see notes above; also sweating; *rarely* nausea, fever, vasculitis, hyperuricaemia

Dose

- By mouth, benign gastric, duodenal or NSAID-associated ulceration, treatment, 300 mg in the evening *or* 150 mg twice daily for 4–8 weeks; maintenance, 150 mg at night

  Gastro-oesophageal reflux disease, 150–300 mg twice daily for up to 12 weeks
- By intravenous infusion, for short-term use in peptic ulcer as alternative to oral route (for hospital inpatients), by intermittent intravenous infusion over 15 minutes, 100 mg 3 times daily, *or* by continuous intravenous infusion, 10 mg/hour; max. 480 mg daily
- CHILD not recommended

[1] **Nizatidine** (Non-proprietary) PoM

Capsules, nizatidine 150 mg, net price 30-cap pack = £12.04; 300 mg, 30-cap pack = £14.28

1. Nizatidine can be sold to the public for the prevention and treatment of symptoms of food-related heartburn and meal-induced indigestion in adults and children over 16 years; max. single dose 75 mg, max. daily dose 150 mg for max. 14 days

Axid® (Flynn) PoM

Capsules, nizatidine 150 mg (pale yellow/dark yellow), net price 28-cap pack (hosp. only) = £6.87, 30-cap pack = £7.97; 300 mg (pale yellow/brown), 30-cap pack = £15.80

Injection, nizatidine 25 mg/mL. For dilution and use as an intravenous infusion. Net price 4-mL amp = £1.14

RANITIDINE

Indications see under Dose, other conditions where reduction of gastric acidity is beneficial (see notes above and section 1.9.4)

Cautions see notes above; also acute porphyria; **interactions:** Appendix 1 (histamine H_2-antagonists) and notes above

Renal impairment use half normal dose if eGFR less than 50 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless essential, but not known to be harmful

Breast-feeding significant amount present in milk, but not known to be harmful

Side-effects see notes above; *less commonly* blurred vision; also reported pancreatitis, involuntary movement disorders, interstitial nephritis, alopecia

Dose

- By mouth, benign gastric and duodenal ulceration, chronic episodic dyspepsia, ADULT and CHILD over 12 years, 150 mg twice daily *or* 300 mg at night for 4–8 weeks in benign gastric and duodenal ulceration, up to 6 weeks in chronic episodic dyspepsia, and up to 8 weeks in NSAID-associated ulceration (in duodenal ulcer 300 mg can be given twice daily for 4 weeks to achieve a higher healing rate); CHILD 3–12 years, (benign gastric and duodenal ulceration) 2–4 mg/kg (max. 150 mg) twice daily for 4–8 weeks

  Prophylaxis of NSAID-associated gastric or duodenal ulcer [unlicensed dose], ADULT and CHILD over 12 years, 300 mg twice daily

  Gastro-oesophageal reflux disease, ADULT and CHILD over 12 years, 150 mg twice daily *or* 300 mg at night for up to 8 weeks or if necessary 12 weeks (moderate to severe, 600 mg daily in 2–4 divided doses for up to 12 weeks); long-term treatment of healed gastro-oesophageal reflux disease, 150 mg twice daily; CHILD 3–12 years, 2.5–5 mg/kg (max. 300 mg) twice daily

  Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics, ADULT and CHILD over 12 years, by mouth, 150 mg at onset of labour, then every 6 hours; surgical procedures, by intramuscular *or* slow intravenous injection, 50 mg 45–60 minutes before induction of anaesthesia (intravenous injection diluted to 20 mL and given over at least 2 minutes), or by mouth, 150 mg 2 hours before induction of anaesthesia and also when possible on the preceding evening
- By intramuscular injection, 50 mg every 6–8 hours
- By slow intravenous injection, ADULT and CHILD over 12 years, 50 mg diluted to 20 mL and given over at least 2 minutes; may be repeated every 6–8 hours
- Prophylaxis of stress ulceration [unlicensed dose], ADULT and CHILD over 12 years, by slow intravenous injection over at least 2 minutes, 50 mg diluted to 20 mL every 8 hours (may be changed to 150 mg twice daily by mouth when oral feeding commences)

Ranitidine (Non-proprietary) PoM

Tablets, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.97; 300 mg, 30-tab pack = £2.17
Brands include *Ranitic®*

Effervescent tablets, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £18.04; 300 mg, 30-tab pack = £17.03. Label: 13
Excipients may include sodium (check with supplier)

Oral solution, ranitidine (as hydrochloride) 75 mg/5 mL, net price 100 mL = £7.44, 300 mL = £19.61
Excipients may include alcohol (check with supplier)

Note Ranitidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks' supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink (max. single dose 75 mg, max. daily dose 300 mg)

Injection, ranitidine (as hydrochloride) 25 mg/mL, net price 2-mL amp = 54p

Zantac® (GSK) PoM

Tablets, f/c, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.30; 300 mg, 30-tab pack = £1.30

Syrup, sugar-free, ranitidine (as hydrochloride) 75 mg/5 mL, net price 300 mL = £20.76
Excipients include alcohol 8%

Injection, ranitidine (as hydrochloride) 25 mg/mL, net price 2-mL amp = 57p

1.3.2 Selective antimuscarinics

Pirenzepine is a selective antimuscarinic drug which was used for the treatment of gastric and duodenal ulcers. It has been discontinued.

1.3.3 Chelates and complexes

Tripotassium dicitratobismuthate is a bismuth chelate effective in healing gastric and duodenal ulcers. For the role of tripotassium dicitratobismuthate in a *Helicobacter pylori* eradication regimen for those who have not responded to first-line regimens, see section 1.3.

The bismuth content of tripotassium dicitratobismuthate is low but absorption has been reported; encephalopathy (described with older high-dose bismuth preparations) has not been reported.

Sucralfate may act by protecting the mucosa from acid-pepsin attack in gastric and duodenal ulcers. It is a complex of aluminium hydroxide and sulphated sucrose but has minimal antacid properties. It should be used with caution in patients under intensive care (**important:** reports of bezoar formation, see Bezoar Formation below)

TRIPOTASSIUM DICITRATOBISMUTHATE

Indications benign gastric and duodenal ulceration; see also *Helicobacter pylori* infection, section 1.3

Cautions see notes above; **interactions:** Appendix 1 (tripotassium dicitratobismuthate)

Renal impairment avoid in severe impairment

Pregnancy manufacturer advises avoid on theoretical grounds

Breast-feeding no information available

Side-effects may darken tongue and blacken faeces; *less commonly* nausea, vomiting, diarrhoea, constipation, rash, and pruritus reported

De-Noltab® (Astellas)

Tablets, f/c, tripotassium dicitratobismuthate 120 mg, net price 112-tab pack = £5.09. Counselling, see below

Electrolytes K^+ 2 mmol/tablet

Dose 2 tablets twice daily *or* 1 tablet 4 times daily; taken for 28 days followed by further 28 days if necessary; maintenance not indicated but course may be repeated after interval of 1 month; CHILD not recommended

Counselling To be swallowed with half a glass of water; twice-daily dosage to be taken 30 minutes before breakfast and main evening meal; four-times-daily dosage to be taken as follows: one dose 30 minutes before breakfast, midday meal and main evening meal, and one dose 2 hours after main evening meal; milk should not be drunk by itself during treatment but small quantities may be taken in tea or coffee or on cereal; antacids, fruit, or fruit juice should not be taken half an hour before or after a dose; may darken tongue and blacken faeces

SUCRALFATE

Indications see under Dose

Cautions administration of sucralfate and enteral feeds should be separated by 1 hour; **interactions:** Appendix 1 (sucralfate)

Bezoar formation Following reports of bezoar formation associated with sucralfate, caution is advised in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying

Renal impairment use with caution; aluminium is absorbed and may accumulate

Pregnancy no evidence of harm; absorption from gastro-intestinal tract negligible

Breast-feeding amount probably too small to be harmful

Side-effects constipation; *less frequently* diarrhoea, nausea, indigestion, flatulence, gastric discomfort, back pain, dizziness, headache, drowsiness, bezoar formation (see above), dry mouth and rash

Dose

- Benign gastric and duodenal ulceration and chronic gastritis, ADULT and CHILD over 15 years, 2 g twice daily (on rising and at bedtime) *or* 1 g 4 times daily 1 hour before meals and at bedtime, taken for 4–6 weeks or in resistant cases up to 12 weeks; max. 8 g daily
- Prophylaxis of stress ulceration, ADULT and CHILD over 15 years, 1 g 6 times daily; max. 8 g daily
- CHILD under 15 years see *BNF for Children*

Antepsin® (Chugai) PoM

Tablets, scored, sucralfate 1 g, net price 50-tab pack = £5.77. Label: 5

Note Crushed tablets may be dispersed in water

Suspension, sucralfate, 1 g/5 mL, net price 250 mL (aniseed- and caramel-flavoured) = £5.77. Label: 5

1.3.4 Prostaglandin analogues

Misoprostol, a synthetic prostaglandin analogue has antisecretory and protective properties, promoting healing of *gastric and duodenal ulcers*. It can prevent NSAID-associated ulcers, its use being most appropriate for the frail or very elderly from whom NSAIDs cannot be withdrawn.

For comment on the use of misoprostol to induce abortion or labour [unlicensed indications], see section 7.1.1.

MISOPROSTOL

Indications see notes above and under Dose

Cautions conditions where hypotension might precipitate severe complications (e.g. cerebrovascular disease, cardiovascular disease)

Contra-indications planning pregnancy (**important:** see Women of Childbearing Age, and also Pregnancy, below)

Women of childbearing age Manufacturer advises that misoprostol should not be used in women of childbearing age unless the patient requires non-steroidal anti-inflammatory (NSAID) therapy and is at high risk of complications from NSAID-induced ulceration. In such patients it is advised that misoprostol should only be used if the patient takes *effective contraceptive measures* and has been advised of the *risks of taking misoprostol if pregnant*.

Pregnancy avoid—potent uterine stimulant (has been used to induce abortion) and may be teratogenic; **important:** see also Women of Childbearing Age, above

Breast-feeding no information available—manufacturer advises avoid

Side-effects diarrhoea (may occasionally be severe and require withdrawal, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids); also reported: abdominal pain, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding (including intermenstrual bleeding, menorrhagia, and postmenopausal bleeding), rashes, dizziness

Dose

- Benign gastric and duodenal ulceration and NSAID-associated ulceration, ADULT over 18 years, 800 micrograms daily (in 2–4 divided doses) with breakfast (or main meals) and at bedtime; treatment should be continued for at least 4 weeks and may be continued for up to 8 weeks if required
- Prophylaxis of NSAID-induced gastric and duodenal ulcer, ADULT over 18 years, 200 micrograms 4 times daily (if not tolerated, reduced to 200 micrograms 2–3 times daily, but less effective)

Cytotec® (Pharmacia) PoM

Tablets, scored, misoprostol 200 micrograms, net price 60-tab pack = £10.03. Label: 21

With diclofenac or naproxen

Section 10.1.1

1.3.5 Proton pump inhibitors

Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell. Proton pump inhibitors are effective short-term treatments for *gastric* and *duodenal ulcers*; they are also used in combination with antibacterials for the eradication of *Helicobacter pylori* (see p. 50 for specific regimens). Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery. Proton pump inhibitors can be used for the treatment of *dyspepsia* and *gastro-oesophageal reflux disease* (section 1.1).

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers (see p. 50). In patients who need to continue NSAID treatment after an

ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur.

A proton pump inhibitor can be used to reduce the degradation of pancreatic enzyme supplements (section 1.9.4) in patients with cystic fibrosis. They can also be used to control excessive secretion of gastric acid in *Zollinger–Ellison syndrome*; high doses are often required.

Cautions Proton pump inhibitors may mask the symptoms of gastric cancer; particular care is required in those presenting with 'alarm features' (see p. 43), in such cases gastric malignancy should be ruled out before treatment.

Side-effects Side-effects of the proton pump inhibitors include gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation), and headache. Less frequent side-effects include dry mouth, peripheral oedema, dizziness, sleep disturbances, fatigue, paraesthesia, arthralgia, myalgia, rash, and pruritus. Other side-effects reported rarely or very rarely include taste disturbance, stomatitis, hepatitis, jaundice, hypersensitivity reactions (including anaphylaxis, bronchospasm), fever, depression, hallucinations, confusion, gynaecomastia, interstitial nephritis, hyponatraemia, blood disorders (including leucopenia, leucocytosis, pancytopenia, thrombocytopenia), visual disturbances, sweating, photosensitivity, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis. By decreasing gastric acidity, proton pump inhibitors may increase the risk of gastro-intestinal infections (including *Clostridium difficile* infection).

ESOMEPRAZOLE

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (proton pump inhibitors)

Hepatic impairment in severe hepatic impairment max. 20 mg daily (CHILD 1–12 years max. 10 mg daily); for severe peptic ulcer bleeding in severe hepatic impairment, initial intravenous infusion of 80 mg, then by continuous intravenous infusion, 4 mg/hour for 72 hours

Renal impairment manufacturer advises caution in severe renal insufficiency

Pregnancy manufacturer advises caution—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above

Dose

- By mouth duodenal ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 50
  NSAID-associated gastric ulcer, ADULT over 18 years, 20 mg once daily for 4–8 weeks; prophylaxis in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment, 20 mg daily
  Gastro-oesophageal reflux disease (in the presence of erosive reflux oesophagitis), ADULT and CHILD over 12 years, 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily; CHILD 1–12 years, body-weight 10–20 kg, 10 mg once daily for 8 weeks; body-weight over 20 kg, 10–20 mg once daily for 8 weeks
  Symptomatic treatment of gastro-oesophageal reflux disease (in the absence of oesophagitis), ADULT and CHILD over 12 years, 20 mg once daily for up to 4 weeks, then 20 mg daily when required; CHILD 1–12 years, body-weight over 10 kg, 10 mg once daily for up to 8 weeks
  Zollinger–Ellison syndrome, ADULT over 18 years, initially 40 mg twice daily, adjusted according to response; usual range 80–160 mg daily (above 80 mg in 2 divided doses)
- By intravenous injection over at least 3 minutes *or* by intravenous infusion, ADULT over 18 years, gastro-oesophageal reflux disease, 40 mg once daily; symptomatic reflux disease without oesophagitis, treatment of NSAID-associated gastric ulcer, prevention of NSAID-associated gastric or duodenal ulcer, 20 mg daily; continue until oral administration possible
- Severe peptic ulcer bleeding (following endoscopic treatment), ADULT over 18 years, initial intravenous infusion of 80 mg over 30 minutes, then by continuous intravenous infusion 8 mg/hour for 72 hours, then by mouth 40 mg once daily for 4 weeks

Nexium® (AstraZeneca) PoM

Tablets, f/c, esomeprazole (as magnesium trihydrate) 20 mg (light pink), net price 28-tab pack = £18.50; 40 mg (pink), 28-tab pack = £25.19. Counselling, administration

Counselling Do not chew or crush tablets, swallow whole *or* disperse in water

Granules, yellow, e/c, esomeprazole (as magnesium trihydrate) 10 mg/sachet, net price 28-sachet pack = £25.19. Label: 25, counselling, administration

Counselling Disperse the contents of each sachet in approx. 15 mL water. Stir and leave to thicken for a few minutes; stir again before administration and use within 30 minutes; rinse container with 15 mL water to obtain full dose; can be administered through nasogastric or gastric tube

Injection, powder for reconstitution, esomeprazole (as sodium salt), net price 40-mg vial = £3.13

With naproxen

Section 10.1.1

LANSOPRAZOLE

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (proton pump inhibitors)

Hepatic impairment use half normal dose in moderate to severe liver disease

Pregnancy manufacturer advises avoid

Breast-feeding avoid unless essential—present in milk in *animal* studies

Side-effects see notes above; also glossitis, pancreatitis, anorexia, restlessness, tremor, impotence, petechiae, and purpura; *very rarely* colitis, raised serum cholesterol or triglycerides

Dose

- Benign gastric ulcer, 30 mg daily in the morning for 8 weeks
- Duodenal ulcer, 30 mg daily in the morning for 4 weeks; maintenance 15 mg daily
- NSAID-associated duodenal or gastric ulcer, 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis, 15–30 mg once daily
- Eradication of *Helicobacter pylori* associated with duodenal ulcer or ulcer-like dyspepsia, see eradication regimens on p. 50

- Zollinger-Ellison syndrome (and other hypersecretory conditions), initially 60 mg once daily adjusted according to response; daily doses of 120 mg or more given in two divided doses
- Gastro-oesophageal reflux disease, 30 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg daily
- Acid-related dyspepsia, 15–30 mg daily in the morning for 2–4 weeks
- CHILD under 18 years see *BNF for Children*

Note Lansoprazole doses in BNF may differ from those in product literature

Lansoprazole (Non-proprietary) PoM

Capsules, enclosing e/c granules, lansoprazole 15 mg, net price 28-cap pack = £1.44; 30 mg, 28-cap pack = £2.23. Label: 5, 22, 25

Dental prescribing on NHS Lansoprazole capsules may be prescribed

Zoton® (Wyeth) PoM

FasTab® (= orodispersible tablet), lansoprazole 15 mg, net price 28-tab pack = £2.99; 30 mg, 28-tab pack = £5.50. Label: 5, 22, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed, or may be swallowed whole with a glass of water. Alternatively, tablets can be dispersed in a small amount of water and administered by an oral syringe or nasogastric tube

OMEPRAZOLE

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (proton pump inhibitors)

Hepatic impairment not more than 20 mg daily should be needed

Pregnancy not known to be harmful

Breast-feeding present in milk but not known to be harmful

Side-effects see notes above; also agitation and impotence

Dose

- By mouth, benign gastric and duodenal ulcers, 20 mg once daily for 4 weeks in duodenal ulceration or 8 weeks in gastric ulceration; in severe or recurrent cases increase to 40 mg daily; maintenance for recurrent duodenal ulcer, 20 mg once daily; prevention of relapse in duodenal ulcer, 10 mg daily increasing to 20 mg once daily if symptoms return

  NSAID-associated duodenal or gastric ulcer and gastroduodenal erosions, 20 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis in patients with a history of NSAID-associated duodenal or gastric ulcers, gastroduodenal lesions, or dyspeptic symptoms who require continued NSAID treatment, 20 mg once daily

  Duodenal or benign gastric ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 50

  Zollinger–Ellison syndrome, initially 60 mg once daily; usual range 20–120 mg daily (above 80 mg in 2 divided doses)

  Gastric acid reduction during general anaesthesia (prophylaxis of acid aspiration), 40 mg on the preceding evening then 40 mg 2–6 hours before surgery

  Gastro-oesophageal reflux disease, 20 mg once daily for 4 weeks, continued for further 4–8 weeks if not fully healed; 40 mg once daily has been given for 8 weeks in gastro-oesophageal reflux disease refractory to other treatment; maintenance 20 mg once daily

  Acid reflux disease (long-term management), 10 mg daily increasing to 20 mg once daily if symptoms return

  Acid-related dyspepsia, 10–20 mg once daily for 2–4 weeks according to response

  Severe ulcerating reflux oesophagitis, CHILD over 1 year, body-weight 10–20 kg, 10 mg once daily increased if necessary to 20 mg once daily for 4–12 weeks; body-weight over 20 kg, 20 mg once daily increased if necessary to 40 mg once daily for 4–12 weeks; to be initiated by hospital paediatrician
- By intravenous injection over 5 minutes *or* by intravenous infusion over 20–30 minutes, prophylaxis of acid aspiration, 40 mg completed 1 hour before surgery

  Benign gastric ulcer, duodenal ulcer and gastro-oesophageal reflux, 40 mg once daily until oral administration possible
- Major peptic ulcer bleeding (following endoscopic treatment) [unlicensed indication], initial intravenous infusion of 80 mg over 40–60 minutes, then by continuous intravenous infusion, 8 mg/hour for 72 hours (then change to oral therapy)

Counselling Swallow whole, *or* disperse *MUPS®* tablets in water, *or* mix capsule contents or *MUPS®* tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should **not** be opened

Omeprazole (Non-proprietary) PoM

Capsules, enclosing e/c granules, omeprazole 10 mg, net price 28-cap pack = £1.81; 20 mg, 28-cap pack = £1.92; 40 mg, 7-cap pack = £1.95, 28-cap pack = £21.65. Counselling, administration

Dental prescribing on NHS Gastro-resistant omeprazole capsules may be prescribed

Capsules, enclosing e/c tablet, omeprazole 10 mg, net price 28-cap pack = £1.81; 20 mg, 28-cap pack = £1.92. Counselling, administration

Brands include *Mepradec®*

Dental prescribing on NHS Gastro-resistant omeprazole capsules may be prescribed

[1] Tablets, e/c, omeprazole 10 mg, net price 28-tab pack = £5.84; 20 mg, 28-tab pack = £5.71; 40 mg, 7-tab pack = £5.15. Label: 25

Intravenous infusion, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £5.18

1. Omeprazole 10 mg tablets can be sold to the public for the short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks, and a pack size of 28 tablets

Losec® (AstraZeneca) PoM

MUPS® (multiple-unit pellet system = dispersible tablets), f/c, omeprazole 10 mg (light pink), net price 28-tab pack = £7.75; 20 mg (pink), 28-tab pack = £11.60; 40 mg (red-brown), 7-tab pack = £5.80. Counselling, administration

Capsules, enclosing e/c granules, omeprazole 10 mg (pink), net price 28-cap pack = £7.75; 20 mg (pink/brown), 28-cap pack = £11.60; 40 mg (brown), 7-cap pack = £5.80. Counselling, administration

Intravenous infusion, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £5.41

Injection, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial (with solvent) = £5.41

With ketoprofen

Section 10.1.1

PANTOPRAZOLE

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (proton pump inhibitors)

Hepatic impairment max. 20 mg daily in severe impairment and cirrhosis—monitor liver function (discontinue if deterioration)

Renal impairment max. oral dose 40 mg daily

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—fetotoxic in *animals*

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—small amount present in milk in *animal* studies

Side-effects see notes above; also hyperlipidaemia, weight changes

Dose

- By mouth, benign gastric ulcer, ADULT over 18 years, 40–80 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed

  Gastro-oesophageal reflux disease, ADULT and CHILD over 12 years, 20–80 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 20 mg daily, increased to 40 mg daily if symptoms return

  Duodenal ulcer, ADULT over 18 years, 40–80 mg daily in the morning for 2 weeks, continued for further 2 weeks if not fully healed

  Duodenal ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 50

  Prophylaxis of NSAID-associated gastric or duodenal ulcer in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment, ADULT over 18 years, 20 mg daily

  Zollinger–Ellison syndrome (and other hypersecretory conditions), ADULT over 18 years, initially 80 mg once daily adjusted according to response (ELDERLY max. 40 mg daily); daily doses above 80 mg given in 2 divided doses

- By intravenous injection over at least 2 minutes *or* by intravenous infusion, ADULT over 18 years, duodenal ulcer, gastric ulcer, and gastro-oesophageal reflux, 40 mg daily until oral administration can be resumed

  Zollinger–Ellison syndrome (and other hypersecretory conditions), ADULT over 18 years, initially 80 mg (160 mg if rapid acid control required) then 80 mg once daily adjusted according to response; daily doses above 80 mg given in 2 divided doses

Pantoprazole (Non-proprietary) PoM

Tablets, e/c, pantoprazole 20 mg, net price 28-tab pack = £1.79; 40 mg, 28-tab pack = £2.82. Label: 25

Note Pantoprazole 20 mg tablets can be sold to the public for the short-term treatment of reflux symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks

Protium® (Nycomed) PoM

Injection, powder for reconstitution, pantoprazole (as sodium salt), net price 40-mg vial = £5.11

RABEPRAZOLE SODIUM

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (proton pump inhibitors)

Hepatic impairment manufacturer advises caution in severe hepatic dysfunction

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also cough, influenza-like syndrome, and rhinitis; *less commonly* chest pain and nervousness; *rarely* anorexia and weight gain

Dose

- Benign gastric ulcer, 20 mg daily in the morning for 6 weeks, continued for further 6 weeks if not fully healed
- Duodenal ulcer, 20 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed
- Gastro-oesophageal reflux disease, 20 mg once daily for 4–8 weeks; maintenance 10–20 mg daily; symptomatic treatment in the absence of oesophagitis, 10 mg daily for up to 4 weeks, then 10 mg daily when required
- Duodenal and benign gastric ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 50
- Zollinger–Ellison syndrome, initially 60 mg once daily adjusted according to response (max. 120 mg daily); doses above 100 mg daily given in 2 divided doses
- CHILD not recommended

Pariet® (Janssen-Cilag, Eisai) PoM

Tablets, e/c, rabeprazole sodium 10 mg (pink), net price 28-tab pack = £11.56; 20 mg (yellow), 28-tab pack = £19.55. Label: 25

1.4 Acute diarrhoea

1.4.1 Adsorbents and bulk-forming drugs
1.4.2 Antimotility drugs

The priority in acute diarrhoea, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in infants and in frail and elderly patients. For details of **oral rehydration preparations**, see section 9.2.1.2. Severe depletion of fluid and electrolytes requires immediate admission to hospital and urgent replacement.

Antimotility drugs (section 1.4.2) relieve symptoms of acute diarrhoea. They are used in the management of uncomplicated acute diarrhoea in adults; fluid and electrolyte replacement may be necessary in case of dehydration. However, antimotility drugs are **not** recommended for acute diarrhoea in young children.

Antispasmodics (section 1.2) are occasionally of value in treating abdominal cramp associated with diarrhoea but they should **not** be used for primary treatment. Antispasmodics and antiemetics should be **avoided** in young children with gastro-enteritis because they are rarely effective and have troublesome side-effects.

Antibacterial drugs are generally unnecessary in simple gastro-enteritis because the complaint usually resolves quickly without them, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment; for drugs used in campylobacter enteritis, shigellosis, and salmonellosis, see Table 1, section 5.1. **Ciprofloxacin** is occasionally used for prophylaxis against travellers' diarrhoea, but routine use is **not** recommended. Lactobacillus preparations have not been shown to be effective.

Colestyramine (section 1.9.2), binds unabsorbed bile salts and provides symptomatic relief of diarrhoea following ileal disease or resection.

1.4.1 Adsorbents and bulk-forming drugs

Adsorbents such as kaolin are **not** recommended for *acute diarrhoeas*. Bulk-forming drugs, such as ispaghula, methylcellulose, and sterculia (section 1.6.1) are useful in controlling diarrhoea associated with diverticular disease.

KAOLIN, LIGHT

Indications diarrhoea but see notes above

Cautions **interactions:** Appendix 1 (kaolin)

Kaolin Mixture, BP
(Kaolin Oral Suspension)
Oral suspension, light kaolin or light kaolin (natural) 20%, light magnesium carbonate 5%, sodium bicarbonate 5% in a suitable vehicle with a peppermint flavour.
Dose 10–20 mL every 4 hours

1.4.2 Antimotility drugs

Antimotility drugs have a role in the management of uncomplicated *acute diarrhoea* in adults but not in young children; see also section 1.4. However, in severe cases, fluid and electrolyte replacement (section 9.2.1.2) are of primary importance.

For comments on the role of antimotility drugs in *chronic bowel disorders* see section 1.5. For their role in *stoma care* see section 1.8.

Loperamide can be used for faecal incontinence [unlicensed indication] after the underlying cause of incontinence has been addressed.

CODEINE PHOSPHATE

Indications see notes above; cough suppression (section 3.9.1); pain (section 4.7.2)

Cautions section 4.7.2; tolerance and dependence may occur with prolonged use; **interactions:** Appendix 1 (opioid analgesics)

Contra-indications section 4.7.2; also conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic-associated colitis

Hepatic impairment section 4.7.2

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding section 4.7.2

Side-effects section 4.7.2

Dose

- Acute diarrhoea, ADULT and CHILD over 12 years, 30 mg 3–4 times daily (range 15–60 mg)

Preparations
Section 4.7.2

CO-PHENOTROPE

A mixture of diphenoxylate hydrochloride and atropine sulphate in the mass proportions 100 parts to 1 part respectively

Indications adjunct to rehydration in acute diarrhoea (but see notes above); control of faecal consistency after colostomy or ileostomy (section 1.8)

Cautions section 4.7.2; also young children are particularly susceptible to **overdosage** and symptoms may be delayed and observation is needed for at least 48 hours after ingestion; presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals or in overdosage (section 1.2); **interactions:** Appendix 1 (antimuscarinics, opioid analgesics)

Contra-indications section 4.7.2 and also see under Antimuscarinics (section 1.2)

Hepatic impairment section 4.7.2; also avoid in jaundice

Renal impairment section 4.7.2

Pregnancy section 4.7.2 and also see under Atropine Sulphate (section 1.2)

Breast-feeding may be present in milk

Side-effects section 4.7.2 and also see under Antimuscarinics (section 1.2); also abdominal pain, anorexia, and fever

Dose

- See preparations

Co-phenotrope (Non-proprietary) PoM
Tablets, co-phenotrope 2.5/0.025 (diphenoxylate hydrochloride 2.5 mg, atropine sulphate 25 micrograms), net price 100 = £8.95
Brands include *Lomotil*®
Dose initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled; CHILD under 4 years see *BNF for Children*, 4–9 years 1 tablet 3 times daily, 9–12 years 1 tablet 4 times daily, 12–16 years 2 tablets 3 times daily, but see also notes above
Note Co-phenotrope 2.5/0.025 can be sold to the public for adults and children over 16 years (provided packs do not contain more than 20 tablets) as an adjunct to rehydration in acute diarrhoea (max. daily dose 10 tablets)

LOPERAMIDE HYDROCHLORIDE

Indications symptomatic treatment of acute diarrhoea; adjunct to rehydration in acute diarrhoea in adults and children over 4 years (but see notes above); chronic diarrhoea in adults only

Cautions see notes above; **interactions:** Appendix 1 (loperamide)

Contra-indications conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis

Hepatic impairment risk of accumulation—manufacturer advises caution

Pregnancy manufacturers advise avoid—no information available

Breast-feeding amount probably too small to be harmful

Side-effects abdominal cramps, dizziness, drowsiness, and skin reactions including urticaria; paralytic ileus and abdominal bloating also reported

Dose

- Acute diarrhoea, 4 mg initially followed by 2 mg after each loose stool for up to 5 days; usual dose 6–8 mg daily; max. 16 mg daily; CHILD under 4 years not

recommended; 4–8 years, 1 mg 3–4 times daily for up to *3 days only*; 8–12 years, 2 mg 4 times daily for up to 5 days

- Chronic diarrhoea in adults, initially, 4–8 mg daily in divided doses, subsequently adjusted according to response and given in 2 divided doses for maintenance; max. 16 mg daily; CHILD under 18 years see *BNF for Children*
- Faecal incontinence [unlicensed indication], initially 500 micrograms daily, adjusted according to response; max. 16 mg daily in divided doses

Loperamide (Non-proprietary) PoM

Capsules, loperamide hydrochloride 2 mg, net price 30-cap pack = £1.07

Tablets, loperamide hydrochloride 2 mg, net price 30-tab pack = £2.15

Brands include *Norimode®*

Note Loperamide can be sold to the public, provided it is licensed and labelled for the treatment of acute diarrhoea in adults and children over 12 years of age, or for acute diarrhoea associated with irritable bowel syndrome (after initial diagnosis by a doctor) in adults over 18 years of age

Imodium® (Janssen-Cilag) PoM

Capsules, green/grey, loperamide hydrochloride 2 mg. Net price 30-cap pack = £1.09

Syrup, sugar free, red, loperamide hydrochloride 1 mg/5 mL. Net price 100 mL = £1.17

Compound preparations

Imodium® Plus (McNeil)

Caplets (= tablets), loperamide hydrochloride 2 mg, simeticone 125 mg, net price 6-tab pack = £2.27, 12-tab pack = £3.58

Dose acute diarrhoea with abdominal colic, initially 2 caplets (CHILD 12–18 years 1 caplet) then 1 caplet after each loose stool; max. 4 caplets daily for up to 2 days; CHILD under 12 years not recommended

MORPHINE

Indications see notes above; cough in terminal disease (section 3.9.1); pain (section 4.7.2)

Cautions see notes above and under Morphine Salts (section 4.7.2)

Contra-indications see notes above and under Morphine Salts (section 4.7.2)

Hepatic impairment section 4.7.2

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding see under Morphine Salts (section 4.7.2)

Side-effects see notes above and under Morphine Salts (section 4.7.2); sedation and the risk of dependence are greater

Dose

- See preparation

Kaolin and Morphine Mixture, BP
(Kaolin and Morphine Oral Suspension)

Oral suspension, light kaolin or light kaolin (natural) 20%, sodium bicarbonate 5%, and chloroform and morphine tincture 4% in a suitable vehicle. Contains anhydrous morphine 550–800 micrograms/10 mL.

Dose ADULT and CHILD over 12 years, 10 mL every 6 hours in water

1.5 Chronic bowel disorders

Once tumours are ruled out individual symptoms of chronic bowel disorders need specific treatment including dietary manipulation as well as drug treatment and the maintenance of a liberal fluid intake.

Inflammatory bowel disease

Chronic inflammatory bowel diseases include *ulcerative colitis* and *Crohn's disease*. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Aminosalicylates (balsalazide, mesalazine, olsalazine, and sulfasalazine), **corticosteroids** (hydrocortisone, beclometasone, budesonide, and prednisolone), and **drugs that affect the immune response** are used in the treatment of inflammatory bowel disease.

Treatment of acute ulcerative colitis and Crohn's disease Acute mild to moderate disease affecting the rectum (proctitis) or the recto-sigmoid is treated initially with local application of an aminosalicylate (section 1.5.1); alternatively, a local corticosteroid can be used but it is less effective. A combination of a local aminosalicylate and a local corticosteroid can be used for proctitis that does not respond to a local aminosalicylate alone. Foam preparations and suppositories are especially useful when patients have difficulty retaining liquid enemas.

Diffuse inflammatory bowel disease or disease that does not respond to local therapy requires oral treatment. Mild disease affecting the proximal colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate can be used in proctitis or distal colitis. Refractory or moderate inflammatory bowel disease usually requires adjunctive use of an oral corticosteroid such as **prednisolone** (section 1.5.2) for 4–8 weeks. Modified-release **budesonide** is licensed for Crohn's disease affecting the ileum and the ascending colon; it causes fewer systemic side-effects than oral prednisolone but may be less effective. **Beclometasone dipropionate** by mouth is licensed as an adjunct to mesalazine for mild to moderate ulcerative colitis, but it is not known whether it is as effective as other corticosteroids.

Severe inflammatory bowel disease or disease that is not responding to an oral corticosteroid requires hospital admission and treatment with an intravenous corticosteroid (such as hydrocortisone or methylprednisolone, section 6.3.2); other therapy may include intravenous fluid and electrolyte replacement, and possibly parenteral nutrition. Specialist supervision is required for patients who fail to respond adequately to these measures. Patients with severe ulcerative colitis that has not responded to intravenous corticosteroids, may benefit from a short course of intravenous **ciclosporin** [unlicensed indication] (section 1.5.3). Patients with unresponsive or chronically active Crohn's disease may benefit from **azathioprine** (section 1.5.3), **mercaptopurine** (section 1.5.3), or once-weekly **methotrexate** (section 1.5.3) [all unlicensed indications]; these drugs have a slower onset of action.

Infliximab (section 1.5.3) is licensed for the management of severe active Crohn's disease and severe ulcerative colitis in patients whose condition has not

responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them.

NICE guidance

Infliximab and adalimumab for Crohn's disease (May 2010)

Infliximab or adalimumab is recommended for the treatment of severe active Crohn's disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications; infliximab can also be used in a similar way in children over 6 years of age. In adults over 18 years of age, infliximab is recommended for the treatment of fistulating Crohn's disease that has not responded to conventional therapy (including antibacterials, drainage, and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.

Infliximab or adalimumab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter. Treatment should be continued beyond 12 months only if there is evidence of active disease—in these cases the need for treatment should be reviewed at least annually. If the disease relapses after stopping treatment, adalimumab or infliximab can be restarted (but see Hypersensitivity Reactions under Infliximab, p. 66).

NICE guidance

Infliximab for subacute manifestations of ulcerative colitis (April 2008)

Infliximab is **not** recommended for the treatment of subacute manifestations of moderate to severe active ulcerative colitis that would normally be managed in an outpatient setting.

NICE guidance

Infliximab for acute exacerbations of ulcerative colitis (December 2008)

Infliximab is recommended as an option for the treatment of acute exacerbations of severe ulcerative colitis when treatment with ciclosporin is contra-indicated or inappropriate.

Adalimumab (section 1.5.3) is licensed for the treatment of severe active Crohn's disease in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional drug that affects the immune response, or who are intolerant of them. For inducing remission, adalimumab should be used in combination with a corticosteroid, but it may be given alone if a corticosteroid is inappropriate or is not tolerated. Adalimumab may also be used for Crohn's disease in patients who have relapsed while taking infliximab or who cannot tolerate infliximab because of hypersensitivity reactions.

Maintenance of remission of acute ulcerative colitis and Crohn's disease Smoking cessation (section 4.10.2) reduces the risk of relapse in Crohn's disease and should be encouraged. **Aminosalicylates** are efficacious in the maintenance of remission of ulcerative colitis, but there is no evidence of efficacy in the maintenance of remission of Crohn's disease. Corticosteroids are **not** suitable for maintenance treatment because of their side-effects. In resistant or frequently relapsing cases either **azathioprine** (section 1.5.3) [unlicensed indication] or **mercaptopurine** (section 1.5.3) [unlicensed indication], given under close supervision may be helpful. Methotrexate (section 1.5.3) is tried in Crohn's disease if azathioprine or mercaptopurine cannot be used [unlicensed indication]. Maintenance therapy with infliximab should be considered for patients with Crohn's disease or ulcerative colitis who respond to the initial induction course of infliximab; fixed-interval dosing is superior to intermittent dosing. **Adalimumab** is licensed for maintenance therapy in Crohn's disease.

Fistulating Crohn's disease Treatment may not be necessary for simple, asymptomatic perianal fistulas. **Metronidazole** (section 5.1.11) or **ciprofloxacin** (section 5.1.12) can improve symptoms of fistulating Crohn's disease but complete healing occurs rarely [unlicensed indication]. Metronidazole by mouth is used at a dose of 10–20 mg/kg daily in divided doses (usual dose 400–500 mg 3 times daily); it is usually given for 1 month but no longer than 3 months because of concerns about peripheral neuropathy. Ciprofloxacin by mouth is given at a dose of 500 mg twice daily. Other antibacterials should be given if specifically indicated (e.g. sepsis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. Fistulas may also require surgical exploration and local drainage.

Either **azathioprine** or **mercaptopurine** is used as a second-line treatment for fistulating Crohn's disease and continued for maintenance [unlicensed indication]. **Infliximab** is used for fistulating Crohn's disease refractory to conventional treatments; fixed-interval dosing is superior to intermittent dosing. Maintenance therapy with infliximab should be considered for patients who respond to the initial induction course of infliximab. **Adalimumab** can be used if there is intolerance to infliximab [unlicensed indication]

Adjunctive treatment of inflammatory bowel disease Due attention should be paid to diet; high-fibre or low-residue diets should be used as appropriate.

Antimotility drugs such as codeine and loperamide, and antispasmodic drugs may precipitate paralytic ileus and megacolon in active ulcerative colitis; treatment of the inflammation is more logical. Laxatives may be required in proctitis. Diarrhoea resulting from the loss of bile-salt absorption (e.g. in terminal ileal disease or bowel resection) may improve with **colestyramine** (section 1.9.2), which binds bile salts.

Clostridium difficile infection

Clostridium difficile infection is caused by colonisation of the colon with *Clostridium difficile* and production of toxin. It often follows antibiotic therapy and is usually of acute onset, but may become chronic. It is a particular hazard of ampicillin, amoxicillin, co-amoxiclav, second- and third-generation cephalosporins, clindamycin, and quinolones, but few antibiotics are free of this side-effect. Oral **metronidazole** (see section 5.1.11) or oral **vancomycin** (see section 5.1.7) are used as specific treatment; vancomycin may be preferred for very sick patients. Metronidazole can be given by intravenous infusion if oral treatment is inappropriate.

Diverticular disease

Diverticular disease is treated with a high-fibre diet, **bran supplements**, and **bulk-forming drugs** (section 1.6.1). **Antispasmodics** may provide symptomatic relief when colic is a problem (section 1.2). **Antibacterials** are used only when the diverticula in the intestinal wall become infected. **Antimotility** drugs which slow intestinal motility, e.g. codeine, diphenoxylate, and loperamide could possibly exacerbate the symptoms of diverticular disease and are **contra-indicated**.

Irritable bowel syndrome

Irritable bowel syndrome can present with pain, constipation, or diarrhoea. In some patients there may be important psychological aggravating factors which respond to reassurance and possibly specific treatment e.g. with an antidepressant.

The **fibre** intake of patients with irritable bowel syndrome should be reviewed. If an increase in dietary fibre is required, soluble fibre (e.g. ispaghula husk, sterculia, or oats) is recommended; insoluble fibre (e.g. bran) may exacerbate symptoms and its use should be discouraged. A **laxative** (section 1.6) can be used to treat constipation. An osmotic laxative, such as a macrogol, is preferred; lactulose may cause bloating. Stimulant laxatives should be avoided or used only occasionally. **Loperamide** (section 1.4.2) may relieve diarrhoea and **antispasmodic drugs** (section 1.2) may relieve pain. Opioids with a central action, such as codeine, are better avoided because of the risk of dependence.

A **tricyclic antidepressant** (section 4.3.1) can be used for abdominal pain or discomfort [unlicensed indication] in patients who have not responded to laxatives, loperamide, or antispasmodics. Low doses of a tricyclic antidepressant are used (e.g. amitriptyline, initially 5–10 mg each night, increased if necessary in steps of 10 mg at intervals of at least 2 weeks to max. 30 mg each night). A **selective serotonin reuptake inhibitor** (section 4.3.3) may be considered in those who do not respond to a tricyclic antidepressant [unlicensed indication].

Malabsorption syndromes

Individual conditions need specific management and also general nutritional consideration. Coeliac disease (gluten enteropathy) usually needs a gluten-free diet and pancreatic insufficiency needs pancreatin supplements (section 1.9.4)

For further information on foods for special diets (ACBS), see Appendix 7.

1.5.1 Aminosalicylates

Sulfasalazine is a combination of 5-aminosalicylic acid ('5-ASA') and sulfapyridine; sulfapyridine acts only as a carrier to the colonic site of action but still causes side-effects. In the newer aminosalicylates, **mesalazine** (5-aminosalicylic acid), **balsalazide** (a prodrug of 5-aminosalicylic acid) and **olsalazine** (a dimer of 5-aminosalicylic acid which cleaves in the lower bowel), the sulphonamide-related side-effects of sulfasalazine are avoided, but 5-aminosalicylic acid alone can still cause side-effects including blood disorders (see recommendation below) and lupus-like syndrome also seen with sulfasalazine.

Cautions Renal function should be monitored before starting an oral aminosalicylate, at 3 months of treatment, and then annually during treatment (more frequently in renal impairment). Blood disorders can occur with aminosalicylates (see recommendation below).

Blood disorders
Patients receiving aminosalicylates should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Contra-indications Aminosalicylates should be avoided in salicylate hypersensitivity.

Side-effects Side-effects of the aminosalicylates include diarrhoea, nausea, vomiting, abdominal pain, exacerbation of symptoms of colitis, headache, hypersensitivity reactions (including rash and urticaria); side-effects that occur rarely include acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders (including eosinophilia and fibrosing alveolitis), peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinaemia, neutropenia, and thrombocytopenia—see also recommendation above), renal dysfunction (interstitial nephritis, nephrotic syndrome), myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Stevens-Johnson syndrome), alopecia.

BALSALAZIDE SODIUM

Indications treatment of mild to moderate ulcerative colitis and maintenance of remission

Cautions see notes above; also history of asthma; **interactions:** Appendix 1 (aminosalicylates)
Blood disorders See recommendation above

Contra-indications see notes above

Hepatic impairment avoid in severe impairment

Renal impairment manufacturer advises avoid in moderate to severe impairment

Pregnancy manufacturer advises avoid

Breast-feeding monitor infant for diarrhoea

Side-effects see notes above; also cholelithiasis

Dose

- Acute attack, 2.25 g 3 times daily until remission occurs or for up to max. 12 weeks
- Maintenance, 1.5 g twice daily, adjusted according to response (max. 6 g daily)
- CHILD under 18 years see *BNF for Children*

Colazide® (Almirall) PoM
Capsules, beige, balsalazide sodium 750 mg. Net price 130-cap pack = £30.42. Label: 21, 25, counselling, blood disorder symptoms (see recommendation above)

MESALAZINE

Indications treatment of mild to moderate ulcerative colitis and maintenance of remission; see also under preparations

Cautions see notes above; elderly; **interactions:** Appendix 1 (aminosalicylates)

Blood disorders See recommendation above

Contra-indications see notes above

Hepatic impairment avoid in severe impairment

Renal impairment use with caution; avoid if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy negligible quantities cross placenta

Breast-feeding diarrhoea reported but negligible amounts detected in breast milk; monitor infant for diarrhoea

Side-effects see notes above

Dose

- See under preparations, below

Note The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable

Asacol® (Warner Chilcott) PoM

Foam enema, mesalazine 1 g/metered application, net price 14-application canister with disposable applicators and plastic bags = £26.72. Counselling, blood disorder symptoms (see recommendation above)

Excipients include disodium edetate, hydroxybenzoates (parabens), polysorbate 20, sodium metabisulphite

Dose acute attack affecting the rectosigmoid region, 1 metered application (mesalazine 1 g) into the rectum daily for 4–6 weeks; acute attack affecting the descending colon, 2 metered applications (mesalazine 2 g) once daily for 4–6 weeks; CHILD 12–18 years, see *BNF for Children*

Suppositories, mesalazine 250 mg, net price 20-suppos pack = £4.82; 500 mg, 10-suppos pack = £4.82. Counselling, blood disorder symptoms (see recommendation above)

Dose acute attack or maintenance, by rectum 0.75–1.5 g daily in divided doses, with last dose at bedtime; CHILD 12–18 years, see *BNF for Children*

Asacol® MR (Warner Chilcott) PoM

Tablets, red, e/c, mesalazine 400 mg, net price 90-tab pack = £29.41, 120-tab pack = £39.21. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ulcerative colitis, acute attack, 2.4 g daily in divided doses; maintenance of remission of ulcerative colitis and Crohn's ileocolitis, 1.2–2.4 g daily in divided doses; CHILD 12–18 years, see *BNF for Children*

Tablets, red-brown, e/c, mesalazine 800 mg, net price 180-tab pack = £117.62. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ADULT over 18 years, ulcerative colitis, acute attack, 2.4–4.8 g daily in divided doses; maintenance of remission of ulcerative colitis and Crohn's ileo-colitis, up to 2.4 g daily in divided doses

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Ipocol® (Sandoz) PoM

Tablets, e/c, mesalazine 400 mg, net price 120-tab pack = £41.62. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose acute attack, 2.4 g daily in divided doses; maintenance, 1.2–2.4 g daily in divided doses; CHILD 12–18 years, see *BNF for Children*

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Mesren® MR (IVAX) PoM

Tablets, red-brown, e/c, mesalazine 400 mg, net price 90-tab pack = £19.50, 120-tab pack = £26.00. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ADULT and CHILD over 12 years, ulcerative colitis, acute attack, 2.4 g daily in divided doses; maintenance of remission of ulcerative colitis and Crohn's ileo-colitis, 1.2–2.4 g daily in divided doses

Mezavant® XL (Shire) PoM

Tablets, m/r, red-brown, e/c, mesalazine 1.2 g, net price 60-tab pack = £62.44. Label: 21, 25, counselling, blood disorder symptoms (see recommendations above)

Dose ADULT over 18 years, acute attack, 2.4 g once daily, increase if necessary to 4.8 g once daily (review treatment at 8 weeks); maintenance, 2.4 g once daily

Pentasa® (Ferring) PoM

Tablets, m/r, scored, mesalazine 500 mg (grey), net price 100-tab pack = £24.21. Counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Dose ADULT and CHILD over 15 years, acute attack, up to 4 g daily in 2–3 divided doses; maintenance, 2 g once daily; tablets may be dispersed in water, but should not be chewed; CHILD 5–15 years see *BNF for Children*

Granules, m/r, pale grey-brown, mesalazine 1 g/sachet, net price 50-sachet pack = £28.82; 2 g/sachet, 60-sachet pack = £72.05. Counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Dose acute attack, up to 4 g daily in 2–4 divided doses; maintenance, 2 g once daily; granules should be placed on tongue and washed down with water or orange juice without chewing; CHILD 5–18 years see *BNF for Children*

Retention enema, mesalazine 1 g in 100-mL pack. Net price 7 enemas = £17.73. Counselling, blood disorder symptoms (see recommendation above)

Dose by rectum ADULT and CHILD over 12 years, 1 enema at bedtime

Suppositories, mesalazine 1 g. Net price 28-suppos pack = £40.01. Counselling, blood disorder symptoms (see recommendation above)

Dose by rectum ulcerative proctitis, ADULT and CHILD over 15 years, acute attack, 1 g daily for 2–4 weeks; maintenance, 1 g daily; CHILD 12–15 years see *BNF for Children*

Salofalk® (Dr Falk) PoM

Tablets, e/c, yellow, mesalazine 250 mg. Net price 100-tab pack = £16.19. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose acute attack, 0.5–1 g 3 times daily; maintenance, 500 mg three times daily; CHILD 12–18 years see *BNF for Children*

Granules, m/r, grey, e/c, vanilla-flavoured, mesalazine 500 mg/sachet, net price 100-sachet pack = £28.74; 1 g/sachet, 50-sachet pack = £28.74; 1.5 g/sachet, 60-sachet pack = £48.85. Label: 25, counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Excipients include aspartame (section 9.4.1)

Dose acute attack, 1.5–3 g once daily (preferably in the morning) *or* 0.5–1 g 3 times daily; maintenance, 500 mg 3 times daily; CHILD 6–18 years see *BNF for Children*

Counselling granules should be placed on tongue and washed down with water without chewing

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Suppositories, mesalazine 500 mg. Net price 30-suppos pack = £14.81. Counselling, blood disorder symptoms (see recommendation above)
Dose ADULT and CHILD over 15 years, acute attack, by rectum, 0.5–1 g 2–3 times daily adjusted according to response; CHILD 12–15 years see *BNF for Children*

Enema, mesalazine 2 g in 59-mL pack. Net price 7 enemas = £29.92. Counselling, blood disorder symptoms (see recommendation above)
Dose acute attack *or* maintenance, by rectum, 2 g daily at bedtime; CHILD 12–18 years see *BNF for Children*

Rectal foam, mesalazine 1 g/metered application, net price 14-application canister with disposable applicators and plastic bags = £30.17. Counselling, blood disorder symptoms (see recommendation above)
Excipients include cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulphite
Dose mild ulcerative colitis affecting sigmoid colon and rectum, ADULT and CHILD over 12 years, 2 metered applications (mesalazine 2 g) into the rectum at bedtime or in 2 divided doses

OLSALAZINE SODIUM

Indications treatment of mild ulcerative colitis and maintenance of remission
Cautions see notes above; **interactions:** Appendix 1 (aminosalicylates)
Blood disorders See recommendation above
Contra-indications see notes above
Renal impairment use with caution; manufacturer advises avoid in significant impairment
Pregnancy manufacturer advises avoid unless potential benefit outweighs risk
Breast-feeding monitor infant for diarrhoea
Side-effects see notes above; watery diarrhoea common; also reported, tachycardia, palpitation, pyrexia, blurred vision, and photosensitivity
Dose
- ADULT and CHILD over 12 years, acute attack, 1 g daily in divided doses after meals increased if necessary over 1 week to max. 3 g daily (max. single dose 1 g); maintenance, 500 mg twice daily after meals
- CHILD under 12 years see *BNF for Children*

Dipentum® (UCB Pharma) PoM
Capsules, brown, olsalazine sodium 250 mg. Net price 112-cap pack = £19.77. Label: 21, counselling, blood disorder symptoms (see recommendation above)

Tablets, yellow, scored, olsalazine sodium 500 mg. Net price 60-tab pack = £21.18. Label: 21, counselling, blood disorder symptoms (see recommendation above)

SULFASALAZINE
(Sulphasalazine)

Indications treatment of mild to moderate and severe ulcerative colitis and maintenance of remission; active Crohn's disease; rheumatoid arthritis (section 10.1.3)
Cautions see notes above; also history of allergy or asthma; G6PD deficiency (section 9.1.5); slow acetylator status; risk of haematological and hepatic toxicity (differential white cell, red cell, and platelet counts initially and at monthly intervals for first 3 months; liver function tests at monthly intervals for first 3 months); maintain adequate fluid intake; upper gastro-intestinal side-effects common over 4 g daily; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (aminosalicylates)
Blood disorders See recommendation above
Contra-indications see notes above; also sulphonamide hypersensitivity; child under 2 years of age
Hepatic impairment use with caution
Renal impairment risk of toxicity, including crystalluria, in moderate impairment—ensure high fluid intake; avoid in severe impairment
Pregnancy theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother
Breast-feeding small amounts in milk (1 report of bloody diarrhoea); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants
Side-effects see notes above; also cough, insomnia, dizziness, fever, blood disorders (including Heinz body anaemia, megaloblastic anaemia), proteinuria, tinnitus, stomatitis, taste disturbances, and pruritus; *less commonly* dyspnoea, depression, convulsions, vasculitis, and alopecia; also reported loss of appetite, hypersensitivity reactions (including exfoliative dermatitis, epidermal necrolysis, photosensitivity, anaphylaxis, serum sickness), ataxia, hallucinations, aseptic meningitis, oligospermia, crystalluria, disturbances of smell, and parotitis; yellow-orange discoloration of skin, urine, and other body fluids; some soft contact lenses may be stained
Dose
- By mouth, acute attack 1–2 g 4 times daily (but see **cautions**) until remission occurs (if necessary corticosteroids may also be given), reducing to a maintenance dose of 500 mg 4 times daily; CHILD 2–12 years see *BNF for Children*
- By rectum, in suppositories, alone or in conjunction with oral treatment 0.5–1 g morning and night after a bowel movement; CHILD 5–12 years see *BNF for Children*

Sulfasalazine (Non-proprietary) PoM
Tablets, sulfasalazine 500 mg, net price 112 = £6.74. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Tablets, e/c, sulfasalazine 500 mg. Net price 112-tab pack = £14.46. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
Brands include *Sulazine EC®*

Suspension, sulfasalazine 250 mg/5 mL, net price 500 mL = £29.50. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
Excipients may include alcohol

Salazopyrin® (Pharmacia) PoM
Tablets, yellow, scored, sulfasalazine 500 mg, net price 112-tab pack = £6.97. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

EN-Tabs® (= tablets e/c), yellow, f/c, sulfasalazine 500 mg, net price 112-tab pack = £8.43. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

Suppositories, yellow, sulfasalazine 500 mg, net price 10 = £3.30. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

1.5.2 Corticosteroids

For the role of corticosteroids in acute ulcerative colitis and Crohn's disease, see Inflammatory Bowel Disease, p. 59.

BECLOMETASONE DIPROPIONATE

Indications adjunct to aminosalicylates in acute mild to moderate ulcerative colitis; asthma (section 3.2); allergic and vasomotor rhinitis (section 12.2.1); oral ulceration [unlicensed indication] (section 12.3.1)

Cautions section 6.3.2; **interactions:** Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Hepatic impairment manufacturer advises avoid in severe impairment—no information available

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2; also nausea, constipation, headache, and drowsiness

Dose

- 5 mg in the morning; max. duration of treatment 4 weeks; CHILD safety and efficacy not established

Clipper® (Chiesi) PoM

Tablets, m/r, ivory, beclometasone dipropionate 5 mg, net price 30-tab pack = £56.56. Label: 25

BUDESONIDE

Indications see preparations

Cautions section 6.3.2; for autoimmune hepatitis, monitor liver function tests every 2 weeks for 1 month, then at least every 3 months; **interactions:** Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Hepatic impairment section 6.3.2

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2

Dose

- See preparations

Budenofalk® (Dr Falk) PoM

Capsules, pink, enclosing e/c granules, budesonide 3 mg, net price 100-cap pack = £75.05. Label: 5, 10, steroid card, 22, 25

Dose mild to moderate Crohn's disease affecting ileum or ascending colon, chronic diarrhoea due to collagenous colitis, ADULT over 18 years, 3 mg 3 times daily for up to 8 weeks; reduce dose for the last 2 weeks of treatment (see also section 6.3.2); CHILD 12–18 years see *BNF for Children*

Autoimmune hepatitis, ADULT over 18 years, induction of remission, 3 mg 3 times daily; maintenance, 3 mg twice daily

Rectal foam, budesonide 2 mg/metered application, net price 14-application canister with disposable applicators and plastic bags = £57.11

Excipients include cetyl alcohol, disodium edetate, propylene glycol, sorbic acid

Dose ulcerative colitis affecting sigmoid colon and rectum, by rectum, ADULT over 18 years, 1 metered application (budesonide 2 mg) once daily for up to 8 weeks

Entocort® (AstraZeneca) PoM

CR Capsules, grey/pink, enclosing e/c, m/r granules, budesonide 3 mg, net price 100-cap pack = £99.00. Label: 5, 10, steroid card, 25

Note Dispense in original container (contains desiccant)

Dose mild to moderate Crohn's disease affecting the ileum or ascending colon, 9 mg once daily in the morning for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment (see also section 6.3.2); CHILD 12–18 years see *BNF for Children*

Enema, budesonide 2 mg/100 mL when dispersible tablet reconstituted in isotonic saline vehicle, net price pack of 7 dispersible tablets and bottles of vehicle = £33.00

Dose ulcerative colitis involving rectal and recto-sigmoid disease, by rectum, 1 enema at bedtime for 4 weeks; CHILD 12–18 years see *BNF for Children*

HYDROCORTISONE

Indications ulcerative colitis, proctitis, proctosigmoiditis

Cautions section 6.3.2; systemic absorption may occur; prolonged use should be avoided

Contra-indications intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

Side-effects section 6.3.2; also local irritation

Dose

- By rectum see preparations

Colifoam® (Meda) PoM

Foam in aerosol pack, hydrocortisone acetate 10%, net price 14-application canister with applicator = £9.28

Excipients include cetyl alcohol, hydroxybenzoates (parabens), propylene glycol

Dose initially 1 metered application (125 mg hydrocortisone acetate) inserted into the rectum once or twice daily for 2–3 weeks, then once on alternate days; CHILD 2–18 years see *BNF for Children*

PREDNISOLONE

Indications ulcerative colitis, and Crohn's disease; other indications, see section 6.3.2, see also preparations

Cautions section 6.3.2; systemic absorption may occur with rectal preparations; prolonged use should be avoided

Contra-indications section 6.3.2; intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

Hepatic impairment section 6.3.2

Renal impairment section 6.3.2

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2

Dose

- By mouth, initially 20–40 mg daily (up to 60 mg daily in some cases), preferably taken in the morning after breakfast; continued until remission occurs, followed by reducing doses
- By rectum, see preparations

Oral preparations

Section 6.3.2

Rectal preparations

Predenema® (Chemidex) PoM

Retention enema, prednisolone 20 mg (as sodium metasulphobenzoate) in 100-mL single-dose disposable pack. Net price 1 (standard tube) = 71p, 1 (long tube) = £1.21

Dose ulcerative colitis, by rectum, ADULT and CHILD over 12 years, initially 20 mg at bedtime for 2–4 weeks, continued if good response

Predfoam® (Forest) PoM

Foam in aerosol pack, prednisolone 20 mg (as metasulphobenzoate sodium)/metered application, net price 14-application canister with disposable applicators = £6.32

Excipients include cetostearyl alcohol, disodium edetate, polysorbate 20, sorbic acid

Dose proctitis and distal ulcerative colitis, 1 metered application (20 mg prednisolone) inserted into the rectum once or twice daily for 2 weeks, continued for further 2 weeks if good response; CHILD not recommended

Predsol® (UCB Pharma) PoM

Retention enema, prednisolone 20 mg (as sodium phosphate) in 100-mL single-dose disposable packs fitted with a nozzle. Net price 7 = £6.00

Dose rectal and rectosigmoidal ulcerative colitis and Crohn's disease, by rectum, initially 20 mg at bedtime for 2–4 weeks, continued if good response; CHILD not recommended

Suppositories, prednisolone 5 mg (as sodium phosphate). Net price 10 = £1.35

Dose ADULT and CHILD proctitis and rectal complications of Crohn's disease, by rectum, 5 mg inserted night and morning after a bowel movement

1.5.3 Drugs affecting the immune response

For the role of **azathioprine**, **ciclosporin**, **mercaptopurine**, and **methotrexate** in the treatment of inflammatory bowel disease, see p. 59.

Folic acid (section 9.1.2) should be given to reduce the possibility of methotrexate toxicity [unlicensed indication]. Folic acid is usually given at a dose of 5 mg once weekly on a different day to the methotrexate; alternative regimens may be used in some settings.

AZATHIOPRINE

Indications see under Inflammatory Bowel Disease, p. 59; autoimmune conditions and prophylaxis of transplant rejection (section 8.2.1); rheumatoid arthritis (section 10.1.3); severe refractory eczema (section 13.5.3)

Cautions section 8.2.1

Contra-indications section 8.2.1

Hepatic impairment section 8.2.1

Renal impairment section 8.2.1

Pregnancy section 8.2.1

Breast-feeding section 8.2.1

Side-effects section 8.2.1

Dose

- Severe acute Crohn's disease, maintenance of remission of Crohn's disease or ulcerative colitis [unlicensed indications], ADULT over 18 years, by mouth, 2–2.5 mg/kg daily; some patients may respond to lower doses

Preparations

Section 8.2.1

CICLOSPORIN

(Ciclosporin)

Indications severe acute ulcerative colitis refractory to corticosteroid treatment [unlicensed indication]; transplantation and graft-versus-host disease, nephrotic syndrome (section 8.2.2); rheumatoid arthritis (section 10.1.3); atopic dermatitis and psoriasis (section 13.5.3)

Cautions section 8.2.2

Hepatic impairment section 8.2.2

Renal impairment section 8.2.2

Pregnancy see Immunosuppresant therapy, p. 553

Breast-feeding section 8.2.2

Side-effects section 8.2.2

Dose

- By continuous intravenous infusion, ADULT over 18 years, 2 mg/kg daily over 24 hours; dose adjusted according to blood-ciclosporin concentration and response

Preparations

Section 8.2.2

MERCAPTOPURINE

(6-Mercaptopurine)

Indications see under Inflammatory Bowel disease, p. 59; acute leukaemias and chronic myeloid leukaemia (section 8.1.3)

Cautions section 8.1.3

Hepatic impairment section 8.1.3

Renal impairment section 8.1.3

Pregnancy section 8.1.3

Breast-feeding section 8.1.3

Side-effects section 8.1.3

Dose

- Severe acute Crohn's disease, maintenance of remission of Crohn's disease or ulcerative colitis [unlicensed indications], ADULT over 18 years, by mouth, 1–1.5 mg/kg daily; some patients may respond to lower doses

Preparations

Section 8.1.3

METHOTREXATE

Indications see under Inflammatory Bowel Disease, p. 59; malignant disease (section 8.1.3); rheumatoid arthritis (section 10.1.3); psoriasis (section 13.5.3)

Cautions section 10.1.3

Contra-indications section 10.1.3

Hepatic impairment section 10.1.3

Renal impairment section 10.1.3

Pregnancy section 10.1.3

Breast-feeding section 10.1.3

Side-effects section 10.1.3

Dose

- By intramuscular injection, severe Crohn's disease [unlicensed indication], ADULT over 18 years, induction of remission, 25 mg once weekly; maintenance, 15 mg once weekly
- By mouth, maintenance of remission of severe Crohn's disease [unlicensed indication], ADULT over 18 years, 10–25 mg once weekly

Important

Note that the above dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:

- the patient is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

Preparations
Section 10.1.3

Cytokine modulators

Infliximab and **adalimumab** are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They should be used under specialist supervision. Adequate resuscitation facilities must be available when infliximab is used.

ADALIMUMAB

Indications see under Inflammatory Bowel Disease, p. 60; ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, (section 10.1.3); psoriasis (section 13.5.3)

Cautions section 10.1.3

Contra-indications section 10.1.3

Pregnancy section 10.1.3

Breast-feeding section 10.1.3

Side-effects section 10.1.3

Dose

- By subcutaneous injection, severe active Crohn's disease, ADULT over 18 years, initially 80 mg, then 40 mg 2 weeks after initial dose *or* accelerated regimen, initially 160 mg in 4 divided doses over 1–2 days, then 80 mg 2 weeks after initial dose; maintenance, 40 mg on alternate weeks, increased if necessary to 40 mg weekly; review treatment if no response within 12 weeks of initial dose

Preparations
Section 10.1.3

INFLIXIMAB

Indications see under Inflammatory Bowel Disease, p. 59; ankylosing spondylitis, rheumatoid arthritis (section 10.1.3); psoriasis (section 13.5.3)

Cautions see section 10.1.3; also history of dysplasia or colon carcinoma

Hypersensitivity reactions Risk of delayed hypersensitivity if drug-free interval exceeds 16 weeks

Contra-indications see section 10.1.3

Pregnancy section 10.1.3

Breast-feeding section 10.1.3

Side-effects see section 10.1.3; also hepatosplenic T-cell lymphoma

Dose

- By intravenous infusion, severe active Crohn's disease, ADULT over 18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks after initial dose; then if the condition has responded, maintenance 5 mg/kg 6 weeks after initial dose, then 5 mg/kg every 8 weeks; CHILD 6–18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then 5 mg/kg every 8 weeks; interval between maintenance doses adjusted according to response; discontinue if no response within 10 weeks of initial dose

  Fistulating Crohn's disease, ADULT over 18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then if condition has responded, consult product literature for guidance on further doses; CHILD under 18 years, see *BNF for Children*

  Severe active ulcerative colitis, ADULT over 18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then 5 mg/kg every 8 weeks; discontinue if no response 14 weeks after initial dose

Preparations
Section 10.1.3

1.5.4 Food allergy

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as shellfish should be managed by strict avoidance. The condition should be distinguished from symptoms of occasional food intolerance in those with irritable bowel syndrome. **Sodium cromoglicate** may be helpful as an adjunct to dietary avoidance.

SODIUM CROMOGLICATE
(Sodium cromoglycate)

Indications food allergy (in conjunction with dietary restriction); asthma (section 3.3.1); allergic conjunctivitis (section 11.4.2); allergic rhinitis (section 12.2.1)

Pregnancy not known to be harmful

Breast-feeding unlikely to be present in milk

Side-effects occasional nausea, rashes, and joint pain

Dose

- 200 mg 4 times daily before meals; may be increased if necessary after 2–3 weeks to a max. of 40 mg/kg daily and then reduced according to response; CHILD 2–14 years 100 mg 4 times daily before meals; may be increased if necessary after 2–3 weeks to a max. of 40 mg/kg daily and then reduced according to response

  Counselling Capsules may be swallowed whole or the contents dissolved in hot water and diluted with cold water before taking

Nalcrom® (Sanofi-Aventis) PoM

Capsules, sodium cromoglicate 100 mg. Net price 100-cap pack = £59.75. Label: 22, counselling, see dose above

1.6 Laxatives

1.6.1 Bulk-forming laxatives
1.6.2 Stimulant laxatives
1.6.3 Faecal softeners
1.6.4 Osmotic laxatives
1.6.5 Bowel cleansing preparations
1.6.6 Peripheral opioid-receptor antagonists
1.6.7 5HT$_4$-receptor agonists

Before prescribing laxatives it is important to be sure that the patient *is* constipated and that the constipation is *not* secondary to an underlying undiagnosed complaint.

It is also important for those who complain of constipation to understand that bowel habit can vary considerably in frequency without doing harm. Some people tend to consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient's own normal pattern and this can be explained to the patient.

Misconceptions about bowel habits have led to excessive laxative use. Abuse may lead to hypokalaemia.

Thus, laxatives should generally be **avoided** except where straining will exacerbate a condition (such as angina) or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are also of value in *drug-induced constipation*, for the expulsion of *parasites* after anthelmintic treatment, and to clear the alimentary tract before *surgery and radiological procedures*. Prolonged treatment of constipation is sometimes necessary.

For the role of laxatives in the treatment of irritable bowel syndrome, see p. 61. For the prevention of opioid-induced constipation in palliative care, see p. 22.

Children Laxatives should be prescribed by a healthcare professional experienced in the management of constipation in children. Delays of greater than 3 days between stools may increase the likelihood of pain on passing hard stools leading to anal fissure, anal spasm and eventually to a learned response to avoid defaecation.

In *infants*, increased intake of fluids, particularly fruit juice containing sorbitol (e.g. prune, pear, or apple), may be sufficient to soften the stool. In infants under 1 year of age with mild constipation, **lactulose** (section 1.6.4) can be used to soften the stool; either an oral preparation containing **macrogols** or, rarely, **glycerol** suppositories can be used to clear faecal impaction. The infant should be referred to a hospital paediatric specialist if these measures fail.

The diet of *children over 1 year of age* should be reviewed to ensure that it includes an adequate intake of fibre and fluid. An osmotic laxative containing **macrogols** (section 1.6.4) can also be used, particularly in children with chronic constipation; **lactulose** is an alternative in children who cannot tolerate a macrogol. If there is an inadequate response to the osmotic laxative, a **stimulant laxative** (section 1.6.2) can be added.

Treatment of faecal impaction may initially increase symptoms of soiling and abdominal pain. In children over 1 year of age with faecal impaction, an oral preparation containing **macrogols** (section 1.6.4) is used to clear faecal mass and to establish and maintain soft well-formed stools. If disimpaction does not occur after 2 weeks, a **stimulant laxative** (section 1.6.2) can be added. If the impacted mass is not expelled following treatment with macrogols and a stimulant laxative, a **sodium citrate** enema can be administered. Although rectal administration of laxatives may be effective, this route is frequently distressing for the child and may lead to persistence of withholding. A **phosphate enema** may be administered under specialist supervision if disimpaction does not occur after a sodium citrate enema; a **bowel cleansing preparation** (section 1.6.5) is an alternative. Manual evacuation under anaesthetic may be necessary if disimpaction does not occur after oral and rectal treatment, or if the child is afraid.

Long-term regular use of laxatives is essential to maintain well-formed stools and prevent recurrence of faecal impaction; intermittent use may provoke relapses.

For children with chronic constipation, it may be necessary to exceed the licensed doses of some laxatives. Parents and carers of children should be advised to adjust the dose of laxative in order to establish a regular pattern of bowel movements in which stools are soft, well-formed, and passed without discomfort.
Laxatives should be administered at a time that produces an effect that is likely to fit in with the child's toilet routine.

Pregnancy If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose, can also be used. Bisacodyl or senna may be suitable, if a stimulant effect is necessary.

The laxatives that follow have been divided into 5 main groups (sections 1.6.1–1.6.5). This simple classification disguises the fact that some laxatives have a complex action.

1.6.1 Bulk-forming laxatives

Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis; patients should be advised that the full effect may take some days to develop.

Bulk-forming laxatives are of particular value in those with small hard stools, but should not be required unless fibre cannot be increased in the diet. A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.

Bulk-forming laxatives are useful in the management of patients with *colostomy*, *ileostomy*, *haemorrhoids*, *anal fissure*, *chronic diarrhoea associated with diverticular disease*, *irritable bowel syndrome*, and as adjuncts in *ulcerative colitis* (section 1.5). Adequate fluid intake must be maintained to avoid intestinal obstruction. Unprocessed wheat **bran**, taken with food or fruit juice, is a most effective bulk-forming preparation.

Finely ground bran, though more palatable, has poorer water-retaining properties, but can be taken as bran bread or biscuits in appropriately increased quantities. Oat bran is also used.

Methylcellulose, **ispaghula**, and **sterculia** are useful in patients who cannot tolerate bran. Methylcellulose also acts as a faecal softener.

ISPAGHULA HUSK

Indications see notes above

Cautions adequate fluid intake should be maintained to avoid intestinal obstruction—it may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility

Contra-indications difficulty in swallowing, intestinal obstruction, colonic atony, faecal impaction

Side-effects flatulence, abdominal distension, gastrointestinal obstruction or impaction; hypersensitivity reported

Dose

- See preparations below

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

Fibrelief® (Manx)

Granules, sugar- and gluten-free, ispaghula husk 3.5 g/sachet (natural or orange flavour), net price 10 sachets = £1.23, 30 sachets = £2.07. Label: 13, counselling, see above

Excipients include aspartame (section 9.4.1)

Dose ADULT and CHILD over 12 years, 1–6 sachets daily in water in 1–3 divided doses, preferably after meals

Fybogel® (Reckitt Benckiser)

Granules, buff, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet (low Na^+), net price 30 sachets (plain, lemon, or orange flavour) = £1.84. Label: 13, counselling, see above

Excipients include aspartame 16 mg/sachet (see section 9.4.1)

Dose 1 sachet or 2 level 5-mL spoonfuls in water twice daily preferably after meals; CHILD (but see section 1.6) 2–12 years ½–1 level 5-mL spoonful in water, twice daily preferably after meals (CHILD 2–6 years on specialist practitioner's advice only)

Isogel® (Potters)

Granules, brown, sugar- and gluten-free, ispaghula husk 90%. Net price 200 g = £2.67. Label: 13, counselling, see above

Dose constipation, 2 level 5-mL spoonfuls in water once or twice daily, preferably at mealtimes; CHILD (but see section 1.6) 2–12 years, 1 level 5-mL spoonful in water once or twice daily, preferably at mealtimes

Diarrhoea (section 1.4.1), 1 level 5-mL spoonful 3 times daily

Note May be difficult to obtain

Ispagel Orange® (LPC)

Granules, beige, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet, net price 30 sachets = £2.10. Label: 13, counselling, see above

Excipients include aspartame (section 9.4.1)

Dose 1 sachet in water 1–3 times daily, preferably after meals; CHILD (but see section 1.6) 2–12 years see *BNF for Children*

Regulan® (Procter & Gamble)

Powder, beige, sugar- and gluten-free, ispaghula husk 3.4 g/5.85-g sachet (orange or lemon/lime flavour). Net price 30 sachets = £2.44. Label: 13, counselling, see above

Excipients include aspartame (section 9.4.1)

Dose 1 sachet in 150 mL water 1–3 times daily, preferably after meals; CHILD (but see section 1.6) 2–6 years, see *BNF for Children*; 6–12 years 2.5–5 mL in water 1–3 times daily, preferably after meals

METHYLCELLULOSE

Indications see notes above

Cautions see under Ispaghula Husk

Contra-indications see under Ispaghula Husk; also infective bowel disease

Side-effects see under Ispaghula Husk

Dose

- See preparations below

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

Celevac® (Amdipharm)

Tablets, pink, scored, methylcellulose '450' 500 mg, net price 112-tab pack = £3.22. Counselling, see above and dose

Dose constipation and diarrhoea, 3–6 tablets twice daily; in constipation the dose should be taken with at least 300 mL liquid; in diarrhoea, ileostomy, and colostomy control, avoid liquid intake for 30 minutes before and after dose; CHILD 7–12 years see *BNF for Children*

STERCULIA

Indications see notes above

Cautions see under Ispaghula Husk

Contra-indications see under Ispaghula Husk

Side-effects see under Ispaghula Husk

Dose

- See under preparations below

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

Normacol® (Norgine)

Granules, coated, gluten-free, sterculia 62%. Net price 500 g = £5.94; 60 × 7-g sachets = £4.99. Label: 25, 27, counselling, see above

Dose 1–2 heaped 5-mL spoonfuls, or the contents of 1–2 sachets, washed down without chewing with plenty of liquid once or twice daily after meals; CHILD (but see section 1.6) 6–12 years half adult dose

Normacol Plus® (Norgine)

Granules, brown, coated, gluten-free, sterculia 62%, frangula (standardised) 8%. Net price 500 g = £6.34; 60 × 7 g sachets = £5.34. Label: 25, 27, counselling, see above

Dose constipation and after haemorrhoidectomy, 1–2 heaped 5-mL spoonfuls *or* the contents of 1–2 sachets washed down without chewing with plenty of liquid once or twice daily after meals; CHILD 6–12 years see *BNF for Children*

1.6.2 Stimulant laxatives

Stimulant laxatives include **bisacodyl**, **sodium picosulfate**, and members of the **anthraquinone** group, **senna** and **dantron**. The indications for dantron are limited (see below) by its potential carcinogenicity (based on *rodent* carcinogenicity studies) and evidence of genotoxicity. Powerful stimulants such as **cascara** (an anthraquinone) and **castor oil** are obsolete. **Docusate sodium** probably acts both as a stimulant and as a softening agent.

Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances (see section 1.6 for the use of stimulant laxatives in children).

Glycerol suppositories act as a rectal stimulant by virtue of the mildly irritant action of glycerol.

The **parasympathomimetics** bethanechol, distigmine, neostigmine, and pyridostigmine (see section 7.4.1 and section 10.2.1) enhance parasympathetic activity in the gut and increase intestinal motility. They are rarely used for their gastro-intestinal effects. Organic obstruction of the gut must first be excluded and they should not be used shortly after bowel anastomosis.

BISACODYL

Indications see under Dose

Cautions see notes above

Contra-indications see notes above, acute surgical abdominal conditions, acute inflammatory bowel disease, severe dehydration

Pregnancy see Pregnancy, p. 67

Side-effects see notes above; nausea and vomiting; colitis also reported; *suppositories*, local irritation

Dose

- Constipation, by mouth, 5–10 mg at night, increased if necessary to max. 20 mg at night; CHILD (but see section 1.6) 4–18 years 5–20 mg once daily, adjusted according to response

  By rectum in suppositories, 10 mg in the morning; CHILD (but see section 1.6) 2–18 years 5–10 mg once daily, adjusted according to response
- Before radiological procedures and surgery, by mouth, 10 mg in the morning and 10 mg in the evening on the day before procedure, and by rectum in suppositories, 10 mg 1–2 hours before procedure the following day; CHILD 4–18 years see *BNF for Children*

Note tablets act in 10–12 hours; suppositories act in 20–60 minutes

Bisacodyl (Non-proprietary)

Tablets, e/c, bisacodyl 5 mg. Net price 100 = £3.27. Label: 5, 25

Suppositories, bisacodyl 10 mg. Net price 12 = £1.11

Paediatric suppositories, bisacodyl 5 mg. Net price 5 = 94p

Note The brand name *Dulcolax®* (Boehringer Ingelheim) is used for bisacodyl tablets, net price 10-tab pack = 74p; suppositories (10 mg), 10 = £1.57; paediatric suppositories (5 mg), 5 = 94p

The brand names *Dulcolax® Pico Liquid* and *Dulcolax® Pico Perles* are used for sodium picosulfate preparations

DANTRON
(Danthron)

Indications only for constipation in terminally ill patients of all ages

Cautions see notes above; *rodent* studies indicate potential carcinogenic risk; avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies)—risk of irritation and excoriation

Contra-indications See notes above

Pregnancy manufacturers of co-danthramer and co-danthrusate advise avoid—no information available

Breast-feeding manufacturers of co-danthramer and co-danthrusate advise avoid—limited information available

Side-effects see notes above; urine may be coloured red

Dose

- See under preparations

With poloxamer '188' (as co-danthramer)

Note Co-danthramer suspension 5 mL = one co-danthramer capsule, **but** strong co-danthramer suspension 5 mL = two strong co-danthramer capsules

Co-danthramer (Non-proprietary) PoM

Capsules, co-danthramer 25/200 (dantron 25 mg, poloxamer '188' 200 mg). Net price 60-cap pack = £12.86. Label: 14, (urine red)

Dose 1–2 capsules at bedtime; CHILD 1 capsule at bedtime (restricted indications, see notes above)

Strong capsules, co-danthramer 37.5/500 (dantron 37.5 mg, poloxamer '188' 500 mg). Net price 60-cap pack = £15.55. Label: 14, (urine red)

Dose ADULT and CHILD over 12 years, 1–2 capsules at bedtime (restricted indications, see notes above)

Suspension, co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer '188' 200 mg/5 mL). Net price 300 mL = £11.27, 1 litre = £37.57. Label: 14, (urine red)

Dose 5–10 mL at night; CHILD 2.5–5 mL (restricted indications, see notes above)

Brands include *Codalax®* ⊞, *Danlax®*

Strong suspension, co-danthramer 75/1000 in 5 mL (dantron 75 mg, poloxamer '188' 1 g/5 mL). Net price 300 mL = £30.13. Label: 14, (urine red)

Dose ADULT and CHILD over 12 years, 5 mL at night (restricted indications, see notes above)

Brands include *Codalax Forte®* ⊞

With docusate sodium (as co-danthrusate)

Co-danthrusate (Non-proprietary) PoM

Capsules, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg). Net price 63-cap pack = £15.87. Label: 14, (urine red)

Dose 1–3 capsules at night; CHILD 6–12 years 1 capsule at night (restricted indications, see notes above)

Brands include *Normax®* ⊞

Suspension, yellow, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/5 mL). Net price 200 mL = £8.75. Label: 14, (urine red)

Dose 5–15 mL at night; CHILD 6–12 years 5 mL at night (restricted indications, see notes above)

Brands include *Normax®*

DOCUSATE SODIUM
(Dioctyl sodium sulphosuccinate)

Indications constipation, adjunct in abdominal radiological procedures

Cautions see notes above; do not give with liquid paraffin; rectal preparations not indicated if haemorrhoids or anal fissure

Contra-indications see notes above

Pregnancy not known to be harmful—manufacturer advises caution

Breast-feeding present in milk following oral administration—manufacturer advises caution; rectal administration not known to be harmful

Side-effects see notes above

Dose

- By mouth, chronic constipation, up to 500 mg daily in divided doses; CHILD (but see section 1.6) 6 months–2 years 12.5 mg 3 times daily, adjusted according to response (use paediatric solution); 2–12 years 12.5–25 mg 3 times daily, adjusted according to response (use paediatric oral solution)

  Note Oral preparations act within 1–2 days

  With barium meal, ADULT and CHILD over 12 years, 400 mg

Dioctyl® (UCB Pharma)

Capsules, yellow/white, docusate sodium 100 mg, net price 30-cap pack = £1.92, 100-cap pack = £6.40

Docusol® (Typharm)

Adult oral solution, sugar-free, docusate sodium 50 mg/5 mL, net price 300 mL = £5.49

Paediatric oral solution, sugar-free, docusate sodium 12.5 mg/5 mL, net price 300 mL = £5.29

Rectal preparations

Norgalax Micro-enema® (Norgine)

Enema, docusate sodium 120 mg in 10-g single-dose disposable packs. Net price 10-g unit = 57p

Dose ADULT and CHILD (but see section 1.6) over 12 years, 10-g unit

GLYCEROL

(Glycerin)

Indications constipation

Dose

- See below

Glycerol Suppositories, BP

(Glycerin Suppositories)

Suppositories, gelatin 140 mg, glycerol 700 mg, purified water to 1 g, net price 12 = £1.27 (1 g), £1.29 (2 g), £1.48 (4 g)

Dose 1 suppository moistened with water before use, when required. The usual sizes are for INFANT under 1 year, small (1-g mould), CHILD 1–12 years medium (2-g mould), ADULT and CHILD over 12 years, large (4-g mould)

SENNA

Indications constipation

Cautions see notes above

Contra-indications see notes above

Pregnancy see Pregnancy, p. 67

Breast-feeding not known to be harmful

Side-effects see notes above

Dose

- See under preparations

Note Acts in 8–12 hours

Senna (Non-proprietary)

Tablets, total sennosides (calculated as sennoside B) 7.5 mg. Net price 60 = £1.47

Dose 2–4 tablets, usually at night; initial dose should be low then gradually increased; CHILD (but see section 1.6) 2–6 years see *BNF for Children*; 6–18 years 1–4 tablets once daily, adjusted according to response

Note Lower dose on packs on sale to the public

Brands include *Senokot®* (NHS)

Manevac® (HFA Healthcare)

Granules, coated, senna fruit 12.4%, ispaghula 54.2%, net price 400 g = £7.45. Label: 25, counselling, administration

Excipients include sucrose 800 mg per level 5-mL spoonful of granules

Dose ADULT and CHILD over 12 years, 1–2 level 5-mL spoonfuls at night with at least 150 mL water, fruit juice, milk or warm drink

Counselling Preparations that swell in contact with liquid should always be carefully swallowed with water or appropriate fluid and should not be taken immediately before going to bed

Senokot® (Reckitt Benckiser)

Tablets (NHS), see above

Syrup, sugar-free, brown, total sennosides (calculated as sennoside B) 7.5 mg/5 mL, net price 500 mL = £2.69

Dose 10–20 mL, usually at bedtime; CHILD (but see section 1.6) 1 month–2 years see *BNF for Children*, 2–4 years 2.5–10 mL once daily, adjusted according to response; 4–18 years 2.5–20 mL once daily, adjusted according to response

Note Lower dose on packs on sale to the public

SODIUM PICOSULFATE

(Sodium picosulphate)

Indications constipation; bowel evacuation before abdominal radiological and endoscopic procedures on the colon, and surgery (section 1.6.5); acts within 6–12 hours

Cautions see notes above; active inflammatory bowel disease (avoid if fulminant)

Contra-indications see notes above; severe dehydration

Pregnancy see Pregnancy, p. 67

Breast-feeding not known to be present in milk but manufacturer advises avoid unless potential benefit outweighs risk

Side-effects see notes above

Dose

- 5–10 mg at night; CHILD (but see section 1.6) 1 month–4 years 2.5–10 mg once daily, adjusted according to response; 4–18 years 2.5–20 mg once daily, adjusted according to response

Note Sodium picosulfate doses in BNF may differ from those in product literature

Sodium Picosulfate (Non-proprietary)

Elixir, sodium picosulfate 5 mg/5 mL, net price 100 mL = £1.85

Note The brand name *Dulcolax® Pico Liquid* (Boehringer Ingelheim) is used for sodium picosulfate elixir 5 mg/5 mL

Dulcolax® Pico (Boehringer Ingelheim)

Perles® (= capsules), sodium picosulfate 2.5 mg, net price 20-cap pack = £1.93, 50-cap pack = £2.73

Note The brand name *Dulcolax®* is also used for bisacodyl tablets and suppositories

Bowel cleansing preparations

Section 1.6.5

Other stimulant laxatives

Unstandardised preparations of cascara, frangula, rhubarb, and senna should be **avoided** as their laxative action is unpredictable. Aloes, colocynth, and jalap should be **avoided** as they have a drastic purgative action.

1.6.3 Faecal softeners

Liquid paraffin, the traditional lubricant, has disadvantages (see below). Bulk laxatives (section 1.6.1) and non-ionic surfactant 'wetting' agents e.g. docusate sodium (section 1.6.2) also have softening properties. Such drugs are useful for oral administration in the management of haemorrhoids and anal fissure; glycerol (section 1.6.2) is useful for rectal use.

Enemas containing **arachis oil** (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

ARACHIS OIL

Indications see notes above

Dose

- See below

Arachis Oil Enema (Non-proprietary)

Enema, arachis (peanut) oil in 130-mL single-dose disposable packs. Net price 130 mL = £7.98

Dose to soften impacted faeces, 130 mL; the enema should be warmed before use; CHILD (but see section 1.6) under 3 years not recommended; over 3 years reduce adult dose in proportion to body-weight (medical supervision only), see *BNF for Children*

LIQUID PARAFFIN

Indications constipation

Cautions avoid prolonged use; contra-indicated in children under 3 years

Side-effects anal seepage of paraffin and consequent anal irritation after prolonged use, granulomatous reactions caused by absorption of small quantities of liquid paraffin (especially from the emulsion), lipoid pneumonia, and interference with the absorption of fat-soluble vitamins

Dose

- See under preparation

Liquid Paraffin Oral Emulsion, BP

Oral emulsion, liquid paraffin 5 mL, vanillin 5 mg, chloroform 0.025 mL, benzoic acid solution 0.2 mL, methylcellulose-20 200 mg, saccharin sodium 500 micrograms, water to 10 mL

Dose ADULT over 18 years, 10–30 mL at night when required

Counselling Should not be taken immediately before going to bed

1.6.4 Osmotic laxatives

Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with.

Lactulose is a semi-synthetic disaccharide which is not absorbed from the gastro-intestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms. It is therefore useful in the treatment of *hepatic encephalopathy*.

Macrogols are inert polymers of ethylene glycol which sequester fluid in the bowel; giving fluid with macrogols may reduce the dehydrating effect sometimes seen with osmotic laxatives.

Saline purgatives such as **magnesium hydroxide** are commonly abused but are satisfactory for occasional use; adequate fluid intake should be maintained. **Magnesium salts** are useful where rapid bowel evacuation is required. **Sodium salts** should be avoided as they may give rise to sodium and water retention in susceptible individuals. **Phosphate enemas** are useful in bowel clearance before radiology, endoscopy, and surgery.

LACTULOSE

Indications constipation (may take up to 48 hours to act), hepatic encephalopathy (portal systemic encephalopathy)

Cautions lactose intolerance; **interactions:** Appendix 1 (lactulose)

Contra-indications galactosaemia, intestinal obstruction

Pregnancy not known to be harmful; see also Pregnancy, p. 67

Side-effects nausea (can be reduced by administration with water, fruit juice or with meals), vomiting, flatulence, cramps, and abdominal discomfort

Dose

- See under preparations below

Lactulose (Non-proprietary)

Solution, lactulose 3.1–3.7 g/5 mL with other ketoses. Net price 300-mL pack = £2.10, 500-mL pack = £2.59

Dose constipation, initially 15 mL twice daily, adjusted according to response; CHILD (but see section 1.6) under 1 year 2.5 mL twice daily, adjusted according to response; 1–5 years 2.5–10 mL twice daily, adjusted according to response; 5–18 years 5–20 mL twice daily, adjusted according to response

Hepatic encephalopathy, 30–50 mL 3 times daily, subsequently adjusted to produce 2–3 soft stools daily; CHILD 12–18 years see *BNF for Children*

Note Lactulose doses in BNF may differ from those in product literature

Brands include *Duphalac®*, *Lactugal®*, *Regulose®*

MACROGOLS

(Polyethylene glycols)

Indications see preparations below

Cautions discontinue if symptoms of fluid and electrolyte disturbance; see also preparations below

Contra-indications intestinal perforation or obstruction, paralytic ileus, severe inflammatory conditions of the intestinal tract (such as Crohn's disease, ulcerative colitis, and toxic megacolon), see also preparations below

Pregnancy manufacturers advice use only if essential—no information available

Breast-feeding manufacturers advice use only if essential—no information available

Side-effects abdominal distension and pain, nausea, flatulence

Dose

- See preparations below

Macrogol Oral Powder, Compound (Non-proprietary)

Oral powder, macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet, net price 20-sachet pack = £4.45, 30-sachet pack = £6.68. Label: 13

Brands include *Laxido® Orange*, *Molaxole®*

Cautions patients with cardiovascular impairment should not take more than 2 sachets in any 1 hour

Dose chronic constipation, ADULT and CHILD over 12 years, 1–3 sachets daily in divided doses usually for up to 2 weeks; contents of each sachet dissolved in half a glass (approx. 125 mL) of water; maintenance, 1–2 sachets daily

Faecal impaction, ADULT and CHILD over 12 years, 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days

After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Movicol® (Norgine)

Oral powder, macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet, net price 20-sachet pack (lime and lemon flavour) = £4.45, 30-sachet pack (lime- and lemon- or chocolate- or plain-flavoured) = £6.68, 50–sachet pack (lime- and lemon- or plain-flavoured) = £11.13. Label: 13

Note Amount of potassium chloride varies according to flavour of *Movicol®* as follows: plain-flavour (sugar-free) = 50.2 mg/sachet; lime and lemon flavour = 46.6 mg/sachet;

chocolate flavour = 31.7 mg/sachet. 1 sachet when reconstituted with 125 mL water provides K^+ 5.4 mmol/litre

Cautions patients with cardiovascular impairment should not take more than 2 sachets in any 1 hour

Dose chronic constipation, ADULT and CHILD over 12 years, 1–3 sachets daily in divided doses usually for up to 2 weeks; contents of each sachet dissolved in half a glass (approx. 125 mL) of water; maintenance, 1–2 sachets daily

Faecal impaction, ADULT and CHILD over 12 years, 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days

After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Movicol®-Half (Norgine)

Oral powder, sugar-free, macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet, net price 20-sachet pack (lime and lemon flavour) = £2.67, 30-sachet pack = £4.01. Label: 13

Cautions patients with cardiovascular impairment should not take more than 4 sachets in any 1 hour

Dose chronic constipation, ADULT and CHILD over 12 years, 2–6 sachets daily in divided doses usually for up to 2 weeks; content of each sachet dissolved in quarter of a glass (approx. 60–65 mL) of water; maintenance, 2–4 sachets daily

Faecal impaction, ADULT and CHILD over 12 years, 16 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days

After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Movicol® Paediatric Plain (Norgine) PoM

Oral powder, sugar-free, macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 25.1 mg/sachet, net price 30-sachet pack = £4.45. Label: 13

Cautions *with high doses*, impaired gag reflex, reflux oesophagitis, impaired consciousness

Contra-indications cardiovascular impairment; renal impairment

Dose chronic constipation and prevention of faecal impaction, CHILD under 2 years see *BNF for Children*; 2–6 years 1 sachet daily, adjusted according to response (max. 4 sachets daily); 6–12 years 2 sachets daily, adjusted according to response (max. 4 sachets daily)

Faecal impaction, CHILD under 5 years see *BNF for Children*; 5–12 years 4 sachets on first day then increased in steps of 2 sachets daily to 12 sachets daily (taken in divided doses over 12 hours each day until impaction resolves); content of each sachet dissolved in quarter of a glass (approx. 60–65 mL) of water

After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours

MAGNESIUM SALTS

Indications see under preparations below

Cautions elderly and debilitated; see also notes above; **interactions:** Appendix 1 (antacids)

Contra-indications acute gastro-intestinal conditions

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid or reduce dose; increased risk of toxicity

Side-effects colic

Dose

- See preparations

Magnesium hydroxide

Magnesium Hydroxide Mixture, BP

Aqueous suspension containing about 8% hydrated magnesium oxide. Do not store in cold place

Dose constipation, 30–45 mL with water at bedtime when required; CHILD 3–12 years, 5–10 mL with water at bedtime when required

Magnesium hydroxide with liquid paraffin

Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP

Oral emulsion, 25% liquid paraffin in aqueous suspension containing 6% hydrated magnesium oxide

Dose constipation, 5–20 mL when required

Note Liquid paraffin and magnesium hydroxide preparations on sale to the public include: *Milpar®* PHS

Magnesium sulphate

Magnesium Sulphate

Label: 13, 23

Dose rapid bowel evacuation (acts in 2–4 hours) 5–10 g in a glass of water preferably before breakfast

Note Magnesium sulphate is on sale to the public as Epsom Salts

Bowel cleansing preparations

Section 1.6.5

PHOSPHATES (RECTAL)

Indications rectal use in constipation; bowel evacuation before abdominal radiological procedures, endoscopy, and surgery

Cautions elderly and debilitated; *with enema*, electrolyte disturbances, congestive heart failure, ascites, uncontrolled hypertension, maintain adequate hydration

Contra-indications acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption)

Renal impairment use enema with caution

Side-effects local irritation; *with enema*, electrolyte disturbances

Dose

- See under preparations

Carbalax® (Chemidex)

Suppositories, sodium acid phosphate (anhydrous) 1.3 g, sodium bicarbonate 1.08 g, net price 12 = £2.01

Dose constipation, ADULT and CHILD over 12 years, 1 suppository, inserted 30 minutes before evacuation required; moisten with water before use

Fleet® Ready-to-use Enema (Casen-Fleet)

Enema, sodium acid phosphate 21.4 g, sodium phosphate 9.4 g/118 mL, net price 133-mL pack (delivers 118 mL dose) with standard tube = 57p

Dose ADULT and CHILD (but see section 1.6) over 12 years, 118 mL; CHILD 3–12 years, on doctor's advice only (under 3 years not recommended)

Phosphates Enema BP Formula B

Enema, sodium dihydrogen phosphate dihydrate 12.8 g, disodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL. Net price 128 mL with standard tube = £2.98, with long rectal tube = £3.98

Dose 128 mL; CHILD (but see section 1.6) over 3 years, reduced according to body weight see *BNF for Children*

SODIUM CITRATE (RECTAL)

Indications rectal use in constipation

Cautions elderly and debilitated; see also notes above

Contra-indications acute gastro-intestinal conditions

Dose

- See under preparations

Micolette Micro-enema® (Pinewood)

Enema, sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, glycerol 625 mg, together with potassium sorbate and sorbitol in a viscous solution,

in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 38p
Dose ADULT and CHILD over 3 years, 5–10 mL (but see section 1.6)

Micralax Micro-enema® (UCB Pharma)
Enema, sodium citrate 450 mg, sodium alkylsulphoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 41p
Dose ADULT and CHILD over 3 years, 5 mL (but see section 1.6)

Relaxit Micro-enema® (Crawford)
Enema, sodium citrate 450 mg, sodium lauryl sulphate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 32p
Dose ADULT and CHILD (but see section 1.6) 5 mL (insert only half nozzle length in child under 3 years)

1.6.5 Bowel cleansing preparations

Bowel cleansing preparations are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents. They are **not** treatments for constipation.

Cautions Renal function should be measured before starting treatment. Bowel cleansing preparations should be used with caution in patients with fluid and electrolyte disturbances. Hypovolaemia should be corrected before administration of bowel cleansing preparations. Adequate hydration should be maintained during treatment. Bowel cleansing preparations should be used with caution in colitis (avoid if acute severe colitis), in children, in the elderly, or in those who are debilitated. They should also be used with caution in patients with an impaired gag reflex, reduced levels of consciousness, or possibility of regurgitation or aspiration. Other oral drugs should not be taken one hour before or after administration of bowel cleansing preparations because absorption may be impaired.

Contra-indications Bowel cleansing preparations are contra-indicated in patients with gastro-intestinal obstruction or perforation, gastric retention, acute severe colitis, or toxic megacolon.

Side-effects Side-effects of bowel cleansing preparations include nausea, vomiting, abdominal pain (usually transient—reduced by taking more slowly), and abdominal distention. Less frequent side-effects include headache, dizziness, dehydration, and electrolyte disturbances.

MACROGOLS

Indications see notes above
Cautions see notes above; also heart failure; acute inflammatory bowel disease
Contra-indications see notes above
Pregnancy manufacturers advise use only if essential—no information available
Breast-feeding manufacturers advise use only if essential—no information available
Side-effects see notes above; also fatigue, sleep disturbances, and anal discomfort
Dose
- See preparations

Klean-Prep® (Norgine)
Oral powder, sugar-free, macrogol '3350' (polyethylene glycol '3350') 59 g, anhydrous sodium sulphate 5.685 g, sodium bicarbonate 1.685 g, sodium chloride 1.465 g, potassium chloride 743 mg/sachet, net price 4 sachets = £8.23. Label: 10, patient information leaflet, 13, counselling
Excipients include aspartame (section 9.4.1)
Electrolytes 1 sachet when reconstituted with 1 litre of water provides Na^+ 125 mmol, K^+ 10 mmol, Cl^- 35 mmol, HCO_3^- 20 mmol
Dose bowel evacuation before surgery, colonoscopy, or radiological examination, a glass (approx. 250 mL) of reconstituted solution every 10–15 minutes, or by nasogastric tube 20–30 mL/minute, starting on the day before procedure until 4 litres have been consumed; alternatively, administration may be divided into two (2 litres of reconstituted solution taken on the evening before procedure and 2 litres of reconstituted solution taken on the morning of procedure). Treatment can be stopped if bowel motions become watery and clear. To facilitate gastric emptying, domperidone or metoclopramide may be given 30 minutes before starting; CHILD 12–18 years see *BNF for Children*
Counselling 1 sachet should be reconstituted with 1 litre of water. Flavouring such as clear fruit cordials may be added if required. Solid food should not be taken for at least 2 hours before starting treatment. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours

Moviprep® (Norgine)
Oral powder, lemon- or orange-flavoured, *Sachet A* (containing macrogol '3350' (polyethylene glycol '3350') 100 g, anhydrous sodium sulphate 7.5 g, sodium chloride 2.691 g, potassium chloride 1.015 g) and *Sachet B* (containing ascorbic acid 4.7 g, sodium ascorbate 5.9 g), net price 4-sachet pack (2 each of sachet A and B) = £9.87. Label: 10, patient information leaflet, 13, counselling, see below
Excipients include aspartame (section 9.4.1)
Electrolytes 1 pair of sachets (A+B) when reconstituted with 1 litre of water provides Na^+ 181.6 mmol (Na^+ 56.2 mmol absorbable), K^+ 14.2 mmol, Cl^- 59.8 mmol
Contra-indications G6PD deficiency
Renal impairment caution if eGFR less than 30 mL/minute/1.73 m^2
Dose bowel evacuation for surgery, colonoscopy or radiological examination, ADULT over 18 years, 2 litres of reconstituted solution on the evening before procedure *or* 1 litre of reconstituted solution on the evening before procedure and 1 litre of reconstituted solution early on the morning of procedure; treatment should be completed at least 1 hour before colonoscopy
Counselling One pair of sachets (A and B) should be reconstituted in 1 litre of water and taken over 1–2 hours. Solid food should not be taken during treatment until procedure completed. 1 litre of other clear fluid should also be taken during treatment. Treatment can be stopped if bowel motions become watery and clear

MAGNESIUM CITRATE

Reconstitution of a sachet containing 11.57 g magnesium carbonate and 17.79 g anhydrous citric acid produces a solution containing magnesium citrate

Indications see preparations
Cautions see notes above
Contra-indications see notes above
Hepatic impairment avoid in hepatic coma if risk of renal failure
Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2—risk of hypermagnesaemia
Pregnancy caution
Breast-feeding caution
Side-effects see notes above
Dose
- See preparations

Citramag® (Sanochemia)

Oral powder, sugar-free, effervescent, magnesium carbonate 11.57 g, anhydrous citric acid 17.79 g/sachet, net price 10-sachet pack (lemon and lime flavour) = £17.20. Label: 10, patient information leaflet, 13, counselling, see below

Electrolytes Mg^{2+} 118 mmol/sachet

Dose bowel evacuation for surgery, colonoscopy or radiological examination, on day before procedure, 1 sachet at 8 a.m. and 1 sachet between 2 and 4 p.m.; CHILD 5–10 years one-third adult dose; over 10 years and frail ELDERLY one-half adult dose

Counselling One sachet should be reconstituted with 200 mL of hot water; the solution should be allowed to cool for approx. 30 minutes before drinking. Low residue or fluid only diet (e.g. water, fruit squash, clear soup, black tea or coffee) recommended before procedure (according to prescriber's advice) and copious intake of clear fluids recommended until procedure

PHOSPHATES (ORAL)

Indications see preparations

Cautions see notes above; also cardiac disease (avoid in congestive cardiac failure)

Contra-indications see notes above; also ascites; congestive cardiac failure

Hepatic impairment use with caution in cirrhosis; avoid in ascites

Renal impairment avoid if eGFR less than 60 mL/minute/1.73 m^2

Pregnancy caution

Breast-feeding caution

Side-effects see notes above; also chest pain, arrhythmias, asthenia, and renal failure

Dose

- See preparations

OsmoPrep® (TMC)

Tablets, monobasic sodium phosphate monohydrate 1.102 g, disodium phosphate 398 mg, net price 32-tab pack = £8.50. Label: 10, patient information leaflet, counselling, see below

Electrolytes Na^+ 13.6 mmol, Mg^{2+} 0.34 mmol, phosphate 10.8 mmol/tablet

Dose bowel evacuation before diagnostic procedure, ADULT over 18 years, 4 tablets every 15 minutes until a total of 20 tablets have been consumed on the evening before procedure, then on the next day (starting 3–5 hours before procedure) 4 tablets every 15 minutes until a total of 12 tablets have been consumed; do not repeat course within 7 days

Counselling On the day before procedure, a light, low-fibre breakfast may be consumed in the morning, clear liquid diet recommended after 12 noon. Each dose of 4 tablets to be taken with 250 mL clear liquid. Copious intake of water or other clear liquids recommended during treatment

Fleet Phospho-soda® (Casen-Fleet)

Oral solution, sugar-free, sodium dihydrogen phosphate dihydrate 24.4 g, disodium phosphate dodecahydrate 10.8 g/45 mL. Net price 2 × 45-mL bottles = £4.79. Label: 10, patient information leaflet, counselling

Electrolytes Na^+ 217 mmol, phosphate 186 mmol/45 mL

Dose bowel evacuation before colonic surgery, colonoscopy or radiological examination, ADULT over 18 years, 45 mL diluted with half a glass (120 mL) of cold water, followed by one full glass (240 mL) of cold water

Timing of doses is dependent on the time of the procedure

For morning procedure, first dose should be taken at 7 a.m. and second at 7 p.m. on day before the procedure

For afternoon procedure, first dose should be taken at 7 p.m. on day before and second dose at 7 a.m. on day of the procedure

Acts within half to 6 hours of first dose

Counselling Intake of solid food should be stopped for at least 6 hours before starting treatment and until procedure completed. Copious intake of water or other clear fluids (e.g. clear soup, strained fruit juice without pulp, black tea or coffee) recommended until midnight before morning procedure and until 8 a.m. before afternoon procedure. At least one glass (approx 240 mL) of water or other clear fluid should also be taken immediately before each dose

SODIUM PICOSULFATE WITH MAGNESIUM CITRATE

Indications see preparations

Cautions see notes above; also recent gastro-intestinal surgery; cardiac disease (avoid in congestive cardiac failure)

Contra-indications see notes above; also gastro-intestinal ulceration; ascites; congestive cardiac failure

Hepatic impairment avoid in hepatic coma if risk of renal failure

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2—risk of hypermagnesaemia

Pregnancy caution

Breast-feeding caution

Side-effects see notes above; also anal discomfort, sleep disturbances, fatigue, and rash

Dose

- See preparations

CitraFleet® (Casen-Fleet)

Oral powder, sodium picosulfate 10 mg/sachet, with magnesium citrate, net price 2-sachet pack (lemon-flavoured) = £3.25. Label: 10, patient information leaflet, 13, counselling, see below

Electrolytes K^+ 5 mmol, Mg^{2+} 86 mmol/sachet

Dose bowel evacuation on day before radiological examination, endoscopy, or surgery, ADULT over 18 years, 1 sachet before 8 a.m. then 1 sachet 6–8 hours later

Acts within 3 hours of first dose

Counselling One sachet should be reconstituted with 150 mL (approx. half a glass) of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking. Low residue diet recommended on the day before procedure and copious intake of water or other clear fluids recommended during treatment

Picolax® (Ferring)

Oral powder, sugar-free, sodium picosulfate 10 mg/sachet, with magnesium citrate, net price 20-sachet pack = £33.90. Label: 10, patient information leaflet, 13, counselling, see below

Electrolytes K^+ 5 mmol, Mg^{2+} 87 mmol/sachet

Dose bowel evacuation on day before radiological procedure, endoscopy, or surgery, ADULT and CHILD over 9 years, 1 sachet before 8 a.m. then 1 sachet 6–8 hours later; CHILD 1–2 years, quarter sachet before 8 a.m. then quarter sachet 6–8 hours later; 2–4 years, half sachet before 8 a.m. then half sachet 6–8 hours later; 4–9 years, 1 sachet before 8 a.m. then half sachet 6–8 hours later

Acts within 3 hours of first dose

Counselling One sachet should be reconstituted with 150 mL (approx. half a glass) of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking. Low residue diet recommended on the day before procedure and copious intake of water or other clear fluids recommended during treatment

1.6.6 Peripheral opioid-receptor antagonists

Methylnaltrexone is a peripherally acting opioid-receptor antagonist that is licensed for the treatment of opioid-induced constipation in patients receiving palliative care, when response to other laxatives is inade-

quate; it should be used as an adjunct to existing laxative therapy. Methylnaltrexone does not alter the central analgesic effect of opioids. For the prevention of opioid-induced constipation in palliative care, see p. 22.

METHYLNALTREXONE BROMIDE

Indications opioid-induced constipation in terminally ill patients, when response to other laxatives is inadequate

Cautions diverticular disease; faecal impaction; patients with colostomy or peritoneal catheter

Contra-indications gastro-intestinal obstruction; acute surgical abdominal conditions

Hepatic impairment manufacturer advises avoid in severe hepatic impairment—no information available

Renal impairment if eGFR less than 30 mL/minute/1.73 m^2, reduce dose as follows: body-weight under 62 kg, 75 micrograms/kg on alternate days; body-weight 62–114 kg, 8 mg on alternate days; body-weight over 114 kg, 75 micrograms/kg on alternate days

Pregnancy toxicity at high doses in *animal* studies—manufacturer advises avoid unless essential

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—present in milk in *animal* studies

Side-effects abdominal pain, nausea, diarrhoea, flatulence; dizziness; injection site reactions, hyperhidrosis; also reported gastro-intestinal perforation

Dose

- By subcutaneous injection, ADULT over 18 years, body-weight under 38 kg, 150 micrograms/kg on alternate days; body-weight 38–62 kg, 8 mg on alternate days; body-weight 62–114 kg, 12 mg on alternate days; body-weight over 114 kg, 150 micrograms/kg on alternate days; may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day; rotate sites of injection; max. duration of treatment 4 months

Note May act within 30–60 minutes

Relistor® (Wyeth) ▼ PoM

Injection, methylnaltrexone bromide 20 mg/mL, net price 0.6-mL vial = £21.05, 7-vial pack (with syringes and needles) = £147.35

1.6.7 5HT$_4$-receptor agonists

Prucalopride is a selective serotonin 5HT$_4$-receptor agonist with prokinetic properties. It is licensed for the treatment of chronic constipation in women, when other laxatives have failed to provide an adequate response. Headache and gastro-intestinal symptoms (including abdominal pain, nausea, and diarrhoea) are the most frequent side-effects. The side-effects generally occur at the start of treatment and are usually transient.

PRUCALOPRIDE

Indications chronic constipation in women when other laxatives fail to provide an adequate response

Cautions history of arrhythmias or ischaemic heart disease; concomitant use with drugs that prolong QT interval; severe, unstable chronic illness

Contra-indications intestinal perforation or obstruction; severe inflammatory conditions of the intestinal tract (such as Crohn's disease, ulcerative colitis, and toxic megacolon)

Hepatic impairment max. 1 mg daily in severe impairment

Renal impairment max. 1 mg daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid and recommends effective contraception during treatment

Breast-feeding manufacturer advises avoid—present in milk

Side-effects nausea, vomiting, abdominal pain, dyspepsia, flatulence, diarrhoea, rectal bleeding; headache, dizziness, fatigue; polyuria; *less commonly* anorexia, palpitation, tremor, and fever

Dose

- ADULT over 18 years, 2 mg once daily; ELDERLY over 65 years, initially 1 mg once daily, increased if necessary to 2 mg once daily

Note Review treatment if no response after 4 weeks

Resolor® (Movetis) ▼ PoM

Tablets, f/c, prucalopride (as succinate) 1 mg (white), net price 28-tab pack = £38.69; 2 mg (pink), 28-tab pack = £59.52

1.7 Local preparations for anal and rectal disorders

1.7.1 Soothing haemorrhoidal preparations
1.7.2 Compound haemorrhoidal preparations with corticosteroids
1.7.3 Rectal sclerosants
1.7.4 Management of anal fissures

Anal and perianal pruritus, soreness, and excoriation are best treated by application of bland ointments and suppositories (section 1.7.1). These conditions occur commonly in patients suffering from haemorrhoids, fistulas, and proctitis. Cleansing with attention to any minor faecal soiling, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran (section 1.6.1) and a high residue diet are helpful. In proctitis these measures may supplement treatment with corticosteroids or sulfasalazine (see section 1.5).

When necessary, topical preparations containing **local anaesthetics** (section 1.7.1) or **corticosteroids** (section 1.7.2) are used, provided perianal thrush has been excluded. Perianal thrush is treated with a topical antifungal preparation (section 13.10.2).

For the management of *anal fissures*, see section 1.7.4.

1.7.1 Soothing haemorrhoidal preparations

Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may give symptomatic relief in haemorrhoids. Many proprietary preparations also contain lubricants, vasoconstrictors, or mild antiseptics.

Local anaesthetics are used to relieve pain associated with *haemorrhoids* and *pruritus ani* but good evidence

is lacking. Lidocaine ointment (section 15.2) is used before emptying the bowel to relieve pain associated with *anal fissure*. Alternative local anaesthetics include tetracaine, cinchocaine (dibucaine), and pramocaine (pramoxine), but they are more irritant. Local anaesthetic ointments can be absorbed through the rectal mucosa therefore excessive application should be **avoided**, particularly in infants and children. Preparations containing local anaesthetics should be used for short periods only (no longer than a few days) since they may cause sensitisation of the anal skin.

1.7.2 Compound haemorrhoidal preparations with corticosteroids

Corticosteroids are often combined with local anaesthetics and soothing agents in preparations for haemorrhoids. They are suitable for occasional short-term use after exclusion of infections, such as herpes simplex; prolonged use can cause atrophy of the anal skin. See section 13.4 for general comments on topical corticosteroids and section 1.7.1 for comment on local anaesthetics.

Children Haemorrhoids in children are rare. Treatment is usually symptomatic and the use of a locally applied cream is appropriate for short periods; however, local anaesthetics can cause stinging initially and this may aggravate the child's fear of defaecation.

Anugesic-HC® (Pfizer) PoM

Cream, benzyl benzoate 1.2%, bismuth oxide 0.875%, hydrocortisone acetate 0.5%, Peru balsam 1.85%, pramocaine hydrochloride 1%, zinc oxide 12.35%. Net price 30 g (with rectal nozzle) = £3.71

Dose apply night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

Suppositories, buff, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 5 mg, Peru balsam 49 mg, pramocaine hydrochloride 27 mg, zinc oxide 296 mg, net price 12 = £2.69

Dose insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

Anusol-HC® (McNeil) PoM

Ointment, benzyl benzoate 1.25%, bismuth oxide 0.875%, bismuth subgallate 2.25%, hydrocortisone acetate 0.25%, Peru balsam 1.875%, zinc oxide 10.75%. Net price 30 g (with rectal nozzle) = £3.29

Dose apply night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

Note A proprietary brand (*Anusol Plus HC®* ointment) is on sale to the public

Suppositories, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 10 mg, Peru balsam 49 mg, zinc oxide 296 mg. Net price 12 = £2.31

Dose insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

Note A proprietary brand (*Anusol Plus HC®* suppositories) is on sale to the public

Perinal® (Dermal)

Spray application, hydrocortisone 0.2%, lidocaine hydrochloride 1%. Net price 30-mL pack = £6.11

Dose ADULT and CHILD over 14 years, spray once over the affected area up to 3 times daily; do not use for longer than 7 days without medical advice; CHILD under 14 years on medical advice only

Proctofoam HC® (Meda) PoM

Foam in aerosol pack, hydrocortisone acetate 1%, pramocaine hydrochloride 1%. Net price 21.2-g pack (approx. 40 applications) with applicator = £5.06

Dose haemorrhoids and proctitis, 1 applicatorful (4–6 mg hydrocortisone acetate, 4–6 mg pramocaine hydrochloride) by rectum 2–3 times daily and after each bowel movement (max. 4 times daily); do not use for longer than 7 days; CHILD not recommended

Proctosedyl® (Sanofi-Aventis) PoM

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%. Net price 30 g = £10.34 (with cannula)

Dose apply morning and night and after a bowel movement, externally or by rectum; do not use for longer than 7 days

Suppositories, cinchocaine (dibucaine) hydrochloride 5 mg, hydrocortisone 5 mg. Net price 12 = £4.66

Dose insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Scheriproct® (Bayer Schering) PoM

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, prednisolone hexanoate 0.19%. Net price 30 g = £2.94

Dose apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

Suppositories, cinchocaine (dibucaine) hydrochloride 1 mg, prednisolone hexanoate 1.3 mg. Net price 12 = £1.38

Dose insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily)

Ultraproct® (Meadow) PoM

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, fluocortolone caproate 0.095%, fluocortolone pivalate 0.092%, net price 30 g (with rectal nozzle) = £4.57

Dose apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

Suppositories, cinchocaine (dibucaine) hydrochloride 1 mg, fluocortolone caproate 630 micrograms, fluocortolone pivalate 610 micrograms, net price 12 = £2.15

Dose insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily) then 1 suppository every other day for 1 week

Uniroid-HC® (Chemidex) PoM

Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%. Net price 30 g (with applicator) = £4.23

Dose ADULT and CHILD over 12 years, apply twice daily and after a bowel movement, externally or by rectum; do not use for longer than 7 days; CHILD under 12 years on medical advice only

Suppositories, cinchocaine (dibucaine) hydrochloride 5 mg, hydrocortisone 5 mg. Net price 12 = £1.91

Dose ADULT and CHILD over 12 years, insert 1 suppository twice daily and after a bowel movement; do not use for longer than 7 days

Xyloproct® (AstraZeneca) PoM
Ointment (water-miscible), aluminium acetate 3.5%, hydrocortisone acetate 0.275%, lidocaine 5%, zinc oxide 18%, net price 20 g (with applicator) = £2.26
Dose apply several times daily; short-term use only

1.7.3 Rectal sclerosants

Oily phenol injection is used to inject haemorrhoids particularly when unprolapsed.

PHENOL

Indications see notes above
Side-effects irritation, tissue necrosis

Oily Phenol Injection, BP PoM
phenol 5% in a suitable fixed oil. Net price 5-mL amp = £4.65
Dose 2–3 mL into the submucosal layer at the base of the pile; several injections may be given at different sites, max. total injected 10 mL at any one time

1.7.4 Management of anal fissures

The management of *anal fissures* requires stool softening by increasing dietary fibre in the form of bran or by using a bulk-forming laxative. Short-term use of local anaesthetic preparations may help (section 1.7.1). If these measures are inadequate, the patient should be referred for specialist treatment in hospital. The use of a topical nitrate (e.g. glyceryl trinitrate 0.4% ointment) may be considered. Before considering surgery, topical diltiazem 2% may be used twice daily [unlicensed indication] in patients with chronic anal fissures unresponsive to topical nitrates.

The *Scottish Medicines Consortium* (p. 4) has advised (January 2008) that glyceryl trinitrate 0.4% ointment (*Rectogesic®*) is **not** recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

GLYCERYL TRINITRATE

Indications anal fissure; angina, left ventricular failure (section 2.6.1); extravasation (section 10.3)
Cautions section 2.6.1
Contra-indications section 2.6.1
Hepatic impairment section 2.6.1
Renal impairment section 2.6.1
Pregnancy section 2.6.1
Breast-feeding section 2.6.1
Side-effects section 2.6.1; also diarrhoea, burning, itching, and rectal bleeding
Dose
- See preparations

Rectogesic® (ProStrakan) PoM
Rectal ointment, glyceryl trinitrate 0.4%, net price 30 g = £34.80
Excipients include lanolin, propylene glycol
Dose ADULT over 18 years, apply 2.5 cm of ointment to anal canal every 12 hours until pain stops; max. duration of use 8 weeks
Note 2.5 cm of ointment contains glyceryl trinitrate 1.5 mg; discard tube 8 weeks after first opening

1.8 Stoma care

Prescribing for patients with stoma calls for special care. The following is a brief account of some of the main points to be borne in mind.

Enteric-coated and *modified-release* preparations are **unsuitable**, particularly in patients with an ileostomy, as there may not be sufficient release of the active ingredient.

Laxatives Enemas and washouts should **not** be prescribed for patients with an ileostomy as they may cause rapid and severe loss of water and electrolytes.

Colostomy patients may suffer from constipation and whenever possible should be treated by increasing fluid intake or dietary fibre. **Bulk-forming drugs** (section 1.6.1) should be tried. If they are insufficient, as small a dose as possible of senna (section 1.6.2) should be used.

Antidiarrhoeals Drugs such as **loperamide**, **codeine phosphate**, or **co-phenotrope** (diphenoxylate with atropine) are effective. Bulk-forming drugs (section 1.6.1) may be tried but it is often difficult to adjust the dose appropriately.

Antibacterials should **not** be given for an episode of acute diarrhoea.

Antacids The tendency to diarrhoea from magnesium salts or constipation from aluminium salts may be increased in these patients.

Diuretics Diuretics should be used with caution in patients with an ileostomy as they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a **potassium-sparing** diuretic (see section 2.2.3).

Digoxin Patients with a stoma are particularly susceptible to hypokalaemia if on digoxin therapy and potassium supplements or a potassium-sparing diuretic may be advisable (for comment see section 9.2.1.1).

Potassium supplements Liquid formulations are preferred to modified-release formulations (see above).

Analgesics Opioid analgesics (see section 4.7.2) may cause troublesome constipation in colostomy patients. When a non-opioid analgesic is required **paracetamol** is usually suitable but anti-inflammatory analgesics may cause gastric irritation and bleeding.

Iron preparations Iron preparations may cause loose stools and sore skin in these patients. If this is troublesome and if iron is definitely indicated an intramuscular iron preparation (see section 9.1.1.2) should be used. Modified-release preparations should be **avoided** for the reasons given above.

Care of stoma Patients are usually given advice about the use of *cleansing agents*, *protective creams*, *lotions*, *deodorants*, or *sealants* whilst in hospital, either by the surgeon or by stoma care nurses. Voluntary organisations offer help and support to patients with stoma.

1.9 Drugs affecting intestinal secretions

1.9.1 Drugs affecting biliary composition and flow
1.9.2 Bile acid sequestrants
1.9.3 Aprotinin
1.9.4 Pancreatin

1.9.1 Drugs affecting biliary composition and flow

The use of laparoscopic cholecystectomy and of endoscopic biliary techniques has limited the place of the bile acid **ursodeoxycholic acid** in gallstone disease. Ursodeoxycholic acid is suitable for patients with unimpaired gall bladder function, small or medium-sized radiolucent stones, and whose mild symptoms are not amenable to other treatment; it should be used cautiously in those with liver disease (but see below). Patients should be given dietary advice (including avoidance of excessive cholesterol and calories) and they require radiological monitoring. Long-term prophylaxis may be needed after complete dissolution of the gallstones has been confirmed because they may recur in up to 25% of patients within one year of stopping treatment.

Ursodeoxycholic acid is also used in primary biliary cirrhosis; liver tests improve in most patients but the effect on overall survival is uncertain.

URSODEOXYCHOLIC ACID

Indications see under Dose and under preparations

Cautions see notes above; **interactions**: Appendix 1 (ursodeoxycholic acid)

Contra-indications radio-opaque stones, non-functioning gall bladder, inflammatory diseases and other conditions of the small intestine, colon and liver which interfere with entero-hepatic circulation of bile salts

Hepatic impairment avoid in chronic liver disease (but used in primary biliary cirrhosis)

Pregnancy no evidence of harm but manufacturer advises avoid

Breast-feeding not known to be harmful but manufacturer advises avoid

Side-effects nausea, vomiting, diarrhoea; gallstone calcification; pruritus

Dose

- Dissolution of gallstones, 8–12 mg/kg daily as a single dose at bedtime *or* in two divided doses, for up to 2 years; treatment is continued for 3–4 months after stones dissolve
- Primary biliary cirrhosis, see under *Ursofalk®*

Ursodeoxycholic Acid (Non-proprietary) PoM
Tablets, ursodeoxycholic acid 150 mg, net price 60-tab pack = £20.48. Label: 21

Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £38.86. Label: 21

Destolit® (Norgine) PoM
Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-tab pack = £17.67. Label: 21

Urdox® (Wockhardt) PoM
Tablets, f/c, ursodeoxycholic acid 300 mg, net price 60-tab pack = £26.50. Label: 21

Ursofalk® (Dr Falk) PoM
Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £30.17, 100-cap pack = £31.88. Label: 21

Suspension, sugar-free, ursodeoxycholic acid 250 mg/5 mL, net price 250 mL = £26.98. Label: 21
Dose primary biliary cirrhosis, 10–15 mg/kg daily as a single daily dose or in 2–4 divided doses
Dissolution of gallstones, see Dose, above

Ursogal® (Galen) PoM
Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-tab pack = £17.05. Label: 21

Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £30.50. Label: 21

Other preparations for biliary disorders

A **terpene** mixture (*Rowachol®*) raises biliary cholesterol solubility. It is not considered to be a useful adjunct.

Rowachol® (Rowa) PoM
Capsules, green, e/c, borneol 5 mg, camphene 5 mg, cineole 2 mg, menthol 32 mg, menthone 6 mg, pinene 17 mg in olive oil. Net price 50-cap pack = £7.35. Label: 22
Dose 1–2 capsules 3 times daily before food (but see notes above)
Interactions: Appendix 1 (*Rowachol®*)

1.9.2 Bile acid sequestrants

Colestyramine is an anion-exchange resin that is not absorbed from the gastro-intestinal tract. It relieves diarrhoea and pruritus by forming an insoluble complex with bile acids in the intestine. Colestyramine can interfere with the absorption of a number of drugs. Colestyramine is also used in hypercholesterolaemia (section 2.12).

COLESTYRAMINE
(Cholestyramine)

Indications pruritus associated with partial biliary obstruction and primary biliary cirrhosis; diarrhoea associated with Crohn's disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation; hypercholesterolaemia (section 2.12)

Cautions section 2.12

Contra-indications section 2.12

Pregnancy section 2.12

Breast-feeding section 2.12

Side-effects section 2.12

Dose

- Pruritus, 4–8 g daily in a suitable liquid; CHILD 1–18 years see *BNF for Children*
- Diarrhoea, initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in a suitable liquid in 1–4

divided doses, then adjusted as required; max. 36 g daily; CHILD 1–18 years see *BNF for Children*

Counselling Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption

Note The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content

Preparations

Section 2.12

1.9.3 Aprotinin

Aprotinin is no longer used for the treatment of acute pancreatitis.

1.9.4 Pancreatin

Supplements of pancreatin are given by mouth to compensate for reduced or absent exocrine secretion in cystic fibrosis, and following pancreatectomy, gastrectomy, or chronic pancreatitis. They assist the digestion of starch, fat, and protein. Pancreatin may also be necessary if a tumour (e.g. pancreatic cancer) obstructs outflow from the pancreas.

Pancreatin is inactivated by gastric acid therefore pancreatin preparations are best taken with food (or immediately before or after food). Gastric acid secretion may be reduced by giving cimetidine or ranitidine an hour beforehand (section 1.3). Concurrent use of antacids also reduces gastric acidity. Enteric-coated preparations deliver a higher enzyme concentration in the duodenum (provided the capsule contents are swallowed whole without chewing). Higher-strength preparations are also available (**important:** see CSM advice below).

Since pancreatin is also inactivated by heat, excessive heat should be avoided if preparations are mixed with liquids or food; the resulting mixtures should not be kept for more than one hour.

Dosage is adjusted according to size, number, and consistency of stools, so that the patient thrives; extra allowance will be needed if snacks are taken between meals.

Pancreatin can irritate the perioral skin and buccal mucosa if retained in the mouth, and excessive doses can cause perianal irritation. The most frequent side-effects are gastro-intestinal, including nausea, vomiting, and abdominal discomfort; hyperuricaemia and hyperuricosuria have been associated with very high doses. Hypersensitivity reactions occur occasionally and may affect those handling the powder.

PANCREATIN

Indications see above

Cautions see above and (for higher-strength preparations) see below

Pregnancy not known to be harmful

Side-effects see above and (for higher-strength preparations) see below

Dose

- See preparations

Creon® 10 000 (Solvay)

Capsules, brown/clear, enclosing buff-coloured e/c granules of pancreatin (pork), providing: protease 600 units, lipase 10 000 units, amylase 8000 units. Net price 100-cap pack = £12.93. Counselling, see dose

Dose ADULT and CHILD initially 1–2 capsules with each meal either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Creon® Micro (Solvay)

Gastro-resistant granules, brown, pancreatin (pork), providing: protease 200 units, lipase 5000 units, amylase 3600 units per 100 mg, net price 20 g = £31.50 Counselling, see dose

Dose ADULT and CHILD initially 100 mg with each meal either taken whole or mixed with acidic fluid or soft food (then swallowed immediately without chewing)

Nutrizym 10® (Merck Serono)

Capsules, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 500 units, lipase 10 000 units, amylase 9000 units. Net price 100 = £14.47. Counselling, see dose

Dose ADULT and CHILD 1–2 capsules with meals and 1 capsule with snacks, swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing); higher doses may be required according to response

Pancrex® (Paines & Byrne)

Granules, pancreatin (pork), providing minimum of: protease 300 units, lipase 5000 units, amylase 4000 units/g. Net price 300 g = £20.39. Label: 25, counselling, see dose

Dose ADULT and CHILD 5–10 g just before meals washed down or mixed with a little milk or water

Pancrex V® (Paines & Byrne)

Capsules, pancreatin (pork), providing minimum of: protease 430 units, lipase 8000 units, amylase 9000 units. Net price 300-cap pack = £15.80. Counselling, see dose

Dose ADULT and CHILD over 1 year 2–6 capsules with each meal, swallowed whole or sprinkled on food; INFANT up to 1 year contents of 1–2 capsules mixed with feeds

Capsules '125', pancreatin (pork), providing minimum of: protease 160 units, lipase 2950 units, amylase 3300 units, net price 300-cap pack = £9.72. Counselling, see dose

Dose NEONATE contents of 1–2 capsules mixed with feeds

Tablets, e/c, pancreatin (pork), providing minimum of: protease 110 units, lipase 1900 units, amylase 1700 units. Net price 300-tab pack = £4.51. Label: 5, 25, counselling, see dose

Dose ADULT and CHILD 5–15 tablets before each meal

Tablets forte, e/c, pancreatin (pork), providing minimum of: protease 330 units, lipase 5600 units, amylase 5000 units. Net price 300-tab pack = £13.74. Label: 5, 25, counselling, see dose

Dose ADULT and CHILD 6–10 tablets before each meal

Powder, pancreatin (pork), providing minimum of: protease 1400 units, lipase 25 000 units, amylase 30 000 units/g. Net price 300 g = £24.28. Counselling, see dose

Dose ADULT and CHILD over 1 month, 0.5–2 g before each meal, washed down or mixed with liquid; NEONATE 250–500 mg with each feed

Higher-strength preparations

The high-strength pancreatin preparations *Nutrizym 22®* and *Pancreatin HL®* have been associated with the development of large bowel strictures (fibrosing colonopathy) in children with cystic fibrosis aged between 2 and 13 years. No association was found with *Creon® 25 000* and *Creon® 40 000*. The following is recommended:

- *Pancrease HL®* and *Nutrizym 22®* should not be used in children aged 15 years or less with cystic fibrosis;
- the total dose of pancreatic enzyme supplements used in patients with cystic fibrosis should not usually exceed 10 000 units of lipase per kg bodyweight daily;
- if a patient on any pancreatin preparation develops new abdominal symptoms (or any change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic damage.

Possible risk factors are gender (boys at greater risk than girls), more severe cystic fibrosis, and concomitant use of laxatives. The peak age for developing fibrosing colonopathy is between 2 and 8 years.

Counselling It is important to ensure adequate hydration at all times in patients receiving higher-strength pancreatin preparations.

Creon® 25 000 (Solvay) PoM

Capsules, orange/clear, enclosing brown-coloured e/c pellets of pancreatin (pork), providing: protease (total) 1000 units, lipase 25 000 units, amylase 18 000 units, net price 100-cap pack = £28.25. Counselling, see above and under dose

Dose ADULT and CHILD initially 1 capsule with meals either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Creon® 40 000 (Solvay) PoM

Capsules, brown/clear, enclosing brown-coloured e/c granules of pancreatin (pork), providing: protease (total) 1600 units, lipase 40 000 units, amylase 25 000 units, net price 100-cap pack = £60.00. Counselling, see above and under dose

Dose ADULT and CHILD initially 1–2 capsules with meals either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Nutrizym 22® (Merck Serono) PoM

Capsules, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 1100 units, lipase 22 000 units, amylase 19 800 units. Net price 100-cap pack = £33.33. Counselling, see above and under dose

Dose ADULT and CHILD over 15 years, 1–2 capsules with meals and 1 capsule with snacks, swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing)

Pancrease HL® (Janssen-Cilag) PoM

Capsules, enclosing light brown e/c minitablets of pancreatin (pork), providing minimum of: protease 1250 units, lipase 25 000 units, amylase 22 500 units. Net price 100 = £31.70. Counselling, see above and under dose

Dose ADULT and CHILD over 15 years, 1–2 capsules during each meal and 1 capsule with snacks swallowed whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing)

2 Cardiovascular system

2.1 Positive inotropic drugs 81
2.1.1 Cardiac glycosides 81
2.1.2 Phosphodiesterase type-3 inhibitors 83
2.2 Diuretics 83
2.2.1 Thiazides and related diuretics 84
2.2.2 Loop diuretics 86
2.2.3 Potassium-sparing diuretics and aldosterone antagonists 87
2.2.4 Potassium-sparing diuretics with other diuretics 89
2.2.5 Osmotic diuretics 89
2.2.6 Mercurial diuretics 90
2.2.7 Carbonic anhydrase inhibitors 90
2.2.8 Diuretics with potassium 90
2.3 Anti-arrhythmic drugs 90
2.3.1 Management of arrhythmias 90
2.3.2 Drugs for arrhythmias 92
2.4 Beta-adrenoceptor blocking drugs 97
2.5 Hypertension and heart failure 104
2.5.1 Vasodilator antihypertensive drugs 107
2.5.2 Centrally acting antihypertensive drugs 110
2.5.3 Adrenergic neurone blocking drugs 111
2.5.4 Alpha-adrenoceptor blocking drugs 112
2.5.5 Drugs affecting the renin-angiotensin system 114
2.5.5.1 Angiotensin-converting enzyme inhibitors 115
2.5.5.2 Angiotensin-II receptor antagonists 121
2.5.5.3 Renin inhibitors 124
2.6 Nitrates, calcium-channel blockers, and other antianginal drugs 124
2.6.1 Nitrates 125
2.6.2 Calcium-channel blockers 128
2.6.3 Other antianginal drugs 134
2.6.4 Peripheral vasodilators and related drugs 135
2.7 Sympathomimetics 137
2.7.1 Inotropic sympathomimetics 137
2.7.2 Vasoconstrictor sympathomimetics 138
2.7.3 Cardiopulmonary resuscitation 139
2.8 Anticoagulants and protamine 139
2.8.1 Parenteral anticoagulants 140
2.8.2 Oral anticoagulants 146
2.8.3 Protamine sulphate 149
2.9 Antiplatelet drugs 149
2.10 Stable angina, acute coronary syndromes, and fibrinolysis 154
2.10.1 Management of stable angina and acute coronary syndromes 154
2.10.2 Fibrinolytic drugs 157
2.11 Antifibrinolytic drugs and haemostatics 159
2.12 Lipid-regulating drugs 161
2.13 Local sclerosants 169

This chapter also includes advice on the drug management of the following:

- angina, p. 154
- arrhythmias, p. 90
- cardiovascular disease risk, p. 104 and p. 161
- heart failure, p. 114
- hypertension, p. 104
- myocardial infarction, p. 154
- phaeochromocytoma, p. 113
- stroke, p. 150

2.1 Positive inotropic drugs

2.1.1 Cardiac glycosides
2.1.2 Phosphodiesterase type-3 inhibitors

Positive inotropic drugs increase the force of contraction of the myocardium; for sympathomimetics with inotropic activity see section 2.7.1.

2.1.1 Cardiac glycosides

Digoxin is a cardiac glycoside that increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node.

Digoxin is most useful for controlling ventricular response in persistent and permanent atrial fibrillation and atrial flutter (section 2.3.1). For reference to the role of digoxin in heart failure, see section 2.5.5.

For management of atrial fibrillation the maintenance dose of digoxin can usually be determined by the ventricular rate at rest, which should not usually be allowed to fall persistently below 60 beats per minute.

Digoxin is now rarely used for rapid control of heart rate (see section 2.3 for the management of supraventricular arrhythmias). Even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose. The intramuscular route is **not** recommended.

In patients with heart failure who are in sinus rhythm a loading dose is not required, and a satisfactory plasma-digoxin concentration can be achieved over a period of about a week.

Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea); renal function is the most important determinant of digoxin dosage.

Unwanted effects depend both on the concentration of digoxin in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease. It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because symptoms of both are similar. The plasma concentration alone cannot indicate toxicity reliably, but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Digoxin should be used with special care in the elderly, who may be particularly susceptible to digitalis toxicity.

Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected. Hypokalaemia predisposes the patient to digitalis toxicity; it is managed by giving a potassium-sparing diuretic or, if necessary, potassium supplementation.

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. **Digoxin-specific antibody fragments** are available for reversal of life-threatening overdosage (see below).

DIGOXIN

Indications heart failure (see also section 2.5.5), supraventricular arrhythmias (particularly atrial fibrillation and atrial flutter; see also section 2.3.2)

Cautions recent myocardial infarction; sick sinus syndrome; thyroid disease; reduce dose in the elderly; severe respiratory disease; hypokalaemia, hypomagnesaemia, hypercalcaemia, and hypoxia (risk of digitalis toxicity); monitor serum electrolytes and renal function; avoid rapid intravenous administration (risk of hypertension and reduced coronary flow); **interactions:** Appendix 1 (cardiac glycosides)

Contra-indications intermittent complete heart block, second degree AV block; supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome; ventricular tachycardia or fibrillation; hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but use with caution); myocarditis; constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—but use with caution)

Renal impairment reduce dose and monitor plasma-digoxin concentration; toxicity increased by electrolyte disturbances

Pregnancy may need dosage adjustment

Breast-feeding amount too small to be harmful

Side-effects see notes above; also nausea, vomiting, diarrhoea; arrhythmias, conduction disturbances; dizziness; blurred or yellow vision; rash, eosinophilia; *less commonly* depression; *very rarely* anorexia, intestinal ischaemia and necrosis, psychosis, apathy, confusion, headache, fatigue, weakness, gynaecomastia on long-term use, and thrombocytopenia

Dose

- Rapid digitalisation, for atrial fibrillation or flutter, by mouth, 0.75–1.5 mg over 24 hours in divided doses
- Maintenance, for atrial fibrillation or flutter, by mouth, according to renal function and initial loading dose; usual range 125–250 micrograms daily
- Heart failure (for patients in sinus rhythm), by mouth, 62.5–125 micrograms once daily
- Emergency loading dose, for atrial fibrillation or flutter, by intravenous infusion (but rarely necessary), 0.75–1 mg over at least 2 hours (see also Cautions) then maintenance dose by mouth on the following day

Note The above doses may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks. Digoxin doses in the BNF may differ from those in product literature. For plasma concentration monitoring, blood should ideally be taken at least 6 hours after a dose

Digoxin (Non-proprietary) PoM

Tablets, digoxin 62.5 micrograms, net price 28-tab pack = £2.03; 125 micrograms, 28-tab pack = £1.12; 250 micrograms, 28-tab pack = £1.13

Injection, digoxin 250 micrograms/mL, net price 2-mL amp = 70p

Paediatric injection, digoxin 100 micrograms/mL
Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Lanoxin® (Aspen) PoM

Tablets, digoxin 125 micrograms, net price 500-tab pack = £8.09; 250 micrograms (scored), 500-tab pack = £8.09

Injection, digoxin 250 micrograms/mL, net price 2-mL amp = 66p

Lanoxin-PG® (Aspen) PoM

Tablets, blue, digoxin 62.5 micrograms, net price 500-tab pack = £8.09

Elixir, yellow, digoxin 50 micrograms/mL. Do not dilute, measure with pipette. Net price 60 mL = £5.35. Counselling, use of pipette

Digoxin-specific antibody

Digoxin-specific antibody fragments are indicated for the treatment of known or strongly suspected digoxin or other cardiac glycoside overdosage when measures beyond the withdrawal of the cardiac glycoside and correction of any electrolyte abnormalities are felt to be necessary (see also notes above).

Digibind® (GSK) PoM

Injection, powder for preparation of infusion, digoxin-specific antibody fragments (F(ab)) 38 mg, net price per vial = £93.97 (hosp. and poisons centres only)
Dose consult product literature

2.1.2 Phosphodiesterase type-3 inhibitors

Enoximone and **milrinone** are phosphodiesterase type-3 inhibitors that exert most of their effect on the myocardium. Sustained haemodynamic benefit has been observed after administration, but there is no evidence of any beneficial effect on survival.

ENOXIMONE

Indications congestive heart failure where cardiac output reduced and filling pressures increased

Cautions heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction; monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count, hepatic enzymes; avoid extravasation; **interactions:** Appendix 1 (phosphodiesterase type-3 inhibitors)

Hepatic impairment dose reduction may be required

Renal impairment consider dose reduction

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution—no information available

Side-effects ectopic beats; less frequently ventricular tachycardia or supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias); hypotension; also headache, insomnia, nausea and vomiting, diarrhoea; occasionally, chills, oliguria, fever, urinary retention; upper and lower limb pain

Dose

- By slow intravenous injection (rate not exceeding 12.5 mg/minute), diluted before use, initially 0.5–1 mg/kg, then 500 micrograms/kg every 30 minutes until satisfactory response or total of 3 mg/kg given; maintenance, initial dose of up to 3 mg/kg may be repeated every 3–6 hours as required
- By intravenous infusion, initially 90 micrograms/kg/minute over 10–30 minutes, followed by continuous or intermittent infusion of 5–20 micrograms/kg/minute Total dose over 24 hours should not usually exceed 24 mg/kg

Perfan® (INCA-Pharm) PoM

Injection, enoximone 5 mg/mL. For dilution before use. Net price 20-mL amp = £15.02

Excipients include alcohol, propylene glycol

Note Plastic apparatus should be used; crystal formation if glass used

MILRINONE

Indications short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy (not immediately after myocardial infarction); acute heart failure, including low output states following heart surgery

Cautions see under Enoximone; also correct hypokalaemia; **interactions:** Appendix 1 (phosphodiesterase type-3 inhibitors)

Renal impairment reduce dose and monitor response if eGFR less than 50 mL/minute/1.73 m^2—consult product literature for details

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution—no information available

Side-effects ectopic beats, ventricular tachycardia, supraventricular arrhythmias (more likely in patients with pre-existing arrhythmias), hypotension; headache; *less commonly* ventricular fibrillation, chest pain, tremor, hypokalaemia, thrombocytopenia; *very rarely* bronchospasm, anaphylaxis, and rash

Dose

- By intravenous injection over 10 minutes, either undiluted or diluted before use, 50 micrograms/kg followed by intravenous infusion at a rate of 375–750 nanograms/kg/minute, usually for up to 12 hours following surgery or for 48–72 hours in congestive heart failure; max. daily dose 1.13 mg/kg

Primacor® (Sanofi-Aventis) PoM

Injection, milrinone (as lactate) 1 mg/mL, net price 10-mL amp = £16.61

2.2 Diuretics

2.2.1 Thiazides and related diuretics
2.2.2 Loop diuretics
2.2.3 Potassium-sparing diuretics and aldosterone antagonists
2.2.4 Potassium-sparing diuretics with other diuretics
2.2.5 Osmotic diuretics
2.2.6 Mercurial diuretics
2.2.7 Carbonic anhydrase inhibitors
2.2.8 Diuretics with potassium

Thiazides (section 2.2.1) are used to relieve oedema due to chronic heart failure (section 2.5.5) and, in lower doses, to reduce blood pressure.

Loop diuretics (section 2.2.2) are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure (section 2.5.5).

Combination diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

Elderly Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

Potassium loss Hypokalaemia can occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.

Hypokalaemia is dangerous in severe cardiovascular disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics (section 2.2.3) avoids the need to take potassium supplements.

In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic

cirrhosis; diuretics can also increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias. Spironolactone, a potassium-sparing diuretic (section 2.2.3), is chosen for oedema arising from cirrhosis of the liver.

Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension (see also section 9.2.1.1).

2.2.1 Thiazides and related diuretics

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of *hypertension* a low dose of a thiazide, e.g. bendroflumethiazide 2.5 mg daily, produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. For reference to the use of thiazides in chronic heart failure see section 2.5.5.

Bendroflumethiazide is widely used for mild or moderate heart failure and for hypertension—alone in the treatment of mild hypertension or with other drugs in more severe hypertension.

Chlortalidone, a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike the altered pattern of micturition caused by other diuretics.

Other thiazide diuretics (including benzthiazide, clopamide, cyclopenthiazide, hydrochlorothiazide, and hydroflumethiazide) do not offer any significant advantage over bendroflumethiazide or chlortalidone.

Metolazone is particularly effective when combined with a loop diuretic (even in renal failure); profound diuresis can occur and the patient should therefore be monitored carefully.

Xipamide and **indapamide** are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

Cautions See also section 2.2. Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus. Electrolytes should be monitored, particularly with high doses, long-term use, or in renal impairment. Thiazides and related diuretics should also be used with caution in nephrotic syndrome, hyperaldosteronism, and malnourishment; **interactions:** Appendix 1 (diuretics)

Contra-indications Thiazides and related diuretics should be avoided in refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia, and Addison's disease.

Hepatic impairment Thiazides and related diuretics should be used with caution in mild to moderate impairment and avoided in severe liver disease. Hypokalaemia may precipitate coma, although hypokalaemia can be prevented by using a potassium-sparing diuretic. There is an increased risk of hypomagnesaemia in alcoholic cirrhosis.

Renal impairment Thiazides and related diuretics are ineffective if eGFR is less than 30 mL/minute/1.73 m^2 and should be avoided; metolazone remains effective but with a risk of excessive diuresis.

Pregnancy Thiazides and related diuretics should not be used to treat gestational hypertension. They may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced. Stimulation of labour, uterine inertia, and meconium staining have also been reported.

Breast-feeding The amount of bendroflumethiazide, chlortalidone, cyclopenthiazide, and metolazone present in milk is too small to be harmful; large doses may suppress lactation. For indapamide and xipamide see individual drugs.

Side-effects Side-effects of thiazides and related diuretics include mild gastro-intestinal disturbances, postural hypotension, altered plasma-lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia (see also notes above), hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, hyperuricaemia, and gout. Less common side-effects include blood disorders such as agranulocytosis, leucopenia, and thrombocytopenia, and impotence. Pancreatitis, intrahepatic cholestasis, cardiac arrhythmias, headache, dizziness, paraesthesia, visual disturbances, and hypersensitivity reactions (including pneumonitis, pulmonary oedema, photosensitivity, and severe skin reactions) have also been reported.

BENDROFLUMETHIAZIDE
(Bendrofluazide)

Indications oedema, hypertension (see also notes above)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- Oedema, initially 5–10 mg daily in the morning *or* on alternate days; maintenance 5–10 mg 1–3 times weekly
- Hypertension, 2.5 mg daily in the morning; higher doses rarely necessary (see notes above)

Bendroflumethiazide (Non-proprietary) PoM

Tablets, bendroflumethiazide 2.5 mg, net price 28 = 79p; 5 mg, 28 = 86p

Brands include *Aprinox®*

CHLORTALIDONE
(Chlorthalidone)

Indications ascites due to cirrhosis in stable patients (under close supervision), oedema due to nephrotic syndrome, hypertension (see also notes above), mild to moderate chronic heart failure; diabetes insipidus (see section 6.5.2)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also *rarely* jaundice and allergic interstitial nephritis
Dose
- Oedema, up to 50 mg daily
- Hypertension, 25 mg daily in the morning, increased to 50 mg daily if necessary (but see notes above)
- Heart failure, 25–50 mg daily in the morning, increased if necessary to 100–200 mg daily (reduce to lowest effective dose for maintenance)

Hygroton® (Alliance) PoM
Tablets, yellow, scored, chlortalidone 50 mg, net price 28-tab pack = £1.64

CYCLOPENTHIAZIDE

Indications oedema, hypertension (see also notes above); heart failure
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also *rarely* depression
Dose
- Heart failure, 250–500 micrograms daily in the morning increased if necessary to 1 mg daily (reduce to lowest effective dose for maintenance)
- Hypertension, initially 250 micrograms daily in the morning, increased if necessary to 500 micrograms daily (but see notes above)
- Oedema, up to 500 micrograms daily for a short period

Navidrex® (Goldshield) PoM
Tablets, scored, cyclopenthiazide 500 micrograms, net price 28-tab pack = £1.27
Excipients include gluten
Note May be difficult to obtain

INDAPAMIDE

Indications essential hypertension
Cautions see notes above; also acute porphyria (section 9.8.2)
Contra-indications see notes above; also hypersensitivity to sulfonamides
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding present in milk—manufacturer advises avoid
Side-effects see notes above; also palpitation, diuresis with doses above 2.5 mg daily
Dose
- 2.5 mg daily in the morning

Indapamide (Non-proprietary) PoM
Tablets, s/c, indapamide 2.5 mg, net price 28-tab pack = £1.27, 56-tab pack = £2.01

Natrilix® (Servier) PoM
Tablets, f/c, indapamide 2.5 mg. Net price 30-tab pack = £3.40, 60-tab pack = £6.80

Modified release

Ethibide XL® (Genus) PoM
Tablets, m/r, indapamide 1.5 mg, net price 30-tab pack = £4.05. Label: 25
Dose hypertension, 1 tablet daily, preferably in the morning

Natrilix SR® (Servier) PoM
Tablets, m/r, indapamide 1.5 mg, net price 30-tab pack = £3.40. Label: 25
Dose hypertension, 1 tablet daily, preferably in the morning

METOLAZONE

Indications oedema, hypertension (see also notes above)
Cautions see notes above; also acute porphyria (section 9.8.2)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also chills, chest pain
Dose
- Oedema, 5–10 mg daily in the morning, increased if necessary to 20 mg daily in resistant oedema, max. 80 mg daily
- Hypertension, initially 5 mg daily in the morning; maintenance 5 mg on alternate days

Metenix 5® (Sanofi-Aventis) PoM
Tablets, blue, metolazone 5 mg, net price 100-tab pack = £18.20

XIPAMIDE

Indications oedema, hypertension (see also notes above)
Cautions see notes above; also acute porphyria (section 9.8.2)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding no information available
Side-effects see notes above
Dose
- Oedema, initially 40 mg daily in the morning, increased to 80 mg in resistant cases; maintenance 20 mg in the morning
- Hypertension, 20 mg daily in the morning

Diurexan® (Meda) PoM
Tablets, scored, xipamide 20 mg, net price 140-tab pack = £19.46

2.2.2 Loop diuretics

Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide 5–10 mg daily or metolazone 5–20 mg daily).

If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure.

Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics.

Furosemide and **bumetanide** are similar in activity; both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration they have a peak effect within 30 minutes. The diuresis associated with these drugs is dose related.

Torasemide has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

Cautions Hypovolaemia and hypotension should be corrected before initiation of treatment with loop diuretics; electrolytes should be monitored during treatment (see also Potassium Loss, section 2.2). Loop diuretics can exacerbate diabetes (but hyperglycaemia is less likely than with thiazides) and gout. If there is an enlarged prostate, urinary retention can occur, although this is less likely if small doses and less potent diuretics are used initially; an adequate urinary output should be established before initiating treatment; **interactions**: Appendix 1 (diuretics).

Contra-indications Loop diuretics should be avoided in severe hypokalaemia, severe hyponatraemia, anuria, comatose and precomatose states associated with liver cirrhosis, and in renal failure due to nephrotoxic or hepatotoxic drugs.

Hepatic impairment Hypokalaemia induced by loop diuretics may precipitate hepatic encephalopathy and coma—potassium-sparing diuretics can be used to prevent this.

Renal impairment High doses of loop diuretics may occasionally be needed; high doses or rapid intravenous administration can cause tinnitus and deafness; high doses of bumetanide can also cause musculoskeletal pain.

Pregnancy Furosemide and bumetanide should not be used to treat gestational hypertension because of the maternal hypovolaemia associated with this condition.

Side-effects Side-effects of loop diuretics include mild gastro-intestinal disturbances, pancreatitis, hepatic encephalopathy, postural hypotension, temporary increase in serum-cholesterol and triglyceride concentration, hyperglycaemia (less common than with thiazides), acute urinary retention, electrolyte disturbances (including hyponatraemia, hypokalaemia (see section 2.2), hypocalcaemia, hypochloraemia, and hypomagnesaemia), metabolic alkalosis, blood disorders (including bone-marrow depression, thrombocytopenia, and leucopenia), hyperuricaemia, visual disturbances, tinnitus and deafness (usually with high parenteral doses and rapid administration, and in renal impairment), and hypersensitivity reactions (including rash, photosensitivity, and pruritus).

FUROSEMIDE
(Frusemide)

Indications oedema (see notes above); resistant hypertension (see notes above)

Cautions see notes above; also hypoproteinaemia may reduce diuretic effect and increase risk of side-effects; hepatorenal syndrome; intravenous administration rate should not usually exceed 4 mg/minute, however single doses of up to 80 mg may be administered more rapidly

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; also lower rate of infusion may be necessary

Pregnancy see notes above

Breast-feeding amount too small to be harmful; may inhibit lactation

Side-effects see notes above; also intrahepatic cholestasis and gout

Dose

- By mouth, oedema, initially 40 mg in the morning; maintenance 20–40 mg daily; CHILD under 18 years see *BNF for Children*

  Resistant oedema, 80–120 mg daily

  Resistant hypertension, 40–80 mg daily
- By intramuscular injection *or* slow intravenous injection (rate of administration, see Cautions above), initially 20–50 mg, increased if necessary in steps of 20 mg not less than every 2 hours; doses greater than 50 mg by intravenous infusion only; max. 1.5 g daily; CHILD under 18 years see *BNF for Children*

Furosemide (Non-proprietary) PoM

Tablets, furosemide 20 mg, net price 28 = 81p; 40 mg, 28 = 84p; 500 mg, 28 = £4.05

Brands include *Rusyde®*

Oral solution, sugar-free, furosemide, net price 20 mg/5 mL, 150 mL = £13.97; 40 mg/5 mL, 150 mL = £18.19; 50 mg/5 mL, 150 mL = £19.35

Brands include *Frusol®* (contains alcohol 10%)

Injection, furosemide 10 mg/mL, net price 2-mL amp = 30p, 5-mL amp = 38p, 25-mL amp = £2.50

Lasix® (Sanofi-Aventis) PoM

Injection, furosemide 10 mg/mL, net price 2-mL amp = 75p

Note Large-volume furosemide injections also available; brands include *Minijet®*

BUMETANIDE

Indications oedema (see notes above)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding no information available; may inhibit lactation
Side-effects see notes above; also gynaecomastia, breast pain, musculoskeletal pain (associated with high doses in renal failure)
Dose
- By mouth, 1 mg in the morning, repeated after 6–8 hours if necessary; severe cases, 5 mg daily increased by 5 mg every 12–24 hours according to response; ELDERLY, 500 micrograms daily may be sufficient
- By intravenous injection, 1–2 mg, repeated after 20 minutes if necessary; ELDERLY, 500 micrograms daily may be sufficient
- By intravenous infusion, 2–5 mg over 30–60 minutes; ELDERLY, 500 micrograms daily may be sufficient
- By intramuscular injection, 1 mg initially then adjusted according to response; ELDERLY, 500 micrograms daily may be sufficient

Bumetanide (Non-proprietary) PoM
Tablets, bumetanide 1 mg, net price 28-tab pack = £1.12; 5 mg, 28-tab pack = £4.33
Oral liquid, bumetanide 1 mg/5 mL, net price 150 mL = £128.00
Injection, bumetanide 500 micrograms/mL, net price 4-mL amp = £1.79

Burinex® (LEO) PoM
Tablets, scored, bumetanide 1 mg, net price 28-tab pack = £1.52; 5 mg, 28 = £9.67

TORASEMIDE

Indications oedema (see notes above), hypertension
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy manufacturer advises avoid—toxicity in *animal* studies
Breast-feeding manufacturer advises avoid—no information available
Side-effects see notes above; also dry mouth; *rarely* limb paraesthesia
Dose
- Oedema, 5 mg once daily, preferably in the morning, increased if required to 20 mg once daily; usual max. 40 mg daily
- Hypertension, 2.5 mg daily, increased if necessary to 5 mg once daily

Torasemide (Non-proprietary) PoM
Tablets, torasemide 5 mg, net price 28-tab pack = £10.36; 10 mg, 28-tab pack = £13.71

Torem® (Meda) PoM
Tablets, torasemide 2.5 mg, net price 28-tab pack = £3.78; 5 mg (scored), 28-tab pack = £5.53; 10 mg (scored), 28-tab pack = £8.14

2.2.3 Potassium-sparing diuretics and aldosterone antagonists

Amiloride and **triamterene** on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements. See section 2.2.4 for compound preparations with thiazides or loop diuretics.

Potassium supplements must **not** be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

AMILORIDE HYDROCHLORIDE

Indications oedema; potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension, congestive heart failure, or hepatic cirrhosis with ascites
Cautions monitor electrolytes; diabetes mellitus; elderly; **interactions:** Appendix 1 (diuretics)
Contra-indications hyperkalaemia; anuria; Addison's disease
Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); manufacturers advise avoid in severe impairment
Pregnancy not used to treat gestational hypertension
Breast-feeding manufacturer advises avoid—no information available
Side-effects include gastro-intestinal disturbances, dry mouth, rashes, confusion, postural hypotension, hyperkalaemia, hyponatraemia
Dose
- Used alone, initially 10 mg daily *or* 5 mg twice daily, adjusted according to response; max. 20 mg daily
- With other diuretics, congestive heart failure and hypertension, initially 5–10 mg daily; cirrhosis with ascites, initially 5 mg daily

Amiloride (Non-proprietary) PoM
Tablets, amiloride hydrochloride 5 mg, net price 28-tab pack = 96p
Oral solution, sugar-free, amiloride hydrochloride 5 mg/5 mL, net price 150 mL = £39.73
Brands include *Amilamont®* (Excipients include propylene glycol, see Excipients, p. 2)

Compound preparations with thiazide or loop diuretics
Section 2.2.4

TRIAMTERENE

Indications oedema, potassium conservation with thiazide and loop diuretics
Cautions see under Amiloride Hydrochloride; may cause blue fluorescence of urine
Contra-indications see under Amiloride Hydrochloride
Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal

impairment); manufacturers advise avoid in severe impairment

Pregnancy not used to treat gestational hypertension

Breast-feeding present in milk—manufacturer advises avoid

Side-effects include gastro-intestinal disturbances, dry mouth, rashes; slight decrease in blood pressure, hyperkalaemia, hyponatraemia; photosensitivity and blood disorders also reported; triamterene found in kidney stones

Dose

- Initially 150–250 mg daily, reducing to alternate days after 1 week; taken in divided doses after breakfast and lunch; lower initial dose when given with other diuretics

Counselling Urine may look slightly blue in some lights

Dytac® (Goldshield) PoM

Capsules, maroon, triamterene 50 mg, net price 30-cap pack = £17.35 Label: 14, (see above), 21

Compound preparations with thiazides or loop diuretics

Section 2.2.4

Aldosterone antagonists

Spironolactone potentiates thiazide or loop diuretics by antagonising aldosterone; it is a potassium-sparing diuretic. Spironolactone is of value in the treatment of oedema and ascites caused by cirrhosis of the liver; furosemide (section 2.2.2) can be used as an adjunct. Low doses of spironolactone are beneficial in moderate to severe heart failure, see section 2.5.5.

Spironolactone is also used in primary hyperaldosteronism (Conn's syndrome). It is given before surgery or if surgery is not appropriate, in the lowest effective dose for maintenance.

Eplerenone is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction (see also section 2.5.5 and section 2.10.1).

Potassium supplements must **not** be given with aldosterone antagonists.

EPLERENONE

Indications adjunct in stable patients with left ventricular dysfunction with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event)

Cautions measure plasma-potassium concentration before treatment, during initiation, and when dose changed; elderly; **interactions:** Appendix 1 (diuretics)

Contra-indications hyperkalaemia; concomitant use of potassium-sparing diuretics or potassium supplements

Hepatic impairment avoid in severe liver disease

Renal impairment increased risk of hyperkalaemia—close monitoring required; avoid if eGFR less than 50 mL/minute/1.73 m^2

Pregnancy manufacturer advises caution—no information available

Breast-feeding manufacturer advises use only if potential benefit outweighs risk

Side-effects diarrhoea, nausea; hypotension; dizziness; hyperkalaemia; rash; *less commonly* flatulence, vomiting, atrial fibrillation, postural hypotension, arterial thrombosis, dyslipidaemia, pharyngitis, headache, insomnia, gynaecomastia, pyelonephritis, hyponatraemia, dehydration, eosinophilia, asthenia, malaise, back pain, leg cramps, impaired renal function, azotaemia, sweating and pruritus

Dose

- Initially 25 mg once daily, increased within 4 weeks to 50 mg once daily; CHILD not recommended

Inspra® (Pfizer) ▼ PoM

Tablets, yellow, f/c, eplerenone 25 mg, net price 28-tab pack = £42.72; 50 mg, 28-tab pack = £42.72

SPIRONOLACTONE

Indications oedema and ascites in cirrhosis of the liver, malignant ascites, nephrotic syndrome, congestive heart failure (section 2.5.5); primary hyperaldosteronism

Cautions potential metabolic products carcinogenic in *rodents*; elderly; monitor electrolytes (discontinue if hyperkalaemia); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (diuretics)

Contra-indications hyperkalaemia, hyponatraemia; anuria; Addison's disease

Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); avoid if rapidly deteriorating or severe impairment

Pregnancy feminisation of male fetus in *animal* studies

Breast-feeding metabolites present in milk, but amount probably too small to be harmful

Side-effects gastro-intestinal disturbances, hepatotoxicity; malaise, headache, confusion, drowsiness, dizziness; gynaecomastia, benign breast tumour, breast pain, menstrual disturbances, changes in libido; hypertrichosis, hyperkalaemia (discontinue), hyponatraemia, acute renal failure, hyperuricaemia, leucopenia, agranulocytosis, thrombocytopenia; leg cramps; alopecia, hirsutism, rash, and Stevens-Johnson syndrome

Dose

- 100–200 mg daily, increased to 400 mg if required; CHILD under 18 years, see *BNF for Children*
- Heart failure, see section 2.5.5

Spironolactone (Non-proprietary) PoM

Tablets, spironolactone 25 mg, net price 28 = £1.50; 50 mg, 28 = £2.11; 100 mg, 28 = £2.46. Label: 21

Oral suspensions, spironolactone 5 mg/5 mL, 10 mg/5 mL, 25 mg/5 mL, 50 mg/5 mL, and 100 mg/5 mL. Label: 21

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Aldactone® (Pharmacia) PoM

Tablets, f/c, spironolactone 25 mg (buff), net price 100-tab pack = £8.89; 50 mg (white), 100-tab pack = £17.78; 100 mg (buff), 28-tab pack = £9.96. Label: 21

With thiazides or loop diuretics

Section 2.2.4

2.2.4 Potassium-sparing diuretics with other diuretics

Although it is preferable to prescribe thiazides (section 2.2.1) and potassium-sparing diuretics (section 2.2.3) separately, the use of fixed combinations may be justified if compliance is a problem. Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops. For **interactions**, see Appendix 1 (diuretics).

Amiloride with thiazides

Co-amilozide (Non-proprietary) PoM

Tablets, co-amilozide 2.5/25 (amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-tab pack = £3.73

Brands include *Moduret 25®*

Dose hypertension, initially 1 tablet daily, increased if necessary to max. 2 tablets daily

Congestive heart failure, initially 1 tablet daily, increased if necessary to max. 4 tablets daily

Oedema and ascites in cirrhosis of the liver, initially 2 tablets daily, increased if necessary to max. 4 tablets daily; reduce for maintenance if possible

Tablets, co-amilozide 5/50 (amiloride hydrochloride 5 mg, hydrochlorothiazide 50 mg), net price 28 = £1.14

Brands include *Amil-Co®*, *Moduretic®*

Dose hypertension, initially ½ tablet daily, increased if necessary to max. 1 tablet daily

Congestive heart failure, initially ½ tablet daily, increased if necessary to max. 2 tablets daily

Oedema and ascites in cirrhosis of the liver, initially 1 tablet daily, increased if necessary to max. 2 tablets daily; reduce for maintenance if possible

Navispare® (Goldshield) PoM

Tablets, f/c, orange, amiloride hydrochloride 2.5 mg, cyclopenthiazide 250 micrograms, net price 28-tab pack = £2.70

Excipients include gluten

Dose hypertension, 1–2 tablets in the morning

Amiloride with loop diuretics

Co-amilofruse (Non-proprietary) PoM

Tablets, co-amilofruse 2.5/20 (amiloride hydrochloride 2.5 mg, furosemide 20 mg), net price 28-tab pack = £1.18, 56-tab pack = £1.83

Brands include *Frumil LS®*

Dose oedema, 1 tablet in the morning

Tablets, co-amilofruse 5/40 (amiloride hydrochloride 5 mg, furosemide 40 mg), net price 28-tab pack = £1.17, 56-tab pack = £1.42

Brands include *Frumil®*

Dose oedema, 1–2 tablets in the morning

Tablets, co-amilofruse 10/80 (amiloride hydrochloride 10 mg, furosemide 80 mg), net price 28-tab pack = £11.51

Dose oedema, 1 tablet in the morning

Amiloride with bumetanide (Non-proprietary) PoM

Tablets, amiloride hydrochloride 5 mg, bumetanide 1 mg, net price 28-tab pack = £29.60

Dose oedema, 1–2 tablets daily

Triamterene with thiazides

Counselling Urine may look slightly blue in some lights

Co-triamterzide (Non-proprietary) PoM

Tablets, co-triamterzide 50/25 (triamterene 50 mg, hydrochlorothiazide 25 mg), net price 30-tab pack = 95p. Label: 14, (see above), 21

Dose hypertension, 1 tablet daily after breakfast, increased if necessary, max. 4 daily

Oedema, 2 tablets daily (1 after breakfast and 1 after midday meal) increased to 3 daily if necessary (2 after breakfast and 1 after midday meal); usual maintenance in oedema, 1 daily or 2 on alternate days; max. 4 daily

Brands include *Triam-Co®*

Dyazide® (Goldshield) PoM

Tablets, peach, scored, co-triamterzide 50/25 (triamterene 50 mg, hydrochlorothiazide 25 mg), net price 30-tab pack = 95p. Label: 14, (see above), 21

Dose hypertension, 1 tablet daily after breakfast, increased if necessary, max. 4 daily

Oedema, 2 tablets daily (1 after breakfast and 1 after midday meal) increased to 3 daily if necessary (2 after breakfast and 1 after midday meal); usual maintenance in oedema, 1 daily or 2 on alternate days; max. 4 daily

Kalspare® (DHP Healthcare) PoM

Tablets, orange, f/c, scored, triamterene 50 mg, chlortalidone 50 mg, net price 28-tab pack = £9.90. Label: 14, (see above), 21

Dose hypertension, oedema, 1–2 tablets in the morning

Triamterene with loop diuretics

Counselling Urine may look slightly blue in some lights

Frusene® (Orion) PoM

Tablets, yellow, scored, triamterene 50 mg, furosemide 40 mg, net price 56-tab pack = £4.34. Label: 14, (see above)

Dose oedema, ½–2 tablets daily in the morning

Spironolactone with thiazides

Co-flumactone (Non-proprietary) PoM

Tablets, co-flumactone 25/25 (hydroflumethiazide 25 mg, spironolactone 25 mg), net price 100-tab pack = £20.23

Brands include *Aldactide 25®*

Dose congestive heart failure, initially 4 tablets daily; range 1–8 tablets daily (but not recommended because spironolactone generally given in lower dose)

Tablets, co-flumactone 50/50 (hydroflumethiazide 50 mg, spironolactone 50 mg), net price 28-tab pack = £10.70

Brands include *Aldactide 50®*

Dose congestive heart failure, initially 2 tablets daily; range 1–4 tablets daily (but not recommended because spironolactone generally given in lower dose)

Spironolactone with loop diuretics

Lasilactone® (Sanofi-Aventis) PoM

Capsules, blue/white, spironolactone 50 mg, furosemide 20 mg, net price 28-cap pack = £7.97

Dose resistant oedema, 1–4 capsules daily

2.2.5 Osmotic diuretics

Mannitol is an osmotic diuretic that can be used to treat cerebral oedema and raised intra-ocular pressure.

MANNITOL

Indications see notes above; glaucoma (section 11.6)

Cautions extravasation causes inflammation and thrombophlebitis; monitor fluid and electrolyte balance, serum osmolality, and pulmonary and renal function; assess cardiac function before and during treatment; **interactions**: Appendix 1 (mannitol)

Contra-indications severe cardiac failure; severe pulmonary oedema; intracranial bleeding (except during craniotomy); anuria; severe dehydration

Renal impairment use with caution in severe impairment

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects *less commonly* hypotension, thrombophlebitis, fluid and electrolyte imbalance; *rarely* dry mouth, thirst, nausea, vomiting, oedema, raised intracranial pressure, arrhythmia, hypertension, pulmonary oedema, chest pain, headache, convulsions, dizziness, chills, fever, urinary retention, focal osmotic nephrosis, dehydration, cramp, blurred vision, rhinitis, skin necrosis, and hypersensitivity reactions (including urticaria and anaphylaxis); *very rarely* congestive heart failure and acute renal failure

Dose

- Cerebral oedema and raised intra-ocular pressure, by intravenous infusion over 30–60 minutes, 0.25–2 g/kg repeated if necessary 1–2 times after 4–8 hours

Note For mannitol 20%, an in-line filter is recommended (15-micron filters have been used)

Mannitol (Baxter) PoM

Intravenous infusion, mannitol 10%, net price 500-mL *Viaflex*® bag = £2.26, 500-mL *Viaflo*® bag = £2.15; 20%, net price 250-mL *Viaflex*® bag = £3.27, 250-mL *Viaflo*® bag = £3.27, 500-mL *Viaflex*® bag = £3.29, 500-mL *Viaflo*® bag = £3.12

2.2.6 Mercurial diuretics

Mercurial diuretics are effective but are now almost never used because of their nephrotoxicity.

2.2.7 Carbonic anhydrase inhibitors

The carbonic anhydrase inhibitor **acetazolamide** is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness [unlicensed indication] but is not a substitute for acclimatisation.

Acetazolamide and eye drops of dorzolamide and brinzolamide inhibit the formation of aqueous humour and are used in glaucoma (section 11.6).

2.2.8 Diuretics with potassium

Many patients on diuretics do not need potassium supplements (section 9.2.1.1). For many of those who do, the amount of potassium in combined preparations may not be enough, and for this reason their use is to be discouraged.

Diuretics with potassium and potassium-sparing diuretics should **not** usually be given together.

Counselling Modified-release potassium tablets should be swallowed whole with plenty of fluid during meals while sitting or standing

Diumide-K Continus® (Teofarma) PoM

Tablets, white/orange, f/c, furosemide 40 mg, potassium 8 mmol for modified release, net price 30-tab pack = £3.00. Label: 25, 27, counselling, see above

Neo-NaClex-K® (Goldshield) PoM

Tablets, pink/white, f/c, bendroflumethiazide 2.5 mg, potassium 8.4 mmol for modified release, net price 100 tab-pack = £8.99. Label: 25, 27, counselling, see above

2.3 Anti-arrhythmic drugs

2.3.1 Management of arrhythmias
2.3.2 Drugs for arrhythmias

2.3.1 Management of arrhythmias

Management of an arrhythmia requires precise diagnosis of the type of arrhythmia, and electrocardiography is essential; underlying causes such as heart failure require appropriate treatment.

Ectopic beats If ectopic beats are spontaneous and the patient has a normal heart, treatment is rarely required and reassurance to the patient will often suffice. If they are particularly troublesome, beta-blockers are sometimes effective and may be safer than other suppressant drugs.

Atrial fibrillation All patients with atrial fibrillation should be assessed for their risk of stroke and thromboembolism, and thromboprophylaxis given if necessary (see below). Atrial fibrillation can be managed by either controlling the ventricular rate or by attempting to restore and maintain sinus rhythm.

All haemodynamically unstable patients with acute-onset atrial fibrillation should undergo electrical cardioversion. Intravenous amiodarone, or alternatively flecainide, can be used in non-life-threatening cases when electrical cardioversion is delayed. If urgent ventricular rate control is required, a beta-blocker, verapamil, or amiodarone can be given intravenously.

In haemodynamically stable patients, a rhythm-control treatment strategy is preferred for patients with paroxysmal atrial fibrillation; rate-control is preferred for those with permanent atrial fibrillation. For patients with persistent atrial fibrillation, the treatment strategy should be based on criteria such as age, co-morbidities, presence of symptoms, and the relative advantages and disadvantages of each treatment.

Ventricular rate can be controlled with a beta-blocker (section 2.4), or diltiazem [unlicensed indication], or verapamil. Digoxin is usually only effective for controlling the ventricular rate at rest, and should therefore

only be used as monotherapy in predominantly sedentary patients. When a single drug fails to adequately control the ventricular rate, patients should receive digoxin with either a beta-blocker, diltiazem, or verapamil. If ventricular function is diminished, the combination of a beta-blocker (that is licensed for use in heart failure) and digoxin is preferred (see section 2.5.5, and **interactions**: Appendix 1 (cardiac glycosides)). Digoxin is also used when atrial fibrillation is accompanied by congestive heart failure.

Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an oral or intravenous anti-arrhythmic drug e.g. flecainide or amiodarone. If necessary, sotalol or amiodarone can be started 4 weeks before electrical cardioversion to increase success of the procedure. If atrial fibrillation has been present for more than 48 hours, cardioversion should not be attempted until the patient has been fully anticoagulated (see section 2.8.2) for at least 3 weeks; if this is not possible, parenteral anticoagulation (section 2.8.1) should be commenced and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks. For atrial fibrillation of over 48 hours duration, electrical cardioversion is preferred to pharmacological methods. If drug treatment is required to maintain sinus rhythm, a beta-blocker is used. If a standard beta-blocker is not appropriate or is ineffective, an oral anti-arrhythmic drug such as sotalol (section 2.4), flecainide, propafenone, or amiodarone, is required.

In symptomatic paroxysmal atrial fibrillation, ventricular rhythm is controlled with a beta-blocker. Alternatively, if symptoms persist or a beta-blocker is not appropriate, an oral anti-arrhythmic drug such as sotalol, flecainide, propafenone, or amiodarone can be given (see also Paroxysmal Supraventricular Tachycardia below, and Supraventricular Arrhythmias). In selected patients with infrequent episodes of symptomatic paroxysmal atrial fibrillation, sinus rhythm can be restored using the 'pill-in-the-pocket' approach; this involves the patient taking oral flecainide or propafenone to self-treat an episode of atrial fibrillation when it occurs.

All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis. Anticoagulants (section 2.8) are indicated for those with a history of ischaemic stroke, transient ischaemic attacks, or thromboembolic events, and those with valve disease, heart failure, or impaired left ventricular function; anticoagulants should be considered for those with cardiovascular disease, diabetes, hypertension, or thyrotoxicosis, and in the elderly. Anticoagulants are also indicated during cardioversion procedures (see above). Aspirin (section 2.9) is less effective than warfarin at preventing emboli, but may be appropriate if there are no other risk factors for stroke, or if warfarin is contra-indicated.

Atrial flutter Like atrial fibrillation, treatment options for atrial flutter involve either controlling the ventricular rate or attempting to restore and maintain sinus rhythm. However, atrial flutter generally responds less well to drug treatment than atrial fibrillation.

Control of the ventricular rate is usually an interim measure pending restoration of sinus rhythm. Ventricular rate can be controlled by administration of a beta-blocker (section 2.4), diltiazem [unlicensed indication], or verapamil (section 2.6.2); an intravenous beta-blocker or verapamil is preferred for rapid control. Digoxin (section 2.1.1) can be added if rate control remains inadequate, and may be particularly useful in those with heart failure.

Conversion to sinus rhythm can be achieved by electrical cardioversion (by cardiac pacing or direct current), pharmacological cardioversion, or catheter ablation. If the duration of atrial flutter is unknown, or it has lasted for over 48 hours, cardioversion should not be attempted until the patient has been fully anticoagulated (see section 2.8.2) for at least 3 weeks; if this is not possible, parenteral anticoagulation (section 2.8.1) should be commenced and a left atrial thrombus ruled out immediately before cardioversion; oral anticoagulation should be given after cardioversion and continued for at least 4 weeks.

Direct current cardioversion is usually the treatment of choice when rapid conversion to sinus rhythm is necessary (e.g. when atrial flutter is associated with haemodynamic compromise); catheter ablation is preferred for the treatment of recurrent atrial flutter. There is a limited role for anti-arrhythmic drugs as their use is not always successful. Flecainide or propafenone can slow atrial flutter, resulting in 1:1 conduction to the ventricles, and should therefore be prescribed in conjunction with a ventricular rate controlling drug such as a beta-blocker, diltiazem [unlicensed indication], or verapamil. Amiodarone can be used when other drug treatments are contra-indicated or ineffective.

All patients should be assessed for their risk of stroke and the need for thromboprophylaxis; the choice of anticoagulant is based on the same criteria as for atrial fibrillation (see notes above).

Paroxysmal supraventricular tachycardia This will often terminate spontaneously or with reflex vagal stimulation such as a Valsalva manoeuvre, immersing the face in ice-cold water, or carotid sinus massage; such manoeuvres should be performed with ECG monitoring.

If the effects of reflex vagal stimulation are transient or ineffective, or if the arrhythmia is causing severe symptoms, intravenous adenosine (section 2.3.2) should be given. If adenosine is ineffective or contra-indicated, intravenous verapamil (section 2.6.2) is an alternative, but it should be avoided in patients recently treated with beta-blockers (see p. 133).

Failure to terminate paroxysmal supraventricular tachycardia with reflex vagal stimulation or drug treatment may suggest an arrhythmia of atrial origin, such as focal atrial tachycardia or atrial flutter.

Treatment with direct current cardioversion is needed in haemodynamically unstable patients or when the above measures have failed to restore sinus rhythm (and an alternative diagnosis has not been found).

Recurrent episodes of paroxysmal supraventricular tachycardia can be treated by catheter ablation, or prevented with drugs such as diltiazem, verapamil, beta-blockers including sotalol (section 2.4), flecainide, or propafenone (section 2.3.2).

Arrhythmias after myocardial infarction In patients with a paroxysmal tachycardia or rapid irregularity of the pulse it is best not to administer an anti-arrhythmic until an ECG record has been obtained. Bradycardia, particularly if complicated by hypotension,

should be treated with 500 micrograms of atropine sulphate given intravenously; the dose may be repeated every 3–5 minutes if necessary up to a maximum total dose of 3 mg. If there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine, adrenaline should be given by intravenous infusion in a dose of 2–10 micrograms/minute, adjusted according to response.

For further advice, refer to the most recent recommendations of the Resuscitation Council (UK) available at www.resus.org.uk.

Ventricular tachycardia Pulseless ventricular tachycardia or ventricular fibrillation should be treated with immediate defibrillation (see Cardiopulmonary Resuscitation, section 2.7.3).

Patients with unstable sustained ventricular tachycardia, who continue to deteriorate with signs of hypotension or reduced cardiac output, should receive direct current cardioversion to restore sinus rhythm. If this fails, intravenous amiodarone (section 2.3.2) should be administered and direct current cardioversion repeated.

Patients with sustained ventricular tachycardia who are haemodynamically stable can be treated with intravenous anti-arrhythmic drugs. Amiodarone is the preferred drug. Flecainide, propafenone (section 2.3.2), and, although less effective, lidocaine (section 2.3.2) have all been used. If sinus rhythm is not restored, direct current cardioversion or pacing should be considered. Catheter ablation is an alternative if cessation of the arrhythmia is not urgent. Non-sustained ventricular tachycardia can be treated with a beta-blocker (section 2.4).

All patients presenting with ventricular tachycardia should be referred to a specialist. Following restoration of sinus rhythm, patients who remain at high risk of cardiac arrest will require maintenance therapy. Most patients will be treated with an implantable cardioverter defibrillator. Beta-blockers or sotalol (in place of a standard beta-blocker), or amiodarone (in combination with a standard beta-blocker), can be used in addition to the device in some patients; alternatively, they can be used alone when use of an implantable cardioverter defibrillator is not appropriate.

Torsade de pointes is a form of ventricular tachycardia associated with a long QT syndrome (usually drug-induced, but other factors including hypokalaemia, severe bradycardia, and genetic predisposition are also implicated). Episodes are usually self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous infusion of magnesium sulphate (section 9.5.1.3) is usually effective. A beta-blocker (but not sotalol) and atrial (or ventricular) pacing can be considered. Anti-arrhythmics can further prolong the QT interval, thus worsening the condition.

2.3.2 Drugs for arrhythmias

Anti-arrhythmic drugs can be classified clinically into those that act on supraventricular arrhythmias (e.g. verapamil), those that act on both supraventricular and ventricular arrhythmias (e.g. amiodarone), and those that act on ventricular arrhythmias (e.g. lidocaine).

Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

Class I: membrane stabilising drugs (e.g. lidocaine, flecainide)

Class II: beta-blockers

Class III: amiodarone; sotalol (also Class II)

Class IV: calcium-channel blockers (includes verapamil but not dihydropyridines)

Cautions The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

Supraventricular arrhythmias

Adenosine is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia. As it has a very short duration of action (half-life only about 8 to 10 seconds, but prolonged in those taking dipyridamole), most side-effects are short lived. Unlike verapamil, adenosine can be used after a beta-blocker. Verapamil may be preferable to adenosine in asthma.

Dronedarone is a multi-channel blocking anti-arrhythmic drug; it is licensed for use in clinically stable patients with previous or current non-permanent atrial fibrillation, to prevent recurrence or to lower the ventricular rate.

The *Scottish Medicines Consortium* (p. 4) has advised (August 2010) that dronedarone (*Multaq*®) is accepted for restricted use within NHS Scotland for the prevention of recurrence of atrial fibrillation in patients in whom conventional first-line anti-arrhythmic drugs are ineffective, contra-indicated, or not tolerated; treatment should be initiated on specialist advice only.

NICE guidance

Dronedarone for the treatment of non-permanent atrial fibrillation (August 2010)

Dronedarone is an option for the treatment of non-permanent atrial fibrillation only in patients who:

- are not controlled on first-line therapy (usually including beta-blockers), **and**
- do not have unstable New York Heart Association class III or IV heart failure, **and**
- have at least one cardiovascular risk factor from the following:
  - hypertension managed by at least two different drug classes
  - diabetes mellitus
  - previous transient ischaemic attack, stroke, or systemic embolism
  - left atrial diameter ≥50 mm
  - left ventricular ejection fraction <40%
  - age ≥70 years

Oral administration of a **cardiac glycoside** (such as digoxin, section 2.1.1) slows the ventricular response in cases of atrial fibrillation and atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate. Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome).

Verapamil (section 2.6.2) is usually effective for supraventricular tachycardias. An initial intravenous dose (**important**: serious beta-blocker interaction hazard, see p. 133) may be followed by oral treatment; hypotension may occur with large doses. It should not be used for tachyarrhythmias where the QRS complex is wide (i.e. broad complex) unless a supraventricular origin has been established beyond reasonable doubt. It is also contra-indicated in atrial fibrillation or atrial flutter associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It should not be used in children with arrhythmias without specialist advice; some supraventricular arrhythmias in childhood can be accelerated by verapamil with dangerous consequences.

Intravenous administration of a **beta-blocker** (section 2.4) such as esmolol or propranolol, can achieve rapid control of the ventricular rate.

Drugs for both supraventricular and ventricular arrhythmias include **amiodarone**, **beta-blockers** (see p. 98), **disopyramide**, **flecainide**, **procainamide** (available from 'special-order' manufacturers or specialist importing companies, see p. 988), and **propafenone**, see below under Supraventricular and Ventricular Arrhythmias.

ADENOSINE

Indications rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome); aid to diagnosis of broad or narrow complex supraventricular tachycardias

Cautions monitor ECG and have resuscitation facilities available; atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); first-degree AV block; bundle branch block; left main coronary artery stenosis; uncorrected hypovolaemia; stenotic valvular heart disease; left to right shunt; pericarditis; pericardial effusion; autonomic dysfunction; stenotic carotid artery disease with cerebrovascular insufficiency; recent myocardial infarction; heart failure; heart transplant (see below); **interactions:** Appendix 1 (adenosine)

Contra-indications second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted); long QT syndrome; severe hypotension; decompensated heart failure; chronic obstructive lung disease (including asthma)

Pregnancy large doses may produce foetal toxicity; manufacturer advises use only if essential

Breast-feeding no information available—unlikely to be present in milk owing to short half-life

Side-effects nausea; arrhythmia (discontinue if asystole or severe bradycardia occur), sinus pause, AV block, flushing, angina (discontinue), dizziness; dyspnoea; headache; *less commonly* metallic taste; palpitation, hyperventilation, weakness, blurred vision, sweating; *very rarely* transient worsening of intracranial hypertension, bronchospasm, injection-site reactions; *also reported* vomiting, syncope, hypotension (discontinue if severe), cardiac arrest, respiratory failure (discontinue), and convulsions

Dose

- By rapid intravenous injection into central or large peripheral vein, 6 mg over 2 seconds with cardiac monitoring; if necessary followed by 12 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes; increments should not be given if high level AV block develops at any particular dose

  Important Patients with a **heart transplant** are very sensitive to effects of adenosine and should receive initial dose of 3 mg over 2 seconds, followed if necessary by 6 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes. Also, if essential to give with dipyridamole reduce adenosine dose to a quarter of the usual dose

  Note Adenosine doses in the BNF may differ from those in product literature

Adenocor® (Sanofi-Aventis) PoM

Injection, adenosine 3 mg/mL in physiological saline, net price 2-mL vial = £4.45 (hosp. only)

Note Intravenous infusion of adenosine (*Adenoscan®*, Sanofi-Aventis) may be used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate—consult product literature

DRONEDARONE

Indications see notes above

Cautions heart failure (avoid in patients with a recent history of moderate heart failure, or with a significantly reduced left ventricular function); correct hypokalaemia and hypomagnesaemia before starting and during treatment; measure serum creatinine 7 days after initiation; **interactions:** Appendix 1 (dronedarone)

Contra-indications second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted); bradycardia; prolonged QT interval; haemodynamically unstable patients (including those with moderate or severe heart failure)

Hepatic impairment avoid in severe impairment

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances; QT-interval prolongation, bradycardia; fatigue, asthenia; rash, pruritus; raised serum creatinine; *less commonly* taste disturbance; erythema, eczema, dermatitis, photosensitivity

Dose

- By mouth, 400 mg twice daily

Multaq® (Sanofi-Aventis) ▼ PoM

Tablets, f/c, dronedarone (as hydrochloride) 400 mg, net price 20-tab pack = £22.50, 60-tab pack = £67.50. Label: 21

Supraventricular and ventricular arrhythmias

Amiodarone is used in the treatment of arrhythmias, particularly when other drugs are ineffective or contra-indicated. It can be used for paroxysmal supraventricu-

lar, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It can also be used for tachyarrhythmias associated with Wolff-Parkinson-White syndrome. It should be initiated only under hospital or specialist supervision. Amiodarone may be given by intravenous infusion as well as by mouth, and has the advantage of causing little or no myocardial depression. Unlike oral amiodarone, intravenous amiodarone acts relatively rapidly.

Intravenous injection of amiodarone can be used in cardiopulmonary resuscitation for ventricular fibrillation or pulseless tachycardia unresponsive to other interventions (section 2.7.3).

Amiodarone has a very long half-life (extending to several weeks) and only needs to be given once daily (but high doses can cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely (see also Appendix 1).

Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought. Because of the possibility of phototoxic reactions, patients should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen (section 13.8.1) to protect against both long-wave ultraviolet and visible light should be used.

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism may occur. Clinical assessment alone is unreliable, and laboratory tests should be performed before treatment and every 6 months. Thyroxine (T4) may be raised in the absence of hyperthyroidism; therefore tri-iodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis. The thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required.

Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodarone. Fresh neurological symptoms should raise the possibility of peripheral neuropathy.

Amiodarone is also associated with hepatotoxicity and treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop.

Beta-blockers act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart, for details see section 2.4. For special reference to the role of **sotalol** in ventricular arrhythmias, see p. 98.

Disopyramide can be given by intravenous injection to control arrhythmias after myocardial infarction (including those not responding to lidocaine), but it impairs cardiac contractility. Oral administration of disopyramide is useful, but it has an antimuscarinic effect which limits its use in patients susceptible to angle-closure glaucoma or with prostatic hyperplasia.

Flecainide belongs to the same general class as lidocaine and may be of value for serious symptomatic ventricular arrhythmias. It may also be indicated for junctional re-entry tachycardias and for paroxysmal atrial fibrillation. However, it can precipitate serious arrhythmias in a small minority of patients (including those with otherwise normal hearts).

Propafenone is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias. It has complex mechanisms of action, including weak beta-blocking activity (therefore caution is needed in obstructive airways disease—contra-indicated if severe).

Drugs for supraventricular arrhythmias include **adenosine**, **cardiac glycosides**, and **verapamil**; see above under Supraventricular Arrhythmias. Drugs for ventricular arrhythmias include **lidocaine**; see under Ventricular Arrhythmias, p. 96.

Mexiletine and procainamide are both available from 'special-order' manufacturers or specialist importing companies, see p. 988. Mexiletine can be used for life-threatening ventricular arrhythmias; procainamide is given by intravenous injection to control ventricular arrhythmias.

AMIODARONE HYDROCHLORIDE

Indications see notes above (should be initiated in hospital or under specialist supervision)

Cautions liver-function and thyroid-function tests required before treatment and then every 6 months (see notes above for tests of thyroid function); hypokalaemia (measure serum-potassium concentration before treatment); chest x-ray required before treatment; heart failure; elderly; severe bradycardia and conduction disturbances in excessive dosage; intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepatocellular toxicity (monitor transaminases closely); administration by central venous catheter recommended if repeated or continuous infusion required—infusion via peripheral veins may cause pain and inflammation; ECG monitoring and resuscitation facilities must be available during intravenous use; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (amiodarone)

Contra-indications (except in cardiac arrest) sinus bradycardia, sino-atrial heart block; unless pacemaker fitted avoid in severe conduction disturbances or sinus node disease; thyroid dysfunction; iodine sensitivity; avoid *intravenous use* in severe respiratory failure, circulatory collapse, or severe arterial hypotension; avoid bolus injection in congestive heart failure or cardiomyopathy

Pregnancy possible risk of neonatal goitre; use only if no alternative

Breast-feeding avoid; present in milk in significant amounts; theoretical risk of neonatal hypothyroidism from release of iodine

Side-effects nausea, vomiting, taste disturbances, raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders), jaundice; bradycardia (see Cautions);

pulmonary toxicity (including pneumonitis and fibrosis); tremor, sleep disorders; hypothyroidism, hyperthyroidism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discoloration (see also notes above), injection-site reactions; *less commonly* onset or worsening of arrhythmia, conduction disturbances (see Cautions), peripheral neuropathy and myopathy (usually reversible on withdrawal); *very rarely* chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating, and hot flushes

Dose

- By mouth, 200 mg 3 times daily for 1 week reduced to 200 mg twice daily for a further week; maintenance, usually 200 mg daily or the minimum required to control the arrhythmia
- By intravenous infusion (see Cautions above), initially 5 mg/kg over 20–120 minutes with ECG monitoring; subsequent infusion given if necessary according to response up to max. 1.2 g in 24 hours
- Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation, section 2.7.3

Amiodarone (Non-proprietary) PoM

Tablets, amiodarone hydrochloride 100 mg, net price 28-tab pack = £1.75; 200 mg, 28-tab pack = £2.22. Label: 11

Injection, amiodarone hydrochloride 30 mg/mL, net price 10-mL prefilled syringe = £19.60
Excipients may include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

Sterile concentrate, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.33, 6-mL amp = £2.86. For dilution and use as an infusion
Excipients may include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

Cordarone X® (Sanofi-Aventis) PoM

Tablets, scored, amiodarone hydrochloride 100 mg, net price 28-tab pack = £4.28; 200 mg, 28-tab pack = £6.99. Label: 11

Sterile concentrate, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.33. For dilution and use as an infusion
Excipients include benzyl alcohol (avoid in neonates unless no safer alternative available, see Excipients, p. 2)

DISOPYRAMIDE

Indications ventricular arrhythmias, especially after myocardial infarction; supraventricular arrhythmias

Cautions monitor for hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or torsade de pointes (discontinue if occur); atrial flutter or atrial tachycardia with partial block, bundle branch block, heart failure (avoid if severe); prostatic enlargement; susceptibility to angle-closure glaucoma; avoid in acute porphyria (section 9.8.2); **interactions**: Appendix 1 (disopyramide)

Contra-indications second- and third-degree heart block and sinus node dysfunction (unless pacemaker fitted); cardiogenic shock; severe uncompensated heart failure

Hepatic impairment half-life prolonged—may need dose reduction

Renal impairment reduce dose by increasing dose interval; adjust according to response; avoid sustained-release preparation

Pregnancy may induce labour if used in third trimester

Breast-feeding present in milk—use only if essential and monitor infant for antimuscarinic effects

Side-effects ventricular tachycardia, ventricular fibrillation or torsade de pointes (usually associated with prolongation of QRS complex or QT interval—see Cautions above), myocardial depression, hypotension, AV block; antimuscarinic effects include dry mouth, blurred vision, urinary retention, and very rarely angle-closure glaucoma; gastro-intestinal irritation; psychosis, cholestatic jaundice, hypoglycaemia also reported (see Cautions above)

Dose

- By mouth, 300–800 mg daily in divided doses
- By slow intravenous injection, 2 mg/kg over at least 5 minutes to a max. of 150 mg, with ECG monitoring, followed immediately *either* by 200 mg by mouth, then 200 mg every 8 hours for 24 hours *or* 400 micrograms/kg/hour by intravenous infusion; max. 300 mg in first hour and 800 mg daily

Disopyramide (Non-proprietary) PoM

Capsules, disopyramide (as phosphate) 100 mg, net price 84 = £24.38; 150 mg, 84 = £32.57

Rythmodan® (Sanofi-Aventis) PoM

Capsules, disopyramide 100 mg (green/beige), net price 84-cap pack = £14.14; 150 mg, 84-cap pack = £18.76

Injection, disopyramide (as phosphate) 10 mg/mL, net price 5-mL amp = £2.61

Modified release

Rythmodan Retard® (Sanofi-Aventis) PoM

Tablets, m/r, scored, f/c, disopyramide (as phosphate) 250 mg, net price 60-tab pack = £27.72. Label: 25

Dose 250–375 mg every 12 hours

FLECAINIDE ACETATE

Indications *capsules, tablets, and injection:* AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily)

Immediate-release tablets only: symptomatic sustained ventricular tachycardia, disabling symptoms of premature ventricular contractions or non-sustained ventricular tachycardia in patients resistant to or intolerant of other therapy

Injection only: ventricular tachyarrhythmias resistant to other treatment

Cautions patients with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably); atrial fibrillation following heart surgery; elderly (accumulation may occur); ECG monitoring and resuscitation facilities

must be available during intravenous use; **interactions:** Appendix 1 (flecainide)

Contra-indications heart failure; abnormal left ventricular function; history of myocardial infarction and either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia; long-standing atrial fibrillation where conversion to sinus rhythm not attempted; haemodynamically significant valvular heart disease; avoid in sinus node dysfunction, atrial conduction defects, second-degree or greater AV block, bundle branch block or distal block unless pacing rescue available

Hepatic impairment avoid (or reduce dose) in severe liver disease

Renal impairment reduce initial oral dose to max. 100 mg daily or reduce intravenous dose by 50%, if eGFR less than 35 mL/minute/1.73 m^2

Pregnancy used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in *animal* studies; infant hyperbilirubinaemia also reported

Breast-feeding significant amount present in milk but not known to be harmful

Side-effects oedema, pro-arrhythmic effects; dyspnoea; dizziness, asthenia, fatigue, fever; visual disturbances; *rarely* pneumonitis, hallucinations, depression, confusion, amnesia, dyskinesia, convulsions, peripheral neuropathy; *also reported* gastrointestinal disturbances, anorexia, hepatic dysfunction, flushing, syncope, drowsiness, tremor, vertigo, headache, anxiety, insomnia, ataxia, paraesthesia, anaemia, leucopenia, thrombocytopenia, corneal deposits, tinnitus, increased antinuclear antibodies, hypersensitivity reactions (including rash, urticaria, and photosensitivity), increased sweating

Dose

- By mouth (initiated under direction of hospital consultant), ventricular arrhythmias, initially 100 mg twice daily (max. 400 mg daily usually reserved for rapid control or in heavily built patients), reduced after 3–5 days to the lowest dose that controls arrhythmia

  Supraventricular arrhythmias, 50 mg twice daily, increased if required to max. 300 mg daily
- By slow intravenous injection (in hospital), 2 mg/kg over 10–30 minutes, max. 150 mg, with ECG monitoring; followed if required by infusion at a rate of 1.5 mg/kg/hour for 1 hour, subsequently reduced to 100–250 micrograms/kg/hour for up to 24 hours; max. cumulative dose in first 24 hours, 600 mg; transfer to *oral* treatment, as above

Flecainide (Non-proprietary) PoM

Tablets, flecainide acetate 50 mg, net price 60-tab pack = £6.04; 100 mg, 60-tab pack = £8.95

Tambocor® (3M) PoM

Tablets, flecainide acetate 50 mg, net price 60-tab pack = £11.57; 100 mg (scored), 60-tab pack = £16.53

Injection, flecainide acetate 10 mg/mL, net price 15-mL amp = £4.40

Modified release

Tambocor® XL (Meda) PoM

Capsules, m/r, grey/pink, flecainide acetate 200 mg, net price 30-cap pack = £14.77. Label: 25

Dose supraventricular arrhythmias, 200 mg once daily

Note Not to be used to control arrhythmias in acute situations; patients stabilised on 200 mg daily immediate-release flecainide may be transferred to *Tambocor® XL*

PROPAFENONE HYDROCHLORIDE

Indications ventricular arrhythmias; paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or fibrillation and paroxysmal re-entrant tachycardias involving the AV node or accessory pathway, where standard therapy ineffective or contra-indicated

Cautions heart failure; elderly; pacemaker patients; potential for conversion of paroxysmal atrial fibrillation to atrial flutter with 2:1 or 1:1 conduction block; great caution in obstructive airways disease owing to beta-blocking activity (contra-indicated if severe); **interactions:** Appendix 1 (propafenone)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications uncontrolled congestive heart failure, cardiogenic shock (except arrhythmia induced), severe bradycardia, electrolyte disturbances, severe obstructive pulmonary disease, marked hypotension; myasthenia gravis; unless adequately paced avoid in sinus node dysfunction, atrial conduction defects, second degree or greater AV block, bundle branch block or distal block

Hepatic impairment reduce dose

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances, dry mouth, bitter taste, anorexia, jaundice, cholestasis, hepatitis; chest pain, bradycardia, sino-atrial, atrioventricular, or intraventricular blocks, hypotension (including postural hypotension), dizziness, syncope, pro-arhythmic effects; anxiety, confusion, ataxia, restlessness, headache, sleep disorders, paraesthesia, fatigue, seizures, extrapyramidal symptoms; impotence, reduced sperm count; blood disorders; lupus syndrome; blurred vision; hypersensitivity (including skin reactions)

Dose

- Body-weight 70 kg and over, initially 150 mg 3 times daily after food under direct hospital supervision with ECG monitoring and blood pressure control (if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits); may be increased at intervals of at least 3 days to 300 mg twice daily and, if necessary, to max. 300 mg 3 times daily; body-weight under 70 kg, reduce dose; ELDERLY may respond to lower doses

Arythmol® (Abbott) PoM

Tablets, f/c, propafenone hydrochloride 150 mg, net price 90-tab pack = £7.37; 300 mg, 60-tab pack = £9.34. Label: 21, 25, counselling, driving

Ventricular arrhythmias

Intravenous **lidocaine** can be used for the treatment of ventricular tachycardia in haemodynamically stable patients (section 2.3.1), and ventricular fibrillation and pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation (section 2.7.3), however it is no longer the anti-arrhythmic drug of first choice.

Drugs for both supraventricular and ventricular arrhythmias include **amiodarone**, **beta-blockers**, **disopyramide**, **flecainide**, **procainamide** (available from 'special-order' manufacturers or specialist importing

companies, see p. 988), and **propafenone**, see above under Supraventricular and Ventricular Arrhythmias.

Mexiletine is available from 'special-order' manufacturers or specialist importing companies (see p. 988) for treatment of life-threatening ventricular arrhythmias.

LIDOCAINE HYDROCHLORIDE

(Lignocaine hydrochloride)

Indications ventricular arrhythmias, especially after myocardial infarction; eye (section 11.7); local anaesthesia (section 15.2)

Cautions lower doses in congestive cardiac failure and following cardiac surgery; monitor ECG and have resuscitation facilities available; elderly; **interactions:** Appendix 1 (lidocaine)

Contra-indications sino-atrial disorders, all grades of atrioventricular block, severe myocardial depression; acute porphyria (section 9.8.2)

Hepatic impairment caution—increased risk of side-effects

Renal impairment possible accumulation of lidocaine and active metabolite; caution in severe impairment

Pregnancy crosses the placenta but not known to be harmful in *animal* studies—use if benefit outweighs risk

Breast-feeding present in milk but amount too small to be harmful

Side-effects dizziness, paraesthesia, or drowsiness (particularly if injection too rapid); other CNS effects include confusion, respiratory depression and convulsions; hypotension and bradycardia (may lead to cardiac arrest); *rarely* hypersensitivity reactions including anaphylaxis

Dose

- By intravenous injection, in patients without gross circulatory impairment, 100 mg as a bolus over a few minutes (50 mg in lighter patients or those whose circulation is severely impaired), followed immediately by infusion of 4 mg/minute for 30 minutes, 2 mg/minute for 2 hours, then 1 mg/minute; reduce concentration further if infusion continued beyond 24 hours (ECG monitoring and specialist advice for infusion)

  Note Following *intravenous injection* lidocaine has a short duration of action (lasting for 15–20 minutes). If an *intravenous infusion* is not immediately available the initial *intravenous injection* of 50–100 mg can be repeated if necessary once or twice at intervals of not less than 10 minutes

Lidocaine (Non-proprietary) PoM

Injection 1%, lidocaine hydrochloride 10 mg/mL, net price 2-mL amp = 21p; 5-mL amp = 26p; 10-mL amp = 39p; 20-mL amp = 78p

Injection 2%, lidocaine hydrochloride 20 mg/mL, net price 2-mL amp = 32p; 5-mL amp = 31p; 10-mL amp = 60p; 20-mL amp = 80p

Infusion, lidocaine hydrochloride 0.1% (1 mg/mL) and 0.2% (2 mg/mL) in glucose intravenous infusion 5%. 500-mL containers

Minijet® Lignocaine (UCB Pharma) PoM

Injection, lidocaine hydrochloride 1% (10 mg/mL), net price 10-mL disposable syringe = £8.48; 2% (20 mg/mL), 5-mL disposable syringe = £8.18

2.4 Beta-adrenoceptor blocking drugs

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver.

Many beta-blockers are now available and in general they are all equally effective. There are, however, differences between them, which may affect choice in treating particular diseases or individual patients.

Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors. **Oxprenolol**, **pindolol**, **acebutolol**, and **celiprolol** have intrinsic sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities.

Some beta-blockers are lipid soluble and some are water soluble. **Atenolol**, **celiprolol**, **nadolol**, and **sotalol** are the most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares. Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are, however, available in modified-release formulations so that administration once daily is adequate for hypertension. For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-blockers, such as atenolol, bisoprolol, carvedilol, celiprolol, and nadolol, have an intrinsically longer duration of action and need to be given only once daily.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure (see also section 2.5.5). **Sotalol** may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias (**important:** particular care is required to avoid hypokalaemia in patients taking sotalol).

Labetalol, **celiprolol**, **carvedilol**, and **nebivolol** are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance. There is no evidence that these drugs have important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers can precipitate bronchospasm and should therefore usually be avoided in patients with a history of asthma. When there is no suitable alternative, it may be necessary for a patient with well-controlled asthma, or chronic obstructive pulmonary disease (without significant reversible airways obstruction), to receive treatment with a beta-blocker for a co-existing condition (e.g. heart failure or following myocardial infarction). In this situation, a cardioselective beta-blocker should be selected and initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects. **Atenolol**, **bisoprolol**, **metoprolol**, **nebivolol**, and (to a lesser extent) **acebutolol**, have less effect on the $beta_2$ (bronchial) receptors and are, therefore, relatively *car-*

dioselective, but they are not *cardiospecific*. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA, see above), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers, see above).

Beta-blockers can affect carbohydrate metabolism, causing hypoglycaemia or hyperglycaemia in patients with or without diabetes; they can also interfere with metabolic and autonomic responses to hypoglycaemia, thereby masking symptoms such as tachycardia. However, beta-blockers are not contra-indicated in diabetes, although the cardioselective beta-blockers (see above) may be preferred. Beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Pregnancy Beta-blockers may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; the risk is greater in severe hypertension. The use of labetalol in maternal hypertension is not known to be harmful, except possibly in the first trimester. Information on the safety of carvedilol during pregnancy is lacking. If beta-blockers are used close to delivery, infants should be monitored for signs of beta-blockade (and alpha-blockade with labetalol or carvedilol). For the treatment of hypertension in pregnancy, see section 2.5.

Breast-feeding Infants should be monitored as there is a risk of possible toxicity due to beta-blockade (and alpha-blockade with labetalol or carvedilol), but the amount of most beta-blockers present in milk is too small to affect infants. Acebutolol, atenolol, nadolol, and sotalol are present in milk in greater amounts than other beta-blockers. The manufacturers of celiprolol, esmolol, and nebivolol advise avoidance if breast-feeding.

Hypertension The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action.

Beta-blockers are effective for reducing blood pressure but other antihypertensives (section 2.5) are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Other antihypertensives are therefore preferred for routine initial treatment of uncomplicated hypertension.

In general, the dose of a beta-blocker does not have to be high; for example, atenolol is given in a dose of 25–50 mg daily and it is rarely necessary to increase the dose to 100 mg.

Beta-blockers can be used to control the pulse rate in patients with *phaeochromocytoma* (section 2.5.4). However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis. For this reason phenoxybenzamine should always be used together with the beta-blocker.

Angina By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with *angina* (for further details on the management of stable angina and acute coronary syndromes, see section 2.10.1). As with hypertension there is no good evidence of the superiority of any one drug, although occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause an exacerbation of angina and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease (**important**: see p. 133).

Myocardial infarction For advice on the management of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction, see section 2.10.1. Several studies have shown that some beta-blockers can reduce the recurrence rate of *myocardial infarction*. However, uncontrolled heart failure, hypotension, bradyarrhythmias, and obstructive airways disease render beta-blockers unsuitable in some patients following a myocardial infarction. **Atenolol** and **metoprolol** may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while **acebutolol**, **metoprolol**, **propranolol**, and **timolol** have protective value when started in the early convalescent phase. The evidence relating to other beta-blockers is less convincing; some have not been tested in trials of secondary prevention. Sudden cessation of a beta-blocker can cause a rebound worsening of myocardial ischaemia.

Arrhythmias Beta-blockers act as *anti-arrhythmic drugs* principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular tachycardias, and are used to control those following myocardial infarction (see above).

Esmolol is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, particularly in the peri-operative period. It may also be used in other situations, such as acute myocardial infarction, when sustained beta-blockade might be hazardous.

Sotalol, a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity, is used for prophylaxis in paroxysmal supraventricular arrhythmias. It also suppresses ventricular ectopic beats and non-sustained ventricular tachycardia. It has been shown to be more effective than lidocaine in the termination of spontaneous sustained ventricular tachycardia due to coronary disease or cardiomyopathy. However, it may induce torsade de pointes in susceptible patients.

Heart failure Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. **Bisoprolol** and **carvedilol** reduce mortality in any grade of stable heart failure; **nebivolol** is licensed for stable mild to moderate heart failure in patients over 70

years. Treatment should be initiated by those experienced in the management of heart failure (section 2.5.5).

Thyrotoxicosis Beta-blockers are used in pre-operative preparation for thyroidectomy. Administration of propranolol can reverse clinical symptoms of *thyrotoxicosis* within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier (section 6.2.2).

Other uses Beta-blockers have been used to alleviate some symptoms of *anxiety*; probably patients with palpitation, tremor, and tachycardia respond best (see also section 4.1.2 and section 4.9.3). Beta-blockers are also used in the *prophylaxis of migraine* (section 4.7.4.2). Betaxolol, carteolol, levobunolol, metipranolol, and timolol are used topically in *glaucoma* (section 11.6).

PROPRANOLOL HYDROCHLORIDE

Indications see under Dose

Cautions see notes above; also avoid abrupt withdrawal especially in ischaemic heart disease; first-degree AV block; portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function—see notes above); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked (also see notes above); psoriasis; history of hypersensitivity—may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine) (see also section 3.4.3); **interactions:** Appendix 1 (beta-blockers), **important:** verapamil interaction, see also p. 133

Contra-indications asthma (but see notes above), uncontrolled heart failure, Prinzmetal's angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third- degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma (apart from specific use with alpha-blockers, see also notes above)

Bronchospasm Beta-blockers, including those considered to be cardioselective, should usually be avoided in patients with a history of asthma or bronchospasm. However, when there is no alternative, a cardioselective beta-blocker can be given to these patients with caution and under specialist supervision.

Hepatic impairment reduce oral dose

Renal impairment manufacturer advises caution—dose reduction may be required

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud's phenomenon); bronchospasm (see above), dyspnoea; headache, fatigue, sleep disturbances, paraesthesia, dizziness, vertigo, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; *rarely* rashes and dry eyes (reversible on withdrawal); **overdosage:** see Emergency Treatment of Poisoning, p. 37

Dose

- By mouth, hypertension, initially 80 mg twice daily, increased at weekly intervals as required; maintenance 160–320 mg daily

  Prophylaxis of variceal bleeding in portal hypertension, initially 40 mg twice daily, increased to 80 mg twice daily according to heart rate; max. 160 mg twice daily

  Phaeochromocytoma (only with an alpha-blocker), 60 mg daily for 3 days before surgery *or* 30 mg daily in patients unsuitable for surgery

  Angina, initially 40 mg 2–3 times daily; maintenance 120–240 mg daily

  Arrhythmias, hypertrophic cardiomyopathy, anxiety tachycardia, and thyrotoxicosis (adjunct), 10–40 mg 3–4 times daily

  Anxiety with symptoms such as palpitation, sweating, tremor, 40 mg once daily, increased to 40 mg 3 times daily if necessary

  Prophylaxis after myocardial infarction, 40 mg 4 times daily for 2–3 days, then 80 mg twice daily, beginning 5 to 21 days after infarction

  Essential tremor, initially 40 mg 2–3 times daily; maintenance 80–160 mg daily

  Migraine prophylaxis, 80–240 mg daily in divided doses

- By intravenous injection, arrhythmias and thyrotoxic crisis, 1 mg over 1 minute; if necessary repeat at 2-minute intervals; max. total dose 10 mg (5 mg in anaesthesia)

  Note Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 37

Propranolol (Non-proprietary) PoM

Tablets, propranolol hydrochloride 10 mg, net price 28 = 92p; 40 mg, 28 = 93p; 80 mg, 56 = £1.54; 160 mg, 56 = £4.02. Label: 8

Brands include *Angilol®*

Oral solution, propranolol hydrochloride 5 mg/5 mL, net price 150 mL = £12.50; 10 mg/5 mL, 150 mL = £16.45; 50 mg/5 mL, 150 mL = £19.98. Label: 8

Brands include *Syprol®*

Inderal® (AstraZeneca) PoM

Injection, propranolol hydrochloride 1 mg/mL, net price 1-mL amp = 21p

Modified release

Note Modified-release preparations can be used for once daily administration

Half-Inderal LA® (AstraZeneca) PoM

Capsules, m/r, lavender/pink, propranolol hydrochloride 80 mg, net price 28-cap pack = £5.40. Label: 8, 25

Note Modified-release capsules containing propranolol hydrochloride 80 mg also available; brands include *Bedranol SR®*, *Half Beta Prograne®*

Inderal-LA® (AstraZeneca) PoM

Capsules, m/r, lavender/pink, propranolol hydrochloride 160 mg, net price 28-cap pack = £1.91. Label: 8, 25

Note Modified-release capsules containing propranolol hydrochloride 160 mg also available; brands include *Bedranol SR®*, *Beta Prograne®*, *Slo-Pro®*

ACEBUTOLOL

Indications see under Dose

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment halve dose if eGFR 25–50 mL/minute/1.73 m^2; use quarter dose if eGFR less than 25 mL/minute/1.73 m^2; do not administer more than once daily

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Dose

- Hypertension, initially 400 mg once daily *or* 200 mg twice daily, increased after 2 weeks to 400 mg twice daily if necessary
- Angina, initially 400 mg once daily *or* 200 mg twice daily; 300 mg 3 times daily in severe angina; up to 1.2 g daily has been used
- Arrhythmias, 0.4–1.2 g daily in 2–3 divided doses

Sectral® (Sanofi-Aventis) PoM

Capsules, acebutolol (as hydrochloride) 100 mg (buff/white), net price 84-cap pack = £14.97; 200 mg (buff/pink), 56-cap pack = £19.18. Label: 8

Tablets, f/c, acebutolol 400 mg (as hydrochloride), net price 28-tab pack = £18.62. Label: 8

ATENOLOL

Indications see under Dose

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment max. 50 mg daily (10 mg on alternate days *intravenously*) if eGFR 15–35 mL/minute/1.73 m^2; max. 25 mg daily or 50 mg on alternate days (10 mg every 4 days *intravenously*) if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Dose

- By mouth, hypertension, 25–50 mg daily (higher doses rarely necessary)

  Angina, 100 mg daily in 1 or 2 doses

  Arrhythmias, 50–100 mg daily

  Migraine prophylaxis [unlicensed], 50–200 mg daily in divided doses
- By intravenous injection, arrhythmias, 2.5 mg at a rate of 1 mg/minute, repeated at 5-minute intervals to a max. of 10 mg

  Note Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 37
- By intravenous infusion, arrhythmias, 150 micrograms/kg over 20 minutes, repeated every 12 hours if required

  Early intervention within 12 hours of myocardial infarction (section 2.10.1), by intravenous injection over 5 minutes, 5 mg, then by mouth, 50 mg after 15 minutes, 50 mg after 12 hours, then 100 mg daily

Atenolol (Non-proprietary) PoM

Tablets, atenolol 25 mg, net price 28-tab pack = 83p; 50 mg, 28-tab pack = 86p; 100 mg, 28-tab pack = 91p. Label: 8

Tenormin® (AstraZeneca) PoM

'25' tablets, f/c, atenolol 25 mg, net price 28-tab pack = £1.16. Label: 8

LS tablets, orange, f/c, scored, atenolol 50 mg, net price 28-tab pack = £2.04. Label: 8

Tablets, orange, f/c, scored, atenolol 100 mg, net price 28-tab pack = £3.46. Label: 8

Syrup, sugar-free, atenolol 25 mg/5 mL, net price 300 mL = £8.55. Label: 8

Injection, atenolol 500 micrograms/mL, net price 10-mL amp = 96p (hosp. only)

With diuretic

Co-tenidone (Non-proprietary) PoM

Tablets, co-tenidone 50/12.5 (atenolol 50 mg, chlortalidone 12.5 mg), net price 28-tab pack = £1.77; co-tenidone 100/25 (atenolol 100 mg, chlortalidone 25 mg), 28-tab pack = £1.57. Label: 8

Dose hypertension, 1 tablet daily (but see also under Dose above)

Kalten® (BPC 100) PoM

Capsules, red/ivory, atenolol 50 mg, co-amilozide 2.5/25 (anhydrous amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-cap pack = £12.17. Label: 8

Dose hypertension, 1 capsule daily

Tenoret 50® (AstraZeneca) PoM

Tablets, brown, f/c, co-tenidone 50/12.5 (atenolol 50 mg, chlortalidone 12.5 mg), net price 28-tab pack = £1.15. Label: 8

Dose hypertension, 1 tablet daily

Tenoretic® (AstraZeneca) PoM

Tablets, brown, f/c, co-tenidone 100/25 (atenolol 100 mg, chlortalidone 25 mg), net price 28-tab pack = £1.25. Label: 8

Dose hypertension, 1 tablet daily (but see also under Dose above)

With calcium-channel blocker

Note Only indicated when calcium-channel blocker or beta-blocker alone proves inadequate. For prescribing information on nifedipine see section 2.6.2

Beta-Adalat® (Bayer Schering) PoM

Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £9.00. Label: 8, 25

Dose hypertension, 1 capsule daily, increased if necessary to twice daily; ELDERLY, 1 daily

Angina, 1 capsule twice daily

Tenif® (AstraZeneca) PoM

Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £10.63. Label: 8, 25

Dose hypertension, 1 capsule daily, increased if necessary to twice daily; ELDERLY, 1 daily

Angina, 1 capsule twice daily

BISOPROLOL FUMARATE

Indications see under Dose

Cautions see under Propranolol Hydrochloride; ensure heart failure not worsening before increasing dose

Contra-indications see under Propranolol Hydrochloride; also acute or decompensated heart failure requiring intravenous inotropes; sino-atrial block

Hepatic impairment max. 10 mg daily in severe impairment

Renal impairment reduce dose if eGFR less than 20 mL/minute/1.73 m^2 (max. 10 mg daily)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride; also *less commonly* depression, muscle weakness, and cramp; *rarely* hypertriglyceridaemia, syncope, and hearing impairment; *very rarely* conjunctivitis

Dose

- Hypertension and angina, usually 10 mg once daily (5 mg may be adequate in some patients); max. 20 mg daily
- Adjunct in heart failure (section 2.5.5), initially 1.25 mg once daily (in the morning) for 1 week then, if well tolerated, increased to 2.5 mg once daily for 1 week, then 3.75 mg once daily for 1 week, then 5 mg once daily for 4 weeks, then 7.5 mg once daily for 4 weeks, then 10 mg once daily; max. 10 mg daily

Bisoprolol Fumarate (Non-proprietary) PoM
Tablets, bisoprolol fumarate 5 mg, net price 28-tab pack = £1.08; 10 mg, 28-tab pack = £1.14. Label: 8

Cardicor® (Merck Serono) PoM
Tablets, f/c, bisoprolol fumarate 1.25 mg (white), net price 28-tab pack = £4.90; 2.5 mg (scored, white), 28-tab pack = £3.40; 3.75 mg (scored, off-white), 28-tab pack = £4.90; 5 mg (scored, light yellow), 28-tab pack = £5.90; 7.5 mg (scored, yellow), 28-tab pack = £5.90; 10 mg (scored, orange), 28-tab pack = £5.90. Label: 8

Emcor® (Merck Serono) PoM
LS Tablets, yellow, f/c, scored, bisoprolol fumarate 5 mg, net price 28-tab pack = £11.30. Label: 8

Tablets, orange, f/c, scored, bisoprolol fumarate 10 mg, net price 28-tab pack = £12.68. Label: 8

CARVEDILOL

Indications hypertension; angina; adjunct to diuretics, digoxin, or ACE inhibitors in symptomatic chronic heart failure

Cautions see under Propranolol Hydrochloride; monitor renal function during dose titration in patients with heart failure who also have renal impairment, low blood pressure, ischaemic heart disease, or diffuse vascular disease

Contra-indications see under Propranolol Hydrochloride; acute or decompensated heart failure requiring intravenous inotropes

Hepatic impairment avoid

Pregnancy see notes above

Breast-feeding see notes above

Side-effects postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, dry eyes, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza-like symptoms; rarely angina, AV block, exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia, heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported

Dose

- Hypertension, initially 12.5 mg once daily, increased after 2 days to usual dose of 25 mg once daily; if necessary may be further increased at intervals of at least 2 weeks to max. 50 mg daily in single or divided doses; ELDERLY initial dose of 12.5 mg daily may provide satisfactory control
- Angina, initially 12.5 mg twice daily, increased after 2 days to 25 mg twice daily
- Adjunct in heart failure (section 2.5.5) initially 3.125 mg twice daily (with food), dose increased at intervals of at least 2 weeks to 6.25 mg twice daily, then to 12.5 mg twice daily, then to 25 mg twice daily; increase to highest dose tolerated, max. 25 mg twice daily in patients with severe heart failure or bodyweight less than 85 kg and 50 mg twice daily in patients over 85 kg

Carvedilol (Non-proprietary) PoM
Tablets, carvedilol 3.125 mg, net price 28-tab pack = £1.10; 6.25 mg, 28-tab pack = £1.25; 12.5 mg, 28-tab pack = £1.37; 25 mg, 28-tab pack = £1.84. Label: 8

Eucardic® (Roche) PoM
Tablets, scored, carvedilol 3.125 mg (pink), net price 28-tab pack = £7.13; 6.25 mg (yellow), 28-tab pack = £7.92; 12.5 mg (peach), 28-tab pack = £8.81; 25 mg, 28-tab pack = £11.00. Label: 8

CELIPROLOL HYDROCHLORIDE

Indications mild to moderate hypertension

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment reduce dose by half if eGFR 15–40 mL/minute/1.73 m^2; avoid if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects headache, dizziness, fatigue, nausea and somnolence; also bradycardia, bronchospasm; depression and pneumonitis reported rarely

Dose

- 200 mg once daily in the morning, increased to 400 mg once daily if necessary

Celiprolol (Non-proprietary) PoM
Tablets, celiprolol hydrochloride 200 mg, net price 28-tab pack = £4.53; 400 mg, 28-tab pack = £24.24. Label: 8, 22

Celectol® (Winthrop) PoM
Tablets, f/c, scored, celiprolol hydrochloride 200 mg (yellow), net price 28-tab pack = £19.83; 400 mg, 28-tab pack = £39.65. Label: 8, 22

ESMOLOL HYDROCHLORIDE

Indications short-term treatment of supraventricular arrhythmias (including atrial fibrillation, atrial flutter, sinus tachycardia); tachycardia and hypertension in peri-operative period

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Renal impairment manufacturer advises caution

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride; also on infusion venous irritation and thrombophlebitis

Dose

- By intravenous infusion, usually within range 50–200 micrograms/kg/minute (consult product literature for details of dose titration and doses during peri-operative period)

Brevibloc® (Baxter) PoM

Injection, esmolol hydrochloride 10 mg/mL, net price 10-mL vial = £7.79, 250-mL infusion bag = £89.69

LABETALOL HYDROCHLORIDE

Indications hypertension (including hypertension in pregnancy, hypertension with angina, and hypertension following acute myocardial infarction); hypertensive crises (see section 2.5); controlled hypotension in anaesthesia

Cautions see under Propranolol Hydrochloride; interferes with laboratory tests for catecholamines; liver damage (see below)

Liver damage Severe hepatocellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted

Contra-indications see under Propranolol Hydrochloride

Hepatic impairment avoid—severe hepatocellular injury reported

Renal impairment dose reduction may be required

Pregnancy see notes above

Breast-feeding see notes above

Side-effects postural hypotension (avoid upright position during and for 3 hours after intravenous administration), tiredness, weakness, headache, rashes, scalp tingling, difficulty in micturition, epigastric pain, nausea, vomiting; liver damage (see above); rarely lichenoid rash

Dose

- By mouth, initially 100 mg (50 mg in elderly) twice daily with food, increased at intervals of 14 days to usual dose of 200 mg twice daily; up to 800 mg daily in 2 divided doses (3–4 divided doses if higher); max. 2.4 g daily
- By intravenous injection, 50 mg over at least 1 minute, repeated after 5 minutes if necessary; max. total dose 200 mg

  Note Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 37
- By intravenous infusion, 2 mg/minute until satisfactory response then discontinue; usual total dose 50–200 mg, (**not** recommended for phaeochromocytoma, see under Phaeochromocytoma, section 2.5.4)

  Hypertension of pregnancy, 20 mg/hour, doubled every 30 minutes; usual max. 160 mg/hour

  Hypertension following myocardial infarction, 15 mg/hour, gradually increased to max. 120 mg/hour

Labetalol Hydrochloride (Non-proprietary) PoM

Tablets, f/c, labetalol hydrochloride 100 mg, net price, 56 = £7.85; 200 mg, 56 = £11.49; 400 mg, 56 = £20.60. Label: 8, 21

Trandate® (UCB Pharma) PoM

Tablets, all orange, f/c, labetalol hydrochloride 50 mg, net price 56-tab pack = £3.64; 100 mg, 56-tab pack = £4.01; 200 mg, 56-tab pack = £6.51; 400 mg, 56-tab pack = £9.05. Label: 8, 21

Injection, labetalol hydrochloride 5 mg/mL, net price 20-mL amp = £2.04

METOPROLOL TARTRATE

Indications see under Dose

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Hepatic impairment reduce dose in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Dose

- By mouth, hypertension, initially 100 mg daily, increased if necessary to 200 mg daily in 1–2 divided doses; max. 400 mg daily (but high doses rarely necessary)

  Angina, 50–100 mg 2–3 times daily

  Arrhythmias, usually 50 mg 2–3 times daily; up to 300 mg daily in divided doses if necessary

  Migraine prophylaxis, 100–200 mg daily in divided doses

  Hyperthyroidism (adjunct), 50 mg 4 times daily
- By intravenous injection, arrhythmias, up to 5 mg at rate 1–2 mg/minute, repeated after 5 minutes if necessary, total dose 10–15 mg

  Note Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 37

  In surgery, by slow intravenous injection 2–4 mg at induction or to control arrhythmias developing during anaesthesia; 2-mg doses may be repeated to a max. of 10 mg

  Early intervention within 12 hours of infarction, by intravenous injection 5 mg every 2 minutes to a max. of 15 mg, followed after 15 minutes by 50 mg by mouth every 6 hours for 48 hours; maintenance 200 mg daily in divided doses

Metoprolol Tartrate (Non-proprietary) PoM

Tablets, metoprolol tartrate 50 mg, net price 28 = £1.31, 56 = £1.74; 100 mg, 28 = £1.59, 56 = £2.51. Label: 8

Betaloc® (AstraZeneca) PoM

Injection, metoprolol tartrate 1 mg/mL, net price 5-mL amp = 42p

Lopresor® (Novartis) PoM

Tablets, f/c, scored, metoprolol tartrate 50 mg (pink), net price 56-tab pack = £2.57; 100 mg (blue), 56-tab pack = £6.68. Label: 8

Modified release

Lopresor SR® (Recordati) PoM
Tablets, m/r, yellow, f/c, metoprolol tartrate 200 mg, net price 28-tab pack = £9.80. Label: 8, 25
Dose hypertension, 200 mg daily; angina, 200–400 mg daily; migraine prophylaxis, 200 mg daily

NADOLOL

Indications see under Dose
Cautions see under Propranolol Hydrochloride
Contra-indications see under Propranolol Hydrochloride
Hepatic impairment manufacturer advises caution
Renal impairment increase dosage interval if eGFR less than 50 mL/minute/1.73 m^2
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Propranolol Hydrochloride
Dose

- Hypertension, initially 80 mg once daily, increased in increments of up to 80 mg at weekly intervals if required; max. 240 mg daily (higher doses rarely necessary)
- Angina, initially 40 mg once daily, increased at weekly intervals if required; usual max. 160 mg daily (rarely up to 240 mg may be required)
- Arrhythmias, initially 40 mg once daily, increased at weekly intervals up to 160 mg if required; reduce to 40 mg if bradycardia occurs
- Migraine prophylaxis, initially 40 mg once daily, increased in 40 mg increments at weekly intervals according to response; usual maintenance dose 80–160 mg once daily
- Thyrotoxicosis (adjunct), 80–160 mg once daily

Corgard® (Sanofi-Aventis) PoM
Tablets, blue, scored, nadolol 80 mg, net price 28-tab pack = £5.00. Label: 8

NEBIVOLOL

Indications essential hypertension; adjunct in stable mild to moderate heart failure in patients over 70 years
Cautions see under Propranolol Hydrochloride
Contra-indications see under Propranolol Hydrochloride; also acute or decompensated heart failure requiring intravenous inotropes
Hepatic impairment no information available—manufacturer advises avoid
Renal impairment for *hypertension*, initially 2.5 mg once daily, increased to 5 mg once daily if required; for *heart failure*, manufacturer advises avoid if serum creatinine greater than 250 micromol/litre
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Propranolol Hydrochloride; also oedema and depression
Dose

- Hypertension, 5 mg daily; ELDERLY initially 2.5 mg daily, increased if necessary to 5 mg daily
- Adjunct in heart failure (section 2.5.5), initially 1.25 mg once daily, then if tolerated increased at intervals of 1–2 weeks to 2.5 mg once daily, then to 5 mg once daily, then to max. 10 mg once daily

Nebivolol (Non-proprietary) PoM
Tablets, nebivolol (as hydrochloride) 5 mg, net price 28-tab pack = £3.98. Label: 8

Nebilet® (Menarini) PoM
Tablets, scored, nebivolol (as hydrochloride) 5 mg, net price 28-tab pack = £9.23. Label: 8
Note Also available as *Hypoloc®*

OXPRENOLOL HYDROCHLORIDE

Indications see under Dose
Cautions see under Propranolol Hydrochloride
Contra-indications see under Propranolol Hydrochloride
Hepatic impairment reduce dose
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Propranolol Hydrochloride
Dose

- Hypertension, 80–160 mg daily in 2–3 divided doses, increased as required; max. 320 mg daily
- Angina, 80–160 mg daily in 2–3 divided doses; max. 320 mg daily
- Arrhythmias, 40–240 mg daily in 2–3 divided doses; max. 240 mg daily
- Anxiety symptoms (short-term use), 40–80 mg daily in 1–2 divided doses

Oxprenolol (Non-proprietary) PoM
Tablets, coated, oxprenolol hydrochloride 20 mg, net price 56 = £1.86; 40 mg, 56 = £3.73; 80 mg, 56 = £6.20; 160 mg, 20 = £2.36. Label: 8

Trasicor® (Amdipharm) PoM
Tablets, f/c, oxprenolol hydrochloride 20 mg (contain gluten), net price 56-tab pack = £1.86; 40 mg (contain gluten), 56-tab pack = £3.73; 80 mg (yellow), 56-tab pack = £6.20. Label: 8

Modified release

Slow-Trasicor® (Amdipharm) PoM
Tablets, m/r, f/c, oxprenolol hydrochloride 160 mg, net price 28-tab pack = £7.50. Label: 8, 25
Dose hypertension, angina, initially 160 mg once daily; if necessary may be increased to max. 320 mg daily

With diuretic

Trasidrex® (Goldshield) PoM
Tablets, red, s/c, co-prenozide 160/0.25 (oxprenolol hydrochloride 160 mg (m/r), cyclopenthiazide 250 micrograms), net price 28-tab pack = £10.66. Label: 8, 25
Dose hypertension, 1 tablet daily, increased if necessary to 2 daily as a single dose

PINDOLOL

Indications see under Dose
Cautions see under Propranolol Hydrochloride
Contra-indications see under Propranolol Hydrochloride
Renal impairment may adversely affect renal function in severe impairment—manufacturer advises avoid
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Propranolol Hydrochloride

Dose

- Hypertension, initially 5 mg 2–3 times daily *or* 15 mg once daily, increased as required at weekly intervals; usual maintenance 15–30 mg daily; max. 45 mg daily
- Angina, 2.5–5 mg up to 3 times daily

Pindolol (Non-proprietary) PoM
Tablets, pindolol 5 mg, net price 100-tab pack = £7.81. Label: 8

Visken® (Amdipharm) PoM
Tablets, scored, pindolol 5 mg, net price 56-tab pack = £5.85; 15 mg, 28-tab pack = £8.79. Label: 8

With diuretic

Viskaldix® (Amdipharm) PoM
Tablets, scored, pindolol 10 mg, clopamide 5 mg, net price 28-tab pack = £6.70. Label: 8
Dose hypertension, 1 tablet daily in the morning, increased if necessary to 2 daily; max. 3 daily

SOTALOL HYDROCHLORIDE

Indications life-threatening arrhythmias including ventricular tachyarrhythmias; symptomatic non-sustained ventricular tachyarrhythmias; prophylaxis of paroxysmal atrial tachycardia or fibrillation, paroxysmal AV re-entrant tachycardias (both nodal and involving accessory pathways), and paroxysmal supraventricular tachycardia after cardiac surgery; maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter

Cautions see under Propranolol Hydrochloride; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances; severe or prolonged diarrhoea; **interactions:** Appendix 1 (beta-blockers), **important:** verapamil interaction see also p. 133

Contra-indications see under Propranolol Hydrochloride; congenital or acquired long QT syndrome; torsade de pointes; renal failure

Renal impairment use half normal dose if eGFR 30–60 mL/minute/1.73 m^2; use one-quarter normal dose if eGFR 10–30 mL/minute/1.73 m^2; avoid if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride; arrhythmogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in women)

Dose

- By mouth with ECG monitoring and measurement of corrected QT interval, arrhythmias, initially 80 mg daily in 1–2 divided doses increased gradually at intervals of 2–3 days to usual dose of 160–320 mg daily in 2 divided doses; higher doses of 480–640 mg daily for life-threatening ventricular arrhythmias under specialist supervision

Sotalol (Non-proprietary) PoM
Tablets, sotalol hydrochloride 40 mg, net price 56 = £1.29; 80 mg, 56 = £1.91; 160 mg, 28 = £2.32. Label: 8

Beta-Cardone® (UCB Pharma) PoM
Tablets, scored, sotalol hydrochloride 40 mg (green), net price 56-tab pack = £1.29; 80 mg (pink), 56-tab pack = £1.91; 200 mg, 28-tab pack = £2.40. Label: 8

Sotacor® (Bristol-Myers Squibb) PoM
Tablets, scored, sotalol hydrochloride 80 mg, net price 28-tab pack = £3.06. Label: 8

TIMOLOL MALEATE

Indications see under Dose; glaucoma (section 11.6)

Cautions see under Propranolol Hydrochloride

Contra-indications see under Propranolol Hydrochloride

Hepatic impairment dose reduction may be necessary

Renal impairment manufacturer advises caution—dose reduction may be required

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Propranolol Hydrochloride

Dose

- Hypertension, initially 10 mg daily in 1–2 divided doses; gradually increased if necessary to max. 60 mg daily, usual maintenance dose 10–30 mg daily (doses above 30 mg daily given in divided doses)
- Angina, initially 5 mg twice daily increased if necessary by 10 mg daily every 3–4 days; max. 30 mg twice daily
- Prophylaxis after myocardial infarction, initially 5 mg twice daily, increased after 2 days to 10 mg twice daily if tolerated
- Migraine prophylaxis, 10–20 mg daily in 1–2 divided doses

Betim® (Meda) PoM
Tablets, scored, timolol maleate 10 mg, net price 30-tab pack = £2.08. Label: 8

With diuretic

Timolol with amiloride and hydrochlorothiazide (Non-proprietary) PoM
Tablets, scored, timolol maleate 10 mg, amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg, net price 28-tab pack = £29.87. Label: 8
Dose hypertension, 1–2 tablets daily

Prestim® (Meda) PoM
Tablets, scored, timolol maleate 10 mg, bendroflumethiazide 2.5 mg, net price 30-tab pack = £3.49. Label: 8
Dose hypertension, 1–2 tablets daily; max. 4 daily

2.5 Hypertension and heart failure

Hypertension Lowering raised blood pressure decreases the risk of stroke, coronary events, heart failure, and renal impairment. Advice on antihypertensive therapy in this section takes into account the recommendations of the Joint British Societies (JBS2: British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91** (Suppl V): v1–v52).

Possible causes of hypertension (e.g. renal disease, endocrine causes), contributory factors, risk factors, and the presence of any complications of hypertension, such as left ventricular hypertrophy, should be established. Patients should be given advice on lifestyle

changes to reduce blood pressure or cardiovascular risk; these include smoking cessation, weight reduction, reduction of excessive intake of alcohol, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake.

Thresholds and targets for treatment The following thresholds for treatment[1] are recommended:

- Severe hypertension with acute target-organ damage, *or* severe hypertension (systolic blood pressure ≥180 mmHg *or* diastolic ≥110 mmHg) without acute target-organ damage, treat promptly (see Hypertensive crises, p. 106)
- When the initial blood pressure is systolic 160–179 mmHg *or* diastolic 100–109 mmHg, *and* the patient has cardiovascular complications, target-organ damage (e.g. left ventricular hypertrophy, renal impairment) or diabetes mellitus (type 1 or 2), confirm over 3–4 weeks then **treat** if these values are sustained;
- When the initial blood pressure is systolic 160–179 mmHg *or* diastolic 100–109 mmHg, but the patient has *no* cardiovascular complications, no target-organ damage, or no diabetes, advise lifestyle changes, reassess weekly initially and **treat** if these values are sustained on repeat measurements over 4–12 weeks;
- When the initial blood pressure is systolic 140–159 mmHg *or* diastolic 90–99 mmHg *and* the patient has cardiovascular complications, target-organ damage or diabetes, confirm within 12 weeks and **treat** if these values are sustained;
- When the initial blood pressure is systolic 140–159 mmHg *or* diastolic 90–99 mmHg and *no* cardiovascular complications, no target-organ damage, or no diabetes, advise lifestyle changes and **reassess** monthly; **treat** persistent mild hypertension if the 10-year cardiovascular disease risk is 20% or more.[2]

A target systolic blood pressure < 140 mmHg *and* diastolic blood pressure < 90 mmHg is suggested. A lower target systolic blood pressure < 130 mmHg *and* diastolic blood pressure < 80 mmHg should be considered for those with established atherosclerotic cardiovascular disease, diabetes, or chronic renal failure. In some individuals it may not be possible to reduce blood pressure below the suggested targets despite the use of appropriate therapy.

Drug treatment of hypertension Response to drug treatment for hypertension may be affected by the patient's age and ethnic background. An **ACE inhibitor** (section 2.5.5.1) or an **angiotensin-II receptor antagonist** (section 2.5.5.2) may be the most appropriate initial drug in younger Caucasians; however a **beta-blocker** may be considered if an ACE inhibitor or an angiotensin-II receptor antagonist is not tolerated or is contra-indicated (see also Hypertension in Pregnancy, p. 106). Afro-Caribbean patients and those aged over 55 years respond less well to ACE inhibitors and angiotensin-II receptor antagonists, therefore a **thiazide** (section 2.2.1) or a **calcium-channel blocker** (section 2.6.2) may be chosen for initial treatment.

Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently, an interval of at least 4 weeks should be allowed to determine response.

When two antihypertensive drugs are needed, an ACE inhibitor *or* an angiotensin-II receptor antagonist can be combined with *either* a thiazide *or* a calcium-channel blocker.

If control is inadequate with 2 drugs, a thiazide *and* a calcium-channel blocker can be added. The addition of an **alpha-blocker** (section 2.5.4), **spironolactone**, another diuretic, or a beta-blocker should be considered in resistant hypertension. In patients with *primary hyperaldosteronism*, spironolactone (section 2.2.3) is effective.

Other measures to reduce cardiovascular risk **Aspirin** (section 2.9) in a dose of 75 mg daily reduces the risk of cardiovascular events and myocardial infarction. Unduly high blood pressure must be controlled before aspirin is given. Unless contra-indicated, aspirin is recommended for all patients with established cardiovascular disease. Use of aspirin in primary prevention, in those with or without diabetes, is of unproven benefit (see also section 2.9).

Lipid-regulating drugs can also be of benefit in cardiovascular disease or in those who are at high risk of developing cardiovascular disease (section 2.12).

Hypertension in the elderly Benefit from antihypertensive therapy is evident up to at least 80 years of age, but it is probably inappropriate to apply a strict age limit when deciding on drug therapy. Patients who reach 80 years of age while taking antihypertensive drugs should continue treatment, provided that it continues to be of benefit and does not cause significant side-effects. The thresholds for treatment are diastolic pressure averaging ≥90 mmHg *or* systolic pressure averaging ≥160 mmHg over 3 to 6 months' observation (despite appropriate lifestyle interventions). Treatment with a low dose of a thiazide or a dihydropyridine calcium-channel blocker is effective. An ACE inhibitor (or an angiotensin-II receptor antagonist) (section 2.5.5) can be added if necessary.

Isolated systolic hypertension Isolated systolic hypertension (systolic pressure ≥160 mmHg, diastolic pressure < 90 mmHg) is associated with an increased cardiovascular disease risk, particularly in those aged over 60 years. Systolic blood pressure averaging 160 mmHg or higher over 3 to 6 months (despite appropriate lifestyle interventions) should be lowered in those over 60 years, even if diastolic hypertension is absent. Treatment with a low dose of a thiazide or a dihydropyridine calcium-channel blocker is effective. An ACE inhibitor (or an angiotensin-II receptor antagonist) (sec-

1. Thresholds and targets for treatment based on blood pressure measured in clinic may not apply to ambulatory or home blood-pressure monitoring, which usually give lower values.
2. Cardiovascular disease risk may be determined from the chart issued by the Joint British Societies (*Heart* 2005; **91** (Suppl V): v1–v52)—see inside back cover. The Joint British Societies' 'Cardiac Risk Assessor' computer programme may also be used to determine cardiovascular disease risk.

tion 2.5.5) can be added if necessary. Patients with severe postural hypotension should not receive blood pressure lowering drugs.

Isolated systolic hypertension in younger patients is uncommon but treatment may be indicated in those with a threshold systolic pressure of 160 mmHg (or less if at increased risk of cardiovascular disease, see above).

Hypertension in diabetes For patients with diabetes, the aim should be to maintain systolic pressure < 130 mmHg and diastolic pressure < 80 mmHg. However, in some individuals, it may not be possible to achieve this level of control despite appropriate therapy. Most patients require a combination of antihypertensive drugs.

Hypertension is common in type 2 diabetes, and antihypertensive treatment prevents macrovascular and microvascular complications. In type 1 diabetes, hypertension usually indicates the presence of diabetic nephropathy. An ACE inhibitor (or an angiotensin-II receptor antagonist) may have a specific role in the management of diabetic nephropathy (section 6.1.5); in patients with type 2 diabetes, an ACE inhibitor (or an angiotensin-II receptor antagonist) can delay progression of microalbuminuria to nephropathy.

Hypertension in renal disease The threshold for antihypertensive treatment in patients with renal impairment or persistent proteinuria is a systolic blood pressure ≥ 140 mmHg *or* a diastolic blood pressure ≥ 90 mmHg. Optimal blood pressure is a systolic blood pressure < 130 mmHg and a diastolic pressure < 80 mmHg, or lower if proteinuria exceeds 1 g in 24 hours. An ACE inhibitor (or an angiotensin-II receptor antagonist) should be considered for patients with proteinuria; however, ACE inhibitors should be used with caution in renal impairment, see section 2.5.5.1. Thiazide diuretics may be ineffective and high doses of loop diuretics may be required. A dihydropyridine calcium channel blocker can be added.

Hypertension in pregnancy Hypertensive complications in pregnancy can be hazardous for both the mother and the fetus, and are associated with a significant risk of morbidity and mortality; complications can occur in pregnant women with pre-existing chronic hypertension, or in those who develop hypertension in the latter half of pregnancy.

Labetalol (section 2.4) is widely used for treating hypertension in pregnancy. **Methyldopa** (section 2.5.2) is considered safe for use in pregnancy. Modified-release preparations of **nifedipine** [unlicensed] are also used, but see section 2.6.2 (p. 132) for warnings on use during pregnancy.

The following advice takes into account the recommendations of NICE Clinical Guideline 107 (August 2010), Hypertension in Pregnancy.

Pregnant women with chronic hypertension who are already receiving antihypertensive treatment should have their drug therapy reviewed. In uncomplicated chronic hypertension, a target blood pressure of <150/100 mmHg is recommended; women with target-organ damage as a result of chronic hypertension, and in women with chronic hypertension who have given birth, a target blood pressure of <140/90 mmHg is advised. Long-term antihypertensive treatment should be reviewed 2 weeks following the birth. Women managed with methyldopa during pregnancy should discontinue treatment and restart their original antihypertensive medication within 2 days of the birth.

Pregnant women are at high risk of developing pre-eclampsia if they have chronic kidney disease, diabetes mellitus, autoimmune disease, chronic hypertension, or if they have had hypertension during a previous pregnancy; these women are advised to take **aspirin** (section 2.9) in a dose of 75 mg once daily [unlicensed indication] from week 12 of pregnancy until the baby is born. Women with more than one moderate risk factor (first pregnancy, aged ≥40 years, pregnancy interval >10 years, BMI ≥35 kg/m^2 at first visit, multiple pregnancy, or family history of pre-eclampsia) for developing pre-eclampsia are also advised to take aspirin 75 mg once daily [unlicensed indication] from week 12 of pregnancy until the baby is born.

Women with pre-eclampsia or gestational hypertension who present with a blood pressure over 150/100 mmHg, should receive initial treatment with oral labetalol to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg. If labetalol is unsuitable, methyldopa or modified-release nifedipine may be considered. Women with gestational hypertension or pre-eclampsia who have been managed with methyldopa during pregnancy should discontinue treatment within 2 days of the birth. Women with a blood pressure of ≥160/110 mmHg who require critical care during pregnancy or after birth should receive immediate treatment with either oral or intravenous labetalol, intravenous hydralazine (section 2.5.1), or oral modified-release nifedipine to achieve a target blood pressure of <150 mmHg systolic, and diastolic 80–100 mmHg.

For use of magnesium sulphate in pre-eclampsia and eclampsia, see section 9.5.1.3.

Hypertensive crises If blood pressure is reduced too quickly in the management of hypertensive crises, there is a risk of reduced organ perfusion leading to cerebral infarction, blindness, deterioration in renal function, and myocardial ischaemia.

A *hypertensive emergency* is defined as severe hypertension with acute damage to the target organs (e.g. signs of papilloedema or retinal haemorrhage, or the presence of clinical conditions such as acute coronary syndromes, acute aortic dissection, acute pulmonary oedema, hypertensive encephalopathy, acute cerebral infarction, intracerebral or subarachnoid haemorrhage, eclampsia, or rapidly progressing renal failure); prompt treatment with intravenous antihypertensive therapy is generally required. Over the first few minutes or within 2 hours, blood pressure should be reduced by 20–25%. When intravenous therapy is indicated, treatment options include sodium nitroprusside [unlicensed] (section 2.5.1), labetalol (section 2.4), glyceryl trinitrate (section 2.6.1), phentolamine (section 2.5.4), hydralazine (section 2.5.1), or esmolol (section 2.4); choice of drug is dependent on concomitant conditions and clinical status of the patient.

Severe hypertension (blood pressure ≥180/110 mmHg) without acute target-organ damage is defined as a *hypertensive urgency*; blood pressure should be reduced gradually over 24–48 hours with oral antihypertensive therapy, such as labetalol, or the calcium-channel block-

ers (section 2.6.2) amlodipine, felodipine, or isradipine. Use of sublingual nifedipine is not recommended.

For advice on short-term management of hypertensive episodes in phaeochromocytoma, see under Phaeochromocytoma, section 2.5.4.

2.5.1 Vasodilator antihypertensive drugs

Vasodilators have a potent hypotensive effect, especially when used in combination with a beta-blocker and a thiazide. **Important:** for a warning on the hazards of a very rapid fall in blood pressure, see Hypertensive crises, p. 106.

Diazoxide has been used by intravenous injection in hypertensive emergencies, however alternative treatments are preferred (see section 2.5)

Hydralazine is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention. The incidence of side-effects is lower if the dose is kept below 100 mg daily, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

Sodium nitroprusside [unlicensed] is given by intravenous infusion to control severe hypertensive emergencies when parenteral treatment is necessary.

Minoxidil should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for women.

Prazosin, doxazosin, and terazosin (section 2.5.4) have alpha-blocking and vasodilator properties.

Ambrisentan, **bosentan**, **iloprost**, **sildenafil**, **sitaxentan**, and **tadalafil** are licensed for the treatment of pulmonary arterial hypertension and should be used under specialist supervision. **Epoprostenol** (section 2.8.1) can be used in patients with primary pulmonary hypertension resistant to other treatments. Bosentan is also licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The *Scottish Medicines Consortium* (p. 4) has advised (November 2005) that iloprost (*Ventavis®*) is accepted for restricted use within NHS Scotland in patients in whom bosentan is ineffective or not tolerated, and should only be prescribed by specialists in the Scottish Pulmonary Vascular Unit.

The *Scottish Medicines Consortium* (p. 4) has advised (October 2008) that ambrisentan (*Volibris®*) should be prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

The *Scottish Medicines Consortium* (p. 4) has advised (January 2010) that sildenafil (*Revatio®*) should be prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

Sitaxentan

Sitaxentan (*Thelin®*) is to be withdrawn from worldwide markets due to severe, sometimes fatal, hepatotoxicity; the benefits of treatment with sitaxentan no longer outweigh the risks. Patients currently taking sitaxentan are advised not to stop until their treatment has been reviewed by their prescriber; patients should be switched to a suitable alternative as soon as possible. Patients with abnormal liver function tests at the time of sitaxentan discontinuation should be monitored regularly until liver enzymes return to within the normal range.

AMBRISENTAN

Indications pulmonary arterial hypertension

Cautions not to be initiated in significant anaemia; monitor haemoglobin concentration or haematocrit after 1 month and 3 months of starting treatment, and periodically thereafter (reduce dose or discontinue treatment if significant decrease in haemoglobin concentration or haematocrit observed); monitor liver function before treatment, and monthly thereafter—discontinue if liver enzymes raised significantly or if symptoms of liver impairment develop

Hepatic impairment avoid in severe impairment

Renal impairment use with caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid (teratogenic in *animal* studies); exclude pregnancy before treatment and ensure effective contraception during treatment; monthly pregnancy tests advised

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, constipation; palpitation, flushing, peripheral oedema; upper respiratory-tract disorders; headache; anaemia; *less commonly* hypersensitivity reactions (including angioedema and rash)

Dose

- ADULT over 18 years, 5 mg once daily, increased if necessary to 10 mg once daily

Volibris® (GSK) ▼ PoM

Tablets, f/c, ambrisentan 5 mg (pale pink), net price 30-tab pack = £1618.08; 10 mg (dark pink), 30-tab pack = £1618.08

BOSENTAN

Indications pulmonary arterial hypertension; systemic sclerosis with ongoing digital ulcer disease (to reduce number of new digital ulcers)

Cautions not to be initiated if systemic systolic blood pressure is below 85 mmHg; monitor haemoglobin before and during treatment (monthly for first 4 months, then 3-monthly); avoid abrupt withdrawal; monitor liver function before treatment, at monthly intervals during treatment, and 2 weeks after dose increase (reduce dose or suspend treatment if liver enzymes raised significantly)—discontinue if symptoms of liver impairment; **interactions:** Appendix 1 (bosentan)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment avoid in moderate and severe impairment

Pregnancy avoid (teratogenic in *animal* studies); effective contraception required during and for at least 3 months after administration (hormonal contraception not considered effective); monthly pregnancy tests advised

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances, dry mouth, rectal haemorrhage, hepatic impairment (see Cautions, above); flushing, hypotension, palpitation, oedema, chest pain; dyspnoea; headache, dizziness, fatigue; back pain and pain in extremities; anaemia; hypersensitivity reactions (including rash, pruritus, and anaphylaxis)

Dose

- Pulmonary arterial hypertension, initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily; CHILD under 12 years see *BNF for Children*
- Systemic sclerosis with ongoing digital ulcer disease, initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily

Tracleer® (Actelion) ▼ PoM

Tablets, f/c, orange, bosentan (as monohydrate) 62.5 mg, net price 56-tab pack = £1510.21; 125 mg, 56-tab pack = £1510.21

DIAZOXIDE

Indications hypertensive emergency including severe hypertension associated with renal disease (but no longer recommended—see section 2.5); hypoglycaemia (section 6.1.4)

Cautions ischaemic heart disease; **interactions:** Appendix 1 (diazoxide)

Renal impairment dose reduction may be required

Pregnancy prolonged use may produce alopecia, hypertrichosis, and impaired glucose tolerance in neonate; inhibits uterine activity during labour

Side-effects tachycardia, hypotension, hyperglycaemia, sodium and water retention; *rarely* cardiomegaly, hyperosmolar non-ketotic coma, leucopenia, thrombocytopenia, and hirsuitism

Dose

- By rapid intravenous injection (less than 30 seconds), 1–3 mg/kg to max. single dose of 150 mg (see below); may be repeated after 5–15 minutes if required
  Note Single doses of 300 mg have been associated with angina and with myocardial and cerebral infarction

Eudemine® (Goldshield) PoM

Injection, diazoxide 15 mg/mL, net price 20-mL amp = £30.00

Tablets, see section 6.1.4

HYDRALAZINE HYDROCHLORIDE

Indications moderate to severe hypertension (adjunct); heart failure (with long-acting nitrate, but see section 2.5.5); hypertensive emergencies (including during pregnancy) (see section 2.5)

Cautions coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilised), cerebrovascular disease; occasionally blood pressure reduction too rapid even with low parenteral doses; manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose above 100 mg daily, but evidence of clinical value unsatisfactory; **interactions:** Appendix 1 (hydralazine)

Contra-indications idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale, dissecting aortic aneurysm; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose

Renal impairment reduce dose if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy neonatal thrombocytopenia reported, but risk should be balanced against risk of uncontrolled maternal hypertension; manufacturer advises avoid before third trimester

Breast-feeding present in milk but not known to be harmful; monitor infant

Side-effects tachycardia, palpitation, flushing, hypotension, fluid retention, gastro-intestinal disturbances; headache, dizziness; systemic lupus erythematosus-like syndrome after long-term therapy with over 100 mg daily (or less in women and in slow acetylator individuals) (see also notes above); rarely rashes, fever, peripheral neuritis, polyneuritis, paraesthesia, arthralgia, myalgia, increased lacrimation, nasal congestion, dyspnoea, agitation, anxiety, anorexia; blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia), abnormal liver function, jaundice, raised plasma creatinine, proteinuria and haematuria reported

Dose

- By mouth, hypertension, 25 mg twice daily, increased to usual max. 50 mg twice daily (see notes above)
  Heart failure (initiated in hospital) 25 mg 3–4 times daily, increased every 2 days if necessary; usual maintenance dose 50–75 mg 4 times daily
- By slow intravenous injection, hypertensive emergencies and hypertension with renal complications, 5–10 mg diluted with 10 mL sodium chloride 0.9%; may be repeated after 20–30 minutes (see Cautions)
- By intravenous infusion, hypertensive emergencies and hypertension with renal complications, initially 200–300 micrograms/minute; maintenance usually 50–150 micrograms/minute

Hydralazine (Non-proprietary) PoM

Tablets, hydralazine hydrochloride 25 mg, net price 56 = £9.32; 50 mg, 56 = £16.84

Apresoline® (Amdipharm) PoM

Tablets, yellow, s/c, hydralazine hydrochloride 25 mg, net price 84-tab pack = £3.38
Excipients include gluten

Injection, powder for reconstitution, hydralazine hydrochloride, net price 20-mg amp = £2.22

ILOPROST

Indications idiopathic or familial pulmonary arterial hypertension

Cautions unstable pulmonary hypertension with advanced right heart failure; hypotension (do not initiate if systolic blood pressure below 85 mmHg); acute pulmonary infection; chronic obstructive pulmonary disease; severe asthma; **interactions:** Appendix 1 (iloprost)

Contra-indications unstable angina; within 6 months of myocardial infarction; decompensated cardiac failure (unless under close medical supervision);

severe arrhythmias; congenital or acquired heart-valve defects; within 3 months of cerebrovascular events; pulmonary veno-occlusive disease; conditions which increase risk of bleeding

Hepatic impairment elimination reduced—initially 2.5 micrograms no more frequently than every 3 hours (max. 6 times daily), adjusted according to response (consult product literature)

Pregnancy manufacturer advises avoid (toxicity in *animal* studies); effective contraception must be used during treatment

Breast-feeding manufacturer advises avoid—no information available

Side-effects vasodilatation, hypotension, syncope, cough, headache, throat or jaw pain; nausea, vomiting, diarrhoea, chest pain, dyspnoea, bronchospasm, and wheezing also reported

Dose

- By inhalation of nebulised solution, initial dose 2.5 micrograms increased to 5 micrograms for second dose, if tolerated maintain at 5 micrograms 6–9 times daily according to response; reduce to 2.5 micrograms 6–9 times daily if higher dose not tolerated; CHILD 8–18 years see *BNF for Children*

Ventavis® (Bayer Schering) PoM

Nebuliser solution, iloprost (as trometamol) 10 micrograms/mL, net price 30 × 1-mL (10 microgram) unit-dose vials = £400.19, 168 × 1-mL = £2241.08. For use with *Prodose®* NHS or *Venta-Neb®* NHS nebuliser

MINOXIDIL

Indications severe hypertension, in addition to a diuretic and a beta-blocker

Cautions see notes above; angina; after myocardial infarction (until stabilised); lower doses in dialysis patients; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (vasodilator antihypertensives)

Contra-indications phaeochromocytoma

Renal impairment use with caution in significant impairment

Pregnancy avoid—possible toxicity including reduced placental perfusion; neonatal hirsutism reported

Breast-feeding present in milk but not known to be harmful

Side-effects sodium and water retention; weight gain, peripheral oedema, tachycardia, hypertrichosis; reversible rise in creatinine and blood urea nitrogen; occasionally, gastro-intestinal disturbances, breast tenderness, rashes

Dose

- Initially 5 mg (ELDERLY, 2.5 mg) daily, in 1–2 divided doses, increased in steps of 5–10 mg at intervals of at least 3 days; max. 100 mg daily (seldom necessary to exceed 50 mg daily)

Loniten® (Pharmacia) PoM

Tablets, scored, minoxidil 2.5 mg, net price 60-tab pack = £8.88; 5 mg, 60-tab pack = £15.83; 10 mg, 60-tab pack = £30.68

SILDENAFIL

Indications pulmonary arterial hypertension; erectile dysfunction (section 7.4.5)

Cautions hypotension (avoid if systolic blood pressure below 90 mmHg); intravascular volume depletion; left ventricular outflow obstruction; cardiovascular disease; autonomic dysfunction; pulmonary veno-occlusive disease; anatomical deformation of the penis, predisposition to priapism; bleeding disorders or active peptic ulceration; consider gradual withdrawal; **interactions:** Appendix 1 (sildenafil)

Contra-indications recent history of stroke or myocardial infarction, history of non-arteritic anterior ischaemic optic neuropathy; hereditary degenerative retinal disorders; avoid concomitant use of nitrates

Hepatic impairment for *pulmonary hypertension*, if usual dose not tolerated, reduce *oral* dose to 20 mg twice daily, or reduce *intravenous* dose to 10 mg twice daily; manufacturer advises avoid in severe impairment

Renal impairment for *pulmonary hypertension*, if usual dose not tolerated, reduce *oral* dose to 20 mg twice daily, or reduce *intravenous* dose to 10 mg twice daily

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no evidence of harm in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances, dry mouth; flushing, oedema; bronchitis, cough; headache, migraine, night sweats, paraesthesia, insomnia, anxiety, tremor, vertigo; fever, influenza-like symptoms; anaemia; back and limb pain, myalgia; visual disturbances, retinal haemorrhage, photophobia, painful red eyes; nasal congestion, epistaxis; cellulitis, alopecia; *less commonly* gynaecomastia, priapism; *also reported* rash, retinal vascular occlusion and non-arteritic anterior ischaemic optic neuropathy (discontinue if sudden visual impairment), and sudden hearing loss (advise patient to seek medical help)

Dose

- By mouth, 20 mg 3 times daily; CHILD under 18 years see *BNF for Children*
- By intravenous injection, when oral route not appropriate, 10 mg three times daily

Revatio® (Pfizer) ▼ PoM

Tablets, f/c, sildenafil (as citrate), 20 mg, net price 90-tab pack = £373.50

Injection, sildenafil (as citrate), 800 micrograms/mL, net price 50-mL vial = £45.28

Viagra® (Pfizer) PoM NHS

Section 7.4.5 (erectile dysfunction)

SITAXENTAN SODIUM

Indications pulmonary arterial hypertension (but see notes above)

Cautions test liver function before treatment and monitor monthly during treatment (discontinue treatment if liver enzymes significantly raised); measure haemoglobin concentration before treatment, after 1–3 months, then every 3 months; **interactions**: Appendix 1 (sitaxentan)

Hepatic impairment avoid

Pregnancy avoid unless essential—toxicity in *animal* studies; manufacturer advises effective contraception during treatment

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances; peripheral oedema, flushing; headache, insomnia, fatigue, dizziness; decreased haemoglobin, prolonged prothrombin time, increased INR; muscle cramp; nasal congestion, epistaxis

Dose

- ADULT over 18 years 100 mg once daily

Thelin® (Encysive) ▼ PoM

Tablets, f/c, yellow-orange, sitaxentan sodium 100 mg, net price 28-tab pack = £1540.00

Note All orders of Thelin should be based on a prescription from a specialist in Pulmonary Arterial Hypertension, who has received appropriate training as part of the Programmed Access to Sitaxentan Sodium (PASS) scheme. Orders should be placed with Polarspeed at 01525 217211

SODIUM NITROPRUSSIDE

Indications hypertensive emergencies (see section 2.5); controlled hypotension in anaesthesia; acute or chronic heart failure

Cautions hypothyroidism, hyponatraemia, ischaemic heart disease, impaired cerebral circulation, elderly; hypothermia; monitor blood pressure and blood-cyanide concentration and if treatment exceeds 3 days, also blood-thiocyanate concentration; avoid sudden withdrawal—terminate infusion over 15–30 minutes; protect infusion from light; **interactions:** Appendix 1 (sodium nitroprusside)

Contra-indications severe vitamin B_{12} deficiency; Leber's optic atrophy; compensatory hypertension

Hepatic impairment use with caution; avoid in hepatic failure—cyanide or thiocyanate metabolites may accumulate

Renal impairment avoid prolonged use—cyanide or thiocyanate metabolites may accumulate

Pregnancy avoid prolonged use—potential for accumulation of cyanide in fetus

Breast-feeding no information available; caution advised due to thiocyanate metabolite

Side-effects associated with over rapid reduction in blood pressure (reduce infusion rate): headache, dizziness, nausea, retching, abdominal pain, perspiration, palpitation, anxiety, retrosternal discomfort; occasionally reduced platelet count, acute transient phlebitis

Cyanide Side-effects caused by excessive plasma concentration of the cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue and give antidote, see p. 39)

Dose

- Hypertensive emergencies, by intravenous infusion, initially 0.5–1.5 micrograms/kg/minute, then increased in steps of 500 nanograms/kg/minute every 5 minutes within range 0.5–8 micrograms/kg/minute (lower doses if already receiving other antihypertensives); stop if response unsatisfactory with max. dose in 10 minutes

  Note Lower initial dose of 300 nanograms/kg/minute has been used

- Maintenance of blood pressure at 30–40% lower than pretreatment diastolic blood pressure, 20–400 micrograms/minute (lower doses for patients being treated with other antihypertensives)
- Controlled hypotension in surgery, by intravenous infusion, max. 1.5 micrograms/kg/minute
- Heart failure, by intravenous infusion, initially 10–15 micrograms/minute, increased every 5–10 minutes as necessary; usual range 10–200 micrograms/minute normally for max. 3 days

Sodium Nitroprusside (Non-proprietary) PoM

Intravenous infusion, powder for reconstitution, sodium nitroprusside 10 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

TADALAFIL

Indications pulmonary arterial hypertension; erectile dysfunction (section 7.4.5)

Cautions hypotension (avoid if systolic blood pressure below 90 mmHg); aortic and mitral valve disease; pericardial constriction; congestive cardiomyopathy; left ventricular dysfunction; life-threatening arrhythmias; coronary artery disease; uncontrolled hypertension; pulmonary veno-occlusive disease; predisposition to priapism; anatomical deformation of the penis; hereditary degenerative retinal disorders; **interactions:** Appendix 1 (tadalafil)

Contra-indications acute myocardial infarction in past 90 days; history of non-arteritic anterior ischaemic optic neuropathy; avoid concomitant use of nitrates

Hepatic impairment initially 20 mg once daily in mild to moderate impairment; avoid in severe impairment

Renal impairment initially 20 mg once daily in mild to moderate impairment, increased to 40 mg once daily if tolerated; avoid in severe impairment

Pregnancy manufacturer advises avoid

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects nausea, vomiting, dyspepsia, gastro-oesophageal reflux, chest pain, palpitation, flushing, hypotension, nasopharyngitis, epistaxis, headache, myalgia, back and limb pain, increased uterine bleeding, blurred vision, facial oedema, rash; *less commonly* tachycardia, hypertension, seizures, amnesia, priapism, hyperhidrosis; *also reported* unstable angina, arrhythmia, myocardial infarction, stroke, hearing loss, non-arteritic anterior ischaemic optic neuropathy, retinal vascular occlusion, visual field defect, Stevens-Johnson syndrome

Dose

- ADULT over 18 years, 40 mg once daily

Adcirca® (Lilly) ▼ PoM

Tablets, f/c, tadalafil 20 mg (orange), net price 56-tab pack = £491.22

2.5.2 Centrally acting antihypertensive drugs

Methyldopa is a centrally acting antihypertensive; it may be used for the management of hypertension in pregnancy. Side-effects are minimised if the daily dose is kept below 1 g.

Clonidine has the disadvantage that sudden withdrawal of treatment may cause severe rebound hypertension.

Moxonidine, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

CLONIDINE HYDROCHLORIDE

Indications hypertension; migraine (section 4.7.4.2); menopausal flushing (section 6.4.1.1)

Cautions must be withdrawn gradually to avoid severe rebound hypertension; Raynaud's syndrome or other occlusive peripheral vascular disease; history of depression; **interactions:** Appendix 1 (clonidine)
Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

Pregnancy may lower fetal heart rate, but risk should be balanced against risk of uncontrolled maternal hypertension; avoid intravenous injection

Breast-feeding manufacturer advises avoid—present in milk

Side-effects dry mouth, sedation, depression, fluid retention, bradycardia, Raynaud's phenomenon, headache, dizziness, euphoria, nocturnal unrest, rash, nausea, constipation, rarely impotence

Dose

- By mouth, 50–100 micrograms 3 times daily, increased every second or third day; usual max. dose 1.2 mg daily

Catapres® (Boehringer Ingelheim) PoM
Tablets, scored, clonidine hydrochloride 100 micrograms, net price 100-tab pack = £5.32; 300 micrograms, 100-tab pack = £12.39. Label: 3, 8

Dixarit® PoM
Section 4.7.4.2

METHYLDOPA

Indications hypertension

Cautions monitor blood counts and liver-function before treatment and at intervals during first 6–12 weeks or if unexplained fever occurs; history of depression; positive direct Coombs' test in up to 20% of patients (may affect blood cross-matching); interference with laboratory tests; **interactions:** Appendix 1 (methyldopa)
Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

Contra-indications depression, phaeochromocytoma; acute porphyria (section 9.8.2)

Hepatic impairment manufacturer advises caution in history of liver disease; avoid in active liver disease

Renal impairment start with small dose; increased sensitivity to hypotensive and sedative effect

Pregnancy not known to be harmful

Breast-feeding amount too small to be harmful

Side-effects gastro-intestinal disturbances, dry mouth, stomatitis, sialadenitis; bradycardia, exacerbation of angina, postural hypotension, oedema; sedation, headache, dizziness, asthenia, myalgia, arthralgia, paraesthesia, nightmares, mild psychosis, depression, impaired mental acuity, parkinsonism, Bell's palsy; hepatitis, jaundice; pancreatitis; haemolytic anaemia; bone-marrow depression, leucopenia, thrombocytopenia, eosinophilia; hypersensitivity reactions including lupus erythematosus-like syndrome, drug fever, myocarditis, pericarditis; rashes (including toxic epidermal necrolysis); nasal congestion, failure of ejaculation, impotence, decreased libido, gynaecomastia, hyperprolactinaemia, amenorrhoea

Dose

- Initially 250 mg 2–3 times daily, increased gradually at intervals of at least 2 days, max. 3 g daily; ELDERLY initially 125 mg twice daily, increased gradually, max. 2 g daily

Methyldopa (Non-proprietary) PoM
Tablets, coated, methyldopa (anhydrous) 125 mg, net price 56-tab pack = £16.29; 250 mg, 56-tab pack = £8.26; 500 mg, 56-tab pack = £11.49. Label: 3, 8

Aldomet® (Iroko) PoM
Tablets, all yellow, f/c, methyldopa (anhydrous) 250 mg, net price 60 = £6.15; 500 mg, 30 = £4.55. Label: 3, 8

MOXONIDINE

Indications mild to moderate essential hypertension

Cautions avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after a few days); severe coronary artery disease; unstable angina; first-degree AV block; moderate heart failure; **interactions:** see Appendix 1 (moxonidine)

Contra-indications conduction disorders (sick sinus syndrome, sino-atrial block, second- or third-degree AV block); bradycardia; severe heart failure

Renal impairment max. single dose 200 micrograms and max. daily dose 400 micrograms if eGFR 30–60 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—no information available

Breast-feeding present in milk—manufacturer advises avoid

Side-effects dry mouth, diarrhoea, nausea, vomiting, dyspepsia, dizziness, somnolence, insomnia, back pain, rash, pruritus; *less commonly* bradycardia, tinnitus, angioedema, oedema, nervousness, neck pain

Dose

- 200 micrograms once daily in the morning, increased if necessary after 3 weeks to 400 micrograms daily in 1–2 divided doses; max. 600 micrograms daily in 2 divided doses (max. single dose 400 micrograms)

Moxonidine (Non-proprietary) PoM
Tablets, f/c, moxonidine 200 micrograms, net price 28-tab pack = £3.76; 300 micrograms, net price 28-tab pack = £4.82; 400 micrograms, net price 28-tab pack = £5.01. Label: 3

Physiotens® (Solvay) PoM
Tablets, f/c, moxonidine 200 micrograms (pink), net price 28-tab pack = £9.72; 300 micrograms (red), 28-tab pack = £11.49; 400 micrograms (red), 28-tab pack = £13.26. Label: 3

2.5.3 Adrenergic neurone blocking drugs

Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use, but may be necessary with other therapy in resistant hypertension.

Guanethidine, which also depletes the nerve endings of noradrenaline, is licensed for rapid control of blood pressure, however alternative treatments are preferred (see section 2.5).

GUANETHIDINE MONOSULPHATE

Indications hypertensive crisis (but no longer recommended—see section 2.5)

Cautions coronary or cerebral arteriosclerosis, asthma, history of peptic ulceration; **interactions:** Appendix 1 (adrenergic neurone blockers)

Contra-indications phaeochromocytoma, heart failure

Renal impairment reduce dose if eGFR 40–65 mL/minute/1.73 m^2; avoid if eGFR less than 40 mL/minute/1.73 m^2

Pregnancy postural hypotension and reduced uteroplacental perfusion; should not be used to treat hypertension in pregnancy

Side-effects postural hypotension, failure of ejaculation, fluid retention, nasal congestion, headache, diarrhoea, drowsiness

Dose

- By intramuscular injection, 10–20 mg, repeated after 3 hours if required

Ismelin® (Amdipharm) PoM

Injection, guanethidine monosulphate 10 mg/mL, net price 1-mL amp = £1.56

2.5.4 Alpha-adrenoceptor blocking drugs

Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may, however, reduce blood pressure rapidly after the first dose and should be introduced with caution. **Doxazosin**, **indoramin**, and **terazosin** have properties similar to those of prazosin.

Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension (section 2.5).

Prostatic hyperplasia Alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, and terazosin are indicated for benign prostatic hyperplasia (section 7.4.1).

DOXAZOSIN

Indications hypertension (see notes above); benign prostatic hyperplasia (section 7.4.1)

Cautions care with initial dose (postural hypotension); pulmonary oedema due to aortic or mitral stenosis; cataract surgery (risk of intra-operative floppy iris syndrome); heart failure; **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications history of hypotension; monotherapy in overflow bladder or anuria

Hepatic impairment use with caution; manufacturer advises avoid in severe impairment—no information available

Pregnancy no evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk

Breast-feeding accumulates in milk—manufacturer advises avoid

Side-effects see section 7.4.1; also dyspnoea, coughing; fatigue, vertigo, paraesthesia, sleep disturbance, anxiety; influenza-like symptoms; back pain, myalgia; *less commonly* weight changes, angina, myocardial infarction, hypoaesthesia, tremor, agitation, micturition disturbance, epistaxis, arthralgia, tinnitus, and gout; *very rarely* cholestasis, hepatitis, jaundice, bradycardia, arrhythmias, bronchospasm, hot flushes, gynaecomastia, abnormal ejaculation, leucopenia, thrombocytopenia, and alopecia

Dose

- Hypertension, 1 mg daily, increased after 1–2 weeks to 2 mg once daily, and thereafter to 4 mg once daily, if necessary; max. 16 mg daily

Doxazosin (Non-proprietary) PoM

Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = 93p; 2 mg, 28-tab pack = 99p; 4 mg, 28-tab pack = £1.39. Counselling, initial dose, driving

Brands include *Doxadura®*

Cardura® (Pfizer) PoM

Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £10.56; 2 mg, 28-tab pack = £14.08. Counselling, initial dose, driving

Modified-release

Doxazosin (Non-proprietary) PoM

Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £6.33. Label: 25, counselling, initial dose, driving

Dose hypertension, benign prostatic hyperplasia, 4 mg once daily, increased to 8 mg once daily after 4 weeks if necessary

Brands include *Doxadura® XL*, *Raporsin® XL*, *Slocinx® XL*

Cardura® XL (Pfizer) PoM

Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £5.70; 8 mg, 28-tab pack = £9.98. Label: 25, counselling, driving, initial dose

Dose hypertension, benign prostatic hyperplasia, 4 mg once daily, increased to 8 mg once daily after 4 weeks if necessary

INDORAMIN

Indications hypertension (see notes above); benign prostatic hyperplasia (section 7.4.1)

Cautions avoid alcohol (enhances rate and extent of absorption); control incipient heart failure before initiating indoramin; elderly; Parkinson's disease (extrapyramidal disorders reported); epilepsy (convulsions in *animal* studies); history of depression; cataract surgery (risk of intra-operative floppy iris syndrome); **interactions:** Appendix 1 (alpha-blockers)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

Contra-indications established heart failure

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy no evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk

Breast-feeding no information available

Side-effects see section 7.4.1; also sedation; *less commonly* fatigue, weight gain, failure of ejaculation;

also reported extrapyramidal disorders, urinary frequency, and incontinence

Dose

- Hypertension, initially 25 mg twice daily, increased by 25–50 mg daily at intervals of 2 weeks; max. daily dose 200 mg in 2–3 divided doses

Baratol® (Amdipharm) PoM

Tablets, blue, f/c, indoramin (as hydrochloride) 25 mg, net price 84-tab pack = £9.00. Label: 2

Doralese® PoM

Section 7.4.1 (prostatic hyperplasia)

PRAZOSIN

Indications hypertension (see notes above); congestive heart failure (but see section 2.5.5); Raynaud's syndrome (see also section 2.6.4); benign prostatic hyperplasia (section 7.4.1)

Cautions first dose may cause collapse due to hypotension (therefore should be taken on retiring to bed); elderly; cataract surgery (risk of intra-operative floppy iris syndrome); **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Contra-indications not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)

Hepatic impairment initially 500 micrograms daily; increased with caution

Renal impairment initially 500 micrograms daily in moderate to severe impairment; increased with caution

Pregnancy no evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful

Side-effects see section 7.4.1; also dyspnoea; nervousness; urinary frequency; *less commonly* insomnia, paraesthesia, sweating, arthralgia, eye disorders, tinnitus, and epistaxis; *rarely* pancreatitis, flushing, vasculitis, bradycardia, hallucinations, worsening of narcolepsy, gynaecomastia, urinary incontinence, and alopecia

Dose

- Hypertension (see notes above), 500 micrograms 2–3 times daily for 3–7 days, the initial dose on retiring to bed at night (to avoid collapse, see Cautions); increased to 1 mg 2–3 times daily for a further 3–7 days; further increased if necessary to max. 20 mg daily in divided doses
- Congestive heart failure (but see section 2.5.5), 500 micrograms 2–4 times daily (initial dose at bedtime, see above), increasing to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses (but rarely used)
- Raynaud's syndrome (but efficacy not established, see section 2.6.4), initially 500 micrograms twice daily (initial dose at bedtime, see above) increased, if necessary, after 3–7 days to usual maintenance 1–2 mg twice daily

Prazosin (Non-proprietary) PoM

Tablets, prazosin (as hydrochloride) 500 micrograms, net price 56-tab pack = £2.51; 1 mg, 56-tab pack = £3.23; 2 mg, 56-tab pack = £4.39; 5 mg, 56-tab pack = £8.75. Counselling, initial dose, driving

Hypovase® (Pfizer) PoM

Tablets, prazosin (as hydrochloride) 500 micrograms, net price 60-tab pack = £2.69; 1 mg, scored, 60-tab pack = £3.46. Counselling, initial dose, driving

TERAZOSIN

Indications mild to moderate hypertension (see notes above); benign prostatic hyperplasia (section 7.4.1)

Cautions first dose may cause collapse due to hypotension (within 30–90 minutes, therefore should be taken on retiring to bed) (may also occur with rapid dose increase); cataract surgery (risk of intra-operative floppy iris syndrome); **interactions:** Appendix 1 (alpha-blockers)

Driving May affect performance of skilled tasks e.g. driving

Pregnancy no evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk

Breast-feeding no information available

Side-effects see section 7.4.1; *also reported* weight gain, dsypnoea, paraesthesia, nervousness, decreased libido, thrombocytopenia, back pain, and pain in extremities

Dose

- Hypertension, 1 mg at bedtime (compliance with bedtime dose important, see Cautions); dose doubled after 7 days if necessary; usual maintenance dose 2–10 mg once daily; more than 20 mg daily rarely improves efficacy

Terazosin (Non-proprietary) PoM

Tablets, terazosin (as hydrochloride) 2 mg, net price 28-tab pack = £2.16; 5 mg, 28-tab pack = £2.58; 10 mg, 28-tab pack = £7.88. Counselling, initial dose, driving

Hytrin® (Amdipharm) PoM

Tablets, terazosin (as hydrochloride) 2 mg (yellow), net price 28-tab pack = £2.29; 5 mg (tan), 28-tab pack = £4.29; 10 mg (blue), 28-tab pack = £8.57; starter pack (for hypertension) of 7 × 1-mg tabs with 21 × 2-mg tabs = £13.00. Counselling, initial dose, driving

Phaeochromocytoma

Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha- and beta-adrenoceptors; the optimal choice of drug therapy remains unclear. Alpha-blockers are used in the short-term management of hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker (section 2.4); a cardioselective beta-blocker is preferred.

Phenoxybenzamine, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects. **Phentolamine** is a short-acting alpha-blocker used mainly during surgery of phaeochromocytoma; its use for the diagnosis of phaeochromocytoma has been superseded by measurement of catecholamines in blood and urine.

Metirosine (available from 'special-order' manufacturers or specialist importing companies, see p. 988) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of phaeochromocytoma, and long term in patients unsuitable for surgery; an

alpha-adrenoceptor blocking drug may also be required. Metirosine should **not** be used to treat essential hypertension.

PHENOXYBENZAMINE HYDROCHLORIDE

Indications hypertensive episodes in phaeochromocytoma

Cautions elderly; congestive heart failure; severe ischaemic heart disease (see also Contra-indications); cerebrovascular disease (avoid if history of cerebrovascular accident); monitor blood pressure regularly during infusion; carcinogenic in *animals*; avoid in acute porphyria (section 9.8.2); avoid extravasation (irritant to tissues)

Contra-indications history of cerebrovascular accident; during recovery period after myocardial infarction (usually 3–4 weeks); avoid infusion in hypovolaemia

Renal impairment use with caution

Pregnancy hypotension may occur in newborn

Breast-feeding may be present in milk

Side-effects postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion, miosis, inhibition of ejaculation; rarely gastro-intestinal disturbances; decreased sweating and dry mouth after intravenous infusion; idiosyncratic profound hypotension within few minutes of starting infusion; convulsions following rapid intravenous infusion also reported

Dose

- See under preparations

Phenoxybenzamine (Goldshield) PoM

Injection concentrate, phenoxybenzamine hydrochloride 50 mg/mL. To be diluted before use, net price 2-mL amp = £57.14 (hosp. only)

Dose by *intravenous infusion* (preferably through large vein), adjunct in severe shock (but rarely used) and phaeochromocytoma, 1 mg/kg daily over at least 2 hours; do not repeat within 24 hours (intensive care facilities needed)

Caution Owing to risk of contact sensitisation healthcare professionals should avoid contamination of hands

Dibenyline® (Goldshield) PoM

Capsules, red/white, phenoxybenzamine hydrochloride 10 mg, net price 30-cap pack = £10.84

Dose phaeochromocytoma, 10 mg daily, increased by 10 mg daily; usual dose 1–2 mg/kg daily in 2 divided doses

PHENTOLAMINE MESILATE

Indications hypertensive episodes due to phaeochromocytoma e.g. during surgery; diagnosis of phaeochromocytoma (but see notes above)

Cautions monitor blood pressure (avoid in hypotension), heart rate; gastritis, peptic ulcer; elderly; **interactions:** Appendix 1 (alpha-blockers)

Contra-indications hypotension; history of myocardial infarction; coronary insufficiency, angina, or other evidence of coronary artery disease

Renal impairment manufacturer advises caution—no information available

Pregnancy use with caution—may cause marked decrease in maternal blood pressure with resulting fetal anoxia

Breast-feeding manufacturer advises avoid—no information available

Side-effects postural hypotension, tachycardia, dizziness, flushing; nausea and vomiting, diarrhoea, nasal congestion; also acute or prolonged hypotension, angina, chest pain, arrhythmias

Dose

- Hypertensive episodes, by intravenous injection, 2–5 mg repeated if necessary
- Diagnosis of phaeochromocytoma, consult product literature

Rogitine® (Alliance) PoM

Injection, phentolamine mesilate 10 mg/mL, net price 1-mL amp = £1.53

Excipients include sulphites

2.5.5 Drugs affecting the renin-angiotensin system

2.5.5.1 Angiotensin-converting enzyme inhibitors
2.5.5.2 Angiotensin-II receptor antagonists
2.5.5.3 Renin inhibitors

Heart failure

Drug treatment of heart failure associated with a reduced left ventricular ejection fraction (left ventricular systolic dysfunction) is covered below; optimal management of heart failure with a preserved left ventricular ejection fraction has not been established..

The treatment of chronic heart failure aims to relieve symptoms, improve exercise tolerance, reduce the incidence of acute exacerbations, and reduce mortality. An **ACE inhibitor**, titrated to a 'target dose' (or the maximum tolerated dose if lower), together with a **beta-blocker**, form the basis of treatment for all patients with heart failure due to left ventricular systolic dysfunction.

An ACE inhibitor (section 2.5.5.1) is generally advised for patients with asymptomatic left ventricular systolic dysfunction or symptomatic heart failure. An **angiotensin-II receptor antagonist** (section 2.5.5.2) may be a useful alternative for patients who, because of side-effects such as cough, cannot tolerate ACE inhibitors; a relatively high dose of the angiotensin-II receptor antagonist may be required to produce benefit. Candesartan, an angiotensin-II receptor antagonist, can also be added to ACE inhibitor and beta-blocker therapy in patients with mild to moderate heart failure who continue to remain symptomatic.

The beta-blockers bisoprolol and carvedilol (section 2.4) are of value in any grade of stable heart failure due to left ventricular systolic dysfunction; nebivolol (section 2.4) is licensed for stable mild to moderate heart failure in patients over 70 years. Beta-blocker treatment should be started by those experienced in the management of heart failure, at a very low dose and titrated very slowly over a period of weeks or months. Symptoms may deteriorate initially, calling for adjustment of concomitant therapy.

The aldosterone antagonist **spironolactone** (section 2.2.3) can be considered for patients with moderate to severe heart failure who are already taking an ACE inhibitor and a beta-blocker; low doses of spironolactone (usually 25 mg daily) reduce symptoms and mortality in these patients. If spironolactone cannot be

used, eplerenone (section 2.2.3) may be considered for the management of heart failure after an acute myocardial infarction with evidence of left ventricular systolic dysfunction. Close monitoring of serum creatinine, eGFR, and potassium is necessary, particularly following any change in treatment or any change in the patient's clinical condition.

Patients who cannot tolerate an ACE inhibitor or an angiotensin-II receptor antagonist, or in whom they are contra-indicated, may be given **isosorbide dinitrate** (section 2.6.1) with **hydralazine** (section 2.5.1), but this combination may be poorly tolerated. In patients of African or Caribbean origin, and those with moderate to severe heart failure, the combination of isosorbide dinitrate and hydralazine may be considered in addition to standard therapy with an ACE inhibitor and a beta-blocker, if necessary.

Digoxin (section 2.1.1) improves symptoms of heart failure and exercise tolerance and reduces hospitalisation due to acute exacerbations but it does not reduce mortality. Digoxin is reserved for patients with worsening or severe heart failure due to left ventricular systolic dysfunction who remain symptomatic despite treatment with an ACE inhibitor and a beta-blocker in combination with either an aldosterone antagonist, candesartan, or isosorbide dinitrate with hydralazine.

Patients with fluid overload should also receive either a loop or a thiazide diuretic (with salt or fluid restriction where appropriate). A **thiazide diuretic** (section 2.2.1) may be of benefit in patients with mild heart failure and good renal function; however, thiazide diuretics are ineffective in patients with poor renal function (eGFR less than 30 mL/minute/1.73 m^2, see Renal Impairment, section 2.2.1) and a **loop diuretic** (section 2.2.2) is preferred. If diuresis with a single diuretic is insufficient, a combination of a loop diuretic and a thiazide diuretic may be tried; addition of metolazone (section 2.2.1) may also be considered but the resulting diuresis may be profound and care is needed to avoid potentially dangerous electrolyte disturbances.

2.5.5.1 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. They have many uses and are generally well tolerated. The main indications of ACE inhibitors are shown below.

Heart failure ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker (section 2.5.5). Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. However, a low dose of spironolactone may be beneficial in severe heart failure (section 2.5.5) and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypotension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (e.g. furosemide 80 mg daily or more). Temporary withdrawal of the loop diuretic reduces the risk, but may cause severe rebound pulmonary oedema. Therefore, for patients on high doses of loop diuretics, the ACE inhibitor may need to be initiated under specialist supervision, see below. An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially.

Hypertension An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well (see section 2.5). ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetes with nephropathy (see also section 6.1.5). They may reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy (see Cautions, below); the first dose should preferably be given at bedtime.

Diabetic nephropathy For comment on the role of ACE inhibitors in the management of diabetic nephropathy, see section 6.1.5.

Prophylaxis of cardiovascular events ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction, see section 2.10.1. ACE inhibitors may also have a role in preventing cardiovascular events.

Initiation under specialist supervision ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:

- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- with hypovolaemia;
- with hyponatraemia (plasma-sodium concentration below 130 mmol/litre);
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

Renal effects Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below present); hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced (see Renal impairment below and under individual drugs). Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease, they also occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly). A specialist should be involved if renal function is significantly reduced as a result of treatment with an ACE inhibitor.

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in

patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.

ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

Cautions ACE inhibitors need to be initiated with care in patients receiving diuretics (**important:** see Concomitant diuretics, below); first doses can cause hypotension especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated, or with heart failure (see above). They should also be used with caution in peripheral vascular disease or generalised atherosclerosis owing to risk of clinically silent renovascular disease; for use in pre-existing renovascular disease, see Renal Effects above. The risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended). ACE inhibitors should be used with care in patients with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should also be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema. If jaundice or marked elevations of hepatic enzymes occur during treatment then the ACE inhibitor should be discontinued—risk of hepatic necrosis (see also Hepatic impairment, below). **Interactions:** Appendix 1 (ACE inhibitors).

Anaphylactoid reactions To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate; they should also be withheld before desensitisation with wasp or bee venom.

Concomitant diuretics ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.

Contra-indications ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors (including angioedema).

Hepatic impairment Use of prodrugs such as cilazapril, enalapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, and trandolapril requires close monitoring in patients with impaired liver function

Renal impairment ACE inhibitors should be used with caution and the response monitored (see Renal effects above); hyperkalaemia and other side effects more common; the dose may need to be reduced, see individual drugs.

Pregnancy ACE inhibitors should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.

Breast-feeding Information on the use of ACE inhibitors in breast-feeding is limited. Cilazapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, ramipril, and trandolapril are not recommended; alternative treatment options, with better established safety information during breast-feeding, are available. Captopril, enalapril, and quinapril should be avoided in the first few weeks after delivery, particularly in preterm infants, due to the risk of profound neonatal hypotension; if essential, they may be used in mothers breast-feeding older infants—the infant's blood pressure should be monitored.

Side-effects ACE inhibitors can cause profound hypotension (see Cautions) and renal impairment (see Renal effects above), and a persistent dry cough. They can also cause angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients), rash (which may be associated with pruritus and urticaria), pancreatitis, and upper respiratory-tract symptoms such as sinusitis, rhinitis, and sore throat. Gastro-intestinal effects reported with ACE inhibitors include nausea, vomiting, dyspepsia, diarrhoea, constipation, and abdominal pain. Altered liver function tests, cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure have been reported—discontinue if marked elevation of hepatic enzymes or jaundice. Hyperkalaemia, hypoglycaemia, and blood disorders including thrombocytopenia, leucopenia, neutropenia, and haemolytic anaemia have also been reported. Other reported side-effects include headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis, and photosensitivity.

Combination products Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.

CAPTOPRIL

Indications mild to moderate essential hypertension alone or with thiazide therapy and severe hypertension resistant to other treatment; congestive heart failure with left ventricular dysfunction (adjunct—see section 2.5.5); following myocardial infarction, see

dose; diabetic nephropathy (microalbuminuria greater than 30 mg/day) in type 1 diabetes

Cautions see notes above

Contra-indications see notes above

Renal impairment see notes above; reduce dose; max. initial dose 25 mg daily (do not exceed 100 mg daily) if eGFR 20–40 mL/minute/1.73 m^2; max. initial dose 12.5 mg daily (do not exceed 75 mg daily) if eGFR 10–20 mL/minute/1.73 m^2; max. initial dose 6.25 mg daily (do not exceed 37.5 mg daily) if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; tachycardia, serum sickness, weight loss, stomatitis, maculopapular rash, photosensitivity, flushing and acidosis

Dose

- Hypertension, used alone, initially 12.5 mg twice daily; if used in addition to diuretic (see notes above), or in elderly, initially 6.25 mg twice daily (first dose at bedtime); usual maintenance dose 25 mg twice daily; max. 50 mg twice daily (rarely 3 times daily in severe hypertension)
- Heart failure (adjunct), initially 6.25–12.5 mg 2–3 times daily under close medical supervision (see notes above), increased gradually at intervals of at least 2 weeks up to max. 150 mg daily in divided doses if tolerated
- Prophylaxis after infarction in clinically stable patients with asymptomatic or symptomatic left ventricular dysfunction (radionuclide ventriculography or echocardiography undertaken before initiation), initially 6.25 mg, starting as early as 3 days after infarction, then increased over several weeks to 150 mg daily (if tolerated) in divided doses
- Diabetic nephropathy, 75–100 mg daily in divided doses; if further blood pressure reduction required, other antihypertensives may be used in conjunction with captopril; in severe renal impairment, initially 12.5 mg twice daily (if concomitant diuretic therapy required, loop diuretic rather than thiazide should be chosen)

Captopril (Non-proprietary) PoM

Tablets, captopril 12.5 mg, net price 56-tab pack = £1.51; 25 mg, 56-tab pack = £1.56; 50 mg, 56-tab pack = £1.96

Brands include *Ecopace®*, *Kaplon®*

Capoten® (Squibb) PoM

Tablets, captopril 25 mg, net price 28-tab pack = £5.26; 50 mg (scored), 56-tab pack = £17.96

With diuretic

Note For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on thiazides, see section 2.2.1

Co-zidocapt (Non-proprietary) PoM

Tablets, co-zidocapt 12.5/25 (hydrochlorothiazide 12.5 mg, captopril 25 mg), net price 28-tab pack = £14.10

Brands include *Capto-co®*

Tablets, co-zidocapt 25/50 (hydrochlorothiazide 25 mg, captopril 50 mg), net price 28-tab pack = £14.00

Brands include *Capto-co®*

Capozide® (Squibb) PoM

LS tablets, scored, co-zidocapt 12.5/25 (hydrochlorothiazide 12.5 mg, captopril 25 mg), net price 28-tab pack = £10.05

Tablets, scored, co-zidocapt 25/50 (hydrochlorothiazide 25 mg, captopril 50 mg), net price 28-tab pack = £7.02

CILAZAPRIL

Indications essential hypertension; congestive heart failure (adjunct—see section 2.5.5)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above; max. dose 500 micrograms daily in liver cirrhosis; manufacturer advises avoid in ascites

Renal impairment see notes above; max. initial dose 500 micrograms once daily (do not exceed 2.5 mg once daily) if eGFR 10–40 mL/minute/1.73 m^2; avoid if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *less commonly* dry mouth, decreased appetite, angina, tachycardia, palpitation, flushing, dyspnoea, impotence, excessive sweating; *rarely* glossitis, bronchitis, interstitial lung disease, gynaecomastia, peripheral neuropathy, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dose

- Hypertension, initially 1 mg once daily (reduced to 500 micrograms daily if used in addition to diuretic (see notes above), or in cardiac decompensation, in severe hypertension, in volume depletion, in the elderly, or in renal impairment), then adjusted according to response; usual maintenance dose 2.5–5 mg once daily; max. 5 mg daily
- Heart failure (adjunct), initially 500 micrograms once daily under close medical supervision (see notes above), increased at weekly intervals to 1–2.5 mg once daily if tolerated; max. 5 mg once daily

Vascace® (Roche) PoM

Tablets, f/c, cilazapril 500 micrograms (white), net price 30-tab pack = £3.68; 1 mg (yellow), 30-tab pack = £6.07; 2.5 mg (pink), 28-tab pack = £7.20; 5 mg (brown), 28-tab pack = £12.51

ENALAPRIL MALEATE

Indications hypertension; symptomatic heart failure (adjunct—see section 2.5.5); prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; max. initial dose 2.5 mg daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also dyspnoea; depression, asthenia; blurred vision; *less commonly* dry mouth, peptic ulcer, anorexia, ileus; arrhythmias, palpitation, flushing; confusion, nervousness, drowsiness, insomnia, vertigo; impotence; muscle cramps; tinnitus; alopecia, sweating; hyponatraemia; *rarely*

stomatitis, glossitis, Raynaud's syndrome, pulmonary infiltrates, allergic alveolitis, dream abnormalities, gynaecomastia, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus; *very rarely* gastro-intestinal angioedema

Dose

- Hypertension, used alone, initially 5 mg once daily; if used in addition to diuretic (see notes above), or in renal impairment, lower initial doses may be required; usual maintenance dose 20 mg once daily; max. 40 mg once daily
- Heart failure (adjunct), asymptomatic left ventricular dysfunction, initially 2.5 mg once daily under close medical supervision (see notes above), increased gradually over 2–4 weeks to 10–20 mg twice daily if tolerated

Enalapril Maleate (Non-proprietary) PoM

Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £1.05; 5 mg, 28-tab pack = 96p; 10 mg, 28-tab pack = £1.05; 20 mg, 28-tab pack = £1.24

Brands include *Ednyt®*

Innovace® (MSD) PoM

Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £5.35; 5 mg (scored), 28-tab pack = £7.51; 10 mg (red), 28-tab pack = £10.53; 20 mg (peach), 28-tab pack = £12.51

With diuretic

Note For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on thiazides, see section 2.2.1

Innozide® (MSD) PoM

Tablets, yellow, scored, enalapril maleate 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £12.82

Note Non-proprietary tablets containing enalapril maleate (20 mg) and hydrochlorothiazide (12.5 mg) are available

FOSINOPRIL SODIUM

Indications hypertension; congestive heart failure (adjunct—see section 2.5.5)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; chest pain; musculoskeletal pain

Dose

- Hypertension, initially 10 mg daily, increased if necessary after 4 weeks; usual dose range 10–40 mg (doses over 40 mg not shown to increase efficacy); if used in addition to diuretic see notes above
- Heart failure (adjunct), initially 10 mg once daily under close medical supervision (see notes above), increased gradually to 40 mg once daily if tolerated

Fosinopril sodium (Non-proprietary) PoM

Tablets, fosinopril sodium 10 mg, net price 28-tab pack = £2.18; 20 mg, 28-tab pack = £2.53

IMIDAPRIL HYDROCHLORIDE

Indications essential hypertension

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; initial dose 2.5 mg daily if eGFR 30–80 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; dry mouth, glossitis, ileus; bronchitis, dyspnoea; sleep disturbances, depression, confusion, blurred vision, tinnitus, impotence

Dose

- Initially 5 mg daily before food; if used in addition to diuretic (see notes above), in elderly, in patients with heart failure, angina or cerebrovascular disease, or in renal or hepatic impairment, initially 2.5 mg daily; if necessary increase dose at intervals of at least 3 weeks; usual maintenance dose 10 mg once daily; max. 20 mg daily (elderly, 10 mg daily)

Tanatril® (Chiesi) PoM

Tablets, scored, imidapril hydrochloride 5 mg, net price 28-tab pack = £6.40; 10 mg, 28-tab pack = £7.22; 20 mg, 28-tab pack = £8.67

LISINOPRIL

Indications hypertension (but see notes above); symptomatic heart failure (adjunct—see section 2.5.5); short-term treatment following myocardial infarction in haemodynamically stable patients; renal complications of diabetes mellitus

Cautions see notes above

Contra-indications see notes above

Renal impairment see notes above; max. initial doses 5–10 mg daily if eGFR 30–80 mL/minute/1.73 m^2 (max. 40 mg daily); 2.5–5 mg daily if eGFR 10–30 mL/minute/1.73 m^2 (max. 40 mg daily); 2.5 mg daily if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *less commonly* tachycardia, palpitation, cerebrovascular accident, myocardial infarction, Raynaud's syndrome, confusion, mood changes, vertigo, sleep disturbances, asthenia, impotence; *rarely* dry mouth, gynaecomastia, alopecia, psoriasis; *very rarely* allergic alveolitis, pulmonary infiltrates, profuse sweating, pemphigus, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

- Hypertension, initially 10 mg once daily; if used in addition to diuretic (see notes above) or in cardiac decompensation or in volume depletion, initially 2.5–5 mg once daily; usual maintenance dose 20 mg once daily; max. 80 mg once daily
- Heart failure (adjunct), initially 2.5 mg once daily under close medical supervision (see notes above); increased in steps no greater than 10 mg at intervals of at least 2 weeks up to max. 35 mg once daily if tolerated
- Prophylaxis after myocardial infarction, systolic blood pressure over 120 mmHg, 5 mg within 24 hours, followed by further 5 mg 24 hours later, then 10 mg after a further 24 hours, and continuing with 10 mg once daily for 6 weeks (or continued if heart failure); sys-

tolic blood pressure 100–120 mmHg, initially 2.5 mg once daily, increased to maintenance dose of 5 mg once daily

Note Should not be started after myocardial infarction if systolic blood pressure less than 100 mmHg; temporarily reduce maintenance dose to 5 mg and if necessary 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour)

- Renal complications of diabetes mellitus, initially 2.5–5 mg once daily adjusted according to response; usual dose range 10–20 mg once daily

Lisinopril (Non-proprietary) PoM

Tablets, lisinopril (as dihydrate) 2.5 mg, net price 28-tab pack = 87p; 5 mg, 28-tab pack = 93p; 10 mg, 28-tab pack = £1.01; 20 mg, 28-tab pack = £1.19

Zestril® (AstraZeneca) PoM

Tablets, lisinopril (as dihydrate) 2.5 mg, net price 28-tab pack = £1.78; 5 mg (pink), 28-tab pack = £1.31; 10 mg (pink), 28-tab pack = £2.05; 20 mg (pink), 28-tab pack = £2.17

With diuretic

Note For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on thiazides, see section 2.2.1

Carace Plus® (MSD) PoM

Carace 10 Plus tablets, blue, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £10.10

Carace 20 Plus tablets, yellow, scored, lisinopril 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £11.43

Lisicostad® (Genus) PoM

Lisicostad 10/12.5 mg tablets, scored, lisinopril (as dihydrate) 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £10.99

Lisicostad 20/12.5 mg tablets, scored, lisinopril (as dihydrate) 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £11.99

Zestoretic® (AstraZeneca) PoM

Zestoretic 10 tablets, peach, lisinopril (as dihydrate) 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £2.27

Zestoretic 20 tablets, lisinopril (as dihydrate) 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £3.84

MOEXIPRIL HYDROCHLORIDE

Indications essential hypertension

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above; initial dose 3.75 mg once daily in hepatic cirrhosis

Renal impairment see notes above; if eGFR less than 40 mL/minute/1.73 m^2, initial dose 3.75 mg once daily titrated to max. 15 mg once daily

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; arrhythmias, angina, chest pain, syncope, cerebrovascular accident, myocardial infarction; appetite and weight changes; dry mouth, photosensitivity, flushing, nervousness, mood changes, anxiety, drowsiness, sleep disturbance, tinnitus, influenza-like syndrome, sweating and dyspnoea

Dose

- Monotherapy, initially 7.5 mg once daily; if used in addition to diuretic (see notes above), with nifedipine, or in elderly, initially 3.75 mg once daily; usual range 7.5–30 mg once daily; doses above 30 mg daily not shown to increase efficacy

Perdix® (UCB Pharma) PoM

Tablets, f/c, pink, scored, moexipril hydrochloride 7.5 mg, net price 28-tab pack = £6.04; 15 mg, 28-tab pack = £6.96

PERINDOPRIL ERBUMINE

Indications hypertension (but see notes above); symptomatic heart failure (adjunct—see section 2.5.5); prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; max. initial dose 2 mg once daily if eGFR 30–60 mL/minute/1.73 m^2; 2 mg once daily on alternate days if eGFR 15–30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also asthenia, mood and sleep disturbances

Dose

- Hypertension, initially 4 mg once daily in the morning for 1 month, subsequently adjusted according to response; if used in addition to diuretic (see notes above), in elderly, in renal impairment, in cardiac decompensation, or in volume depletion, initially 2 mg once daily; max. 8 mg daily
- Heart failure (adjunct), initially 2 mg once daily in the morning under close medical supervision (see notes above), increased after at least 2 weeks to max. 4 mg once daily if tolerated
- Following myocardial infarction or revascularisation, initially 4 mg once daily in the morning increased after 2 weeks to 8 mg once daily if tolerated; ELDERLY 2 mg once daily for 1 week, then 4 mg once daily for 1 week, thereafter increased to 8 mg once daily if tolerated

Perindopril (Non-proprietary) PoM

Tablets, perindopril erbumine (= *tert*-butylamine) 2 mg, net price 30-tab pack = £1.72; 4 mg, 30-tab pack = £1.81; 8 mg, 30-tab pack = £1.94. Label: 22

PERINDOPRIL ARGININE

Indications see under Perindopril Erbumine and notes above

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; max. initial dose 2.5 mg once daily if eGFR 30–60 mL/minute/1.73 m^2; 2.5 mg once daily on alternate days if eGFR 15–30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Perindopril Erbumine and notes above

Dose

- Hypertension, initially 5 mg once daily in the morning for 1 month, subsequently adjusted according to response; if used in addition to diuretic (see notes above), in elderly, in renal impairment, in cardiac decompensation, or in volume depletion, initially 2.5 mg once daily; max. 10 mg daily
- Heart failure (adjunct), initially 2.5 mg once daily in the morning under close medical supervision (see notes above), increased after 2 weeks to max. 5 mg once daily if tolerated
- Following myocardial infarction or revascularisation, initially 5 mg once daily in the morning increased after 2 weeks to 10 mg once daily if tolerated; ELDERLY 2.5 mg once daily for 1 week, then 5 mg once daily for 1 week, thereafter increased to 10 mg once daily if tolerated

Coversyl® Arginine (Servier) PoM

Tablets, f/c, perindopril arginine 2.5 mg (white), net price 30-tab pack = £8.27; 5 mg (light green, scored), 30-tab pack = £9.36; 10 mg (green), 30-tab pack = £11.02. Label: 22

Perindopril arginine with diuretic

Note For hypertension not adequately controlled by perindopril alone. For prescribing information on indapamide, see section 2.2.1

Coversyl® Arginine Plus (Servier) PoM

Tablets, f/c, perindopril arginine 5 mg, indapamide 1.25 mg, net price 30-tab pack = £12.65. Label: 22

QUINAPRIL

Indications essential hypertension; congestive heart failure (adjunct—see section 2.5.5)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; max. initial dose 2.5 mg once daily if eGFR less than 40 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; asthenia, chest pain, oedema, flatulence, nervousness, depression, insomnia, blurred vision, impotence, and back pain

Dose

- Hypertension, initially 10 mg once daily; with a diuretic (see notes above), in elderly, or in renal impairment initially 2.5 mg daily; usual maintenance dose 20–40 mg daily in single or 2 divided doses; up to 80 mg daily has been given
- Heart failure (adjunct), initial dose 2.5 mg daily under close medical supervision (see notes above), increased gradually to 10–20 mg daily in 1–2 divided doses if tolerated; max. 40 mg daily

Quinapril (Non-proprietary) PoM

Tablets, quinapril (as hydrochloride) 5 mg, net price 28-tab pack = £2.05; 10 mg, 28-tab pack = £1.91; 20 mg, 28-tab pack = £2.39; 40 mg, 28-tab pack = £2.81

Brands include *Quinil®*

Accupro® (Pfizer) PoM

Tablets, f/c, quinapril (as hydrochloride) 5 mg (brown), net price 28-tab pack = £8.60; 10 mg (brown), 28-tab pack = £8.60; 20 mg (brown), 28-tab pack = £10.79; 40 mg (red-brown), 28-tab pack = £9.75

With diuretic

Note For hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on thiazides, see section 2.2.1

Accuretic® (Pfizer) PoM

Tablets, pink, f/c, scored, quinapril (as hydrochloride) 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £11.75

RAMIPRIL

Indications hypertension; symptomatic heart failure (adjunct—see section 2.5.5); following myocardial infarction in patients with clinical evidence of heart failure; prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or with diabetes mellitus and at least one additional risk factor for cardiovascular disease; nephropathy (consult product literature)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment max. daily dose 2.5 mg; see also notes above

Renal impairment see notes above; max. daily dose 5 mg if eGFR 30–60 mL/minute/1.73 m^2; max. initial dose 1.25 mg once daily (do not exceed 5 mg once daily) if eGFR 10–30 mL/minute/1.73 m^2; max. initial dose 1.25 mg once daily (do not exceed 2.5 mg once daily) if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; arrhythmias, angina, chest pain, syncope, cerebrovascular accident, myocardial infarction, loss of appetite, stomatitis, dry mouth, skin reactions including erythema multiforme and pemphigoid exanthema; precipitation or exacerbation of Raynaud's syndrome; conjunctivitis, onycholysis, confusion, nervousness, depression, anxiety, impotence, decreased libido, alopecia, bronchitis and muscle cramps

Dose

- Hypertension, initially 1.25–2.5 mg once daily, increased at intervals of 2–4 weeks to max. 10 mg once daily; if used in addition to diuretic see notes above
- Heart failure (adjunct), initially 1.25 mg once daily under close medical supervision (see notes above), increased gradually at intervals of 1–2 weeks to max. 10 mg daily if tolerated (preferably taken in 2 divided doses)
- Prophylaxis after myocardial infarction (started at least 48 hours after infarction), initially 2.5 mg twice daily, increased after 3 days to 5 mg twice daily
  Note If initial 2.5-mg dose not tolerated, give 1.25 mg twice daily for 2 days before increasing to 2.5 mg twice daily, then 5 mg twice daily; withdraw if dose cannot be increased to 2.5 mg twice daily
- Prophylaxis of cardiovascular events, initially 2.5 mg once daily, increased after 1–2 weeks to 5 mg once daily, then increased after a further 2–3 weeks to 10 mg once daily

- Nephropathy, initially 1.25 mg once daily, increased after 2 weeks to 2.5 mg once daily, then increased after a further 2 weeks to 5 mg once daily if tolerated

Ramipril (Non-proprietary) PoM

Capsules, ramipril 1.25 mg, net price 28-cap pack = £1.10; 2.5 mg, 28-cap pack = £1.18; 5 mg, 28-cap pack = £1.25; 10 mg, 28-cap pack = £1.41

Tablets, ramipril 1.25 mg, net price 28-tab pack = £1.71; 2.5 mg, 28-tab pack = £1.42; 5 mg, 28-tab pack = £1.66; 10 mg, 28-tab pack = £1.89

Tritace® (Sanofi-Aventis) PoM

Tablets, scored, ramipril 1.25 mg (white), net price 28-tab pack = £5.09; 2.5 mg (yellow), 28-tab pack = £7.22; 5 mg (red), 28-tab pack = £10.05; 10 mg (white), 28-tab pack = £13.68

Titration pack, tablets, 35-day starter pack of ramipril 7 × 2.5 mg with 21 × 5 mg and 7 × 10 mg, net price = £13.00

With calcium-channel blocker

Note For hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on felodipine, see section 2.6.2

Triapin® (Sanofi-Aventis) PoM

Triapin® tablets, f/c, brown, ramipril 5 mg, felodipine 5 mg (m/r), net price 28-tab pack = £16.13. Label: 25

Triapin mite® tablets, f/c, orange, ramipril 2.5 mg, felodipine 2.5 mg (m/r), net price 28-tab pack = £24.55. Label: 25

TRANDOLAPRIL

Indications mild to moderate hypertension; following myocardial infarction in patients with left ventricular dysfunction

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above; max. 2 mg daily if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also ileus, dry mouth; tachycardia, palpitation, arrhythmias, angina, transient ischaemic attacks, cerebral haemorrhage, myocardial infarction, syncope; dyspnoea, bronchitis; asthenia, nervousness, sleep disturbances; hot flushes; alopecia, sweating, skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and psoriasis-like efflorescence

Dose

- Hypertension, initially 500 micrograms once daily, increased at intervals of 2–4 weeks; usual range 1–2 mg once daily; max. 4 mg daily; if used in addition to diuretic see notes above
- Prophylaxis after myocardial infarction (starting as early as 3 days after infarction), initially 500 micrograms once daily, gradually increased to max. 4 mg once daily

Note If symptomatic hypotension develops during titration, do not increase dose further; if possible, reduce dose of any adjunctive treatment and if this is not effective or feasible, reduce dose of trandolapril

Trandolapril (Non-proprietary) PoM

Capsules, trandolapril 500 micrograms, net price 14-cap pack = £1.49; 1 mg, 28-cap pack = £7.23; 2 mg, 28-cap pack = £3.75; 4 mg, 28-cap pack = £12.31

Gopten® (Abbott) PoM

Capsules, trandolapril 500 micrograms (red/yellow), net price 14-cap pack = £1.19; 1 mg (red/orange), 28-cap pack = £5.81; 2 mg (red/red), 28-cap pack = £5.81; 4 mg (red/maroon), 28-cap pack = £9.86

With calcium-channel blocker

Note For hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on verapamil, see section 2.6.2

Tarka® (Abbott) ▼ PoM

Capsules, pink, trandolapril 2 mg, verapamil hydrochloride 180 mg (m/r), net price 28 cap-pack = £10.29. Label: 25

2.5.5.2 Angiotensin-II receptor antagonists

Candesartan, **eprosartan**, **irbesartan**, **losartan**, **olmesartan**, **telmisartan**, and **valsartan** are angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are less likely to cause the persistent dry cough which can complicate ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure (section 2.5.5) or diabetic nephropathy (section 6.1.5).

Cautions Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal Effects under ACE Inhibitors, section 2.5.5.1). Monitoring of plasma-potassium concentration is advised, particularly in the elderly and in patients with renal impairment; lower initial doses may be appropriate in these patients. Angiotensin-II receptor antagonists should be used with caution in aortic or mitral valve stenosis and in hypertrophic cardiomyopathy. Those with primary aldosteronism, and Afro-Caribbean patients (particularly those with left ventricular hypertrophy), may not benefit from an angiotensin-II receptor antagonist. **Interactions:** Appendix 1 (angiotensin-II receptor antagonists).

Pregnancy Angiotensin-II receptor antagonists should be avoided in pregnancy unless essential. They may adversely affect fetal and neonatal blood pressure control and renal function; skull defects and oligohydramnios have also been reported.

Breast-feeding Information on the use of angiotensin-II receptor antagonists in breast-feeding is limited. They are not recommended in breast-feeding and alternative treatment options, with better established safety information during breast-feeding, are available.

Side-effects Side-effects are usually mild. Symptomatic hypotension including dizziness may occur, particularly in patients with intravascular volume depletion

(e.g. those taking high-dose diuretics). Hyperkalaemia occurs occasionally; angioedema has also been reported with some angiotensin-II receptor antagonists.

CANDESARTAN CILEXETIL

Indications hypertension; heart failure with impaired left ventricular systolic function in conjunction with an ACE inhibitor, or when ACE inhibitors are not tolerated (see also section 2.5.5)

Cautions see notes above

Contra-indications cholestasis

Hepatic impairment initially 4 mg once daily in mild or moderate impairment; avoid in severe impairment

Renal impairment initially 4 mg daily

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also vertigo, headache; *very rarely* nausea, hepatitis, blood disorders, hyponatraemia, back pain, arthralgia, myalgia, rash, urticaria, pruritus

Dose

- Hypertension, initially 8 mg (intravascular volume depletion 4 mg) once daily, increased if necessary at intervals of 4 weeks to max. 32 mg once daily; usual maintenance dose 8 mg once daily
- Heart failure, initially 4 mg once daily, increased at intervals of at least 2 weeks to 'target' dose of 32 mg once daily or to max. tolerated dose

Amias® (Takeda) PoM

Tablets, candesartan cilexetil 2 mg (white), net price 7-tab pack = £3.39; 4 mg (white, scored), 7-tab pack = £3.68, 28-tab pack = £9.25; 8 mg (pink, scored), 28-tab pack = £9.89; 16 mg (pink, scored), 28-tab pack = £12.72; 32 mg (pink, scored), 28-tab pack = £16.13

EPROSARTAN

Indications hypertension (see also notes above)

Cautions see notes above

Hepatic impairment halve initial dose in mild or moderate liver disease; avoid if severe

Renal impairment halve initial dose if eGFR less than 60 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also flatulence, hypertriglyceridaemia, arthralgia, rhinitis; *rarely* headache, asthenia, anaemia, hypersensitivity reactions (including rash, pruritus, urticaria); *very rarely* nausea

Dose

- 600 mg once daily (elderly over 75 years, mild to moderate hepatic impairment, renal impairment, initially 300 mg once daily); if necessary increased after 2–3 weeks to 800 mg once daily

Teveten® (Solvay) PoM

Tablets, f/c, eprosartan (as mesilate) 300 mg (white), net price 28-tab pack = £7.31; 400 mg (pink), 56-tab pack = £15.77; 600 mg (white), 28-tab pack = £14.31. Label: 21

IRBESARTAN

Indications hypertension; renal disease in hypertensive type 2 diabetes mellitus (see also notes above)

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also nausea, vomiting; fatigue; musculoskeletal pain; *less commonly* diarrhoea, dyspepsia, flushing, tachycardia, chest pain, cough, and sexual dysfunction; *rarely* rash, urticaria; *very rarely* headache, myalgia, arthralgia, tinnitus, taste disturbance, hepatitis, renal dysfunction, and cutaneous vasculitis

Dose

- Hypertension, initially 150 mg once daily, increased if necessary to 300 mg once daily (in haemodialysis or in ELDERLY over 75 years, initial dose of 75 mg once daily may be used); CHILD not recommended
- Renal disease in hypertensive type 2 diabetes mellitus, initially 150 mg once daily, increased to 300 mg once daily if tolerated (in haemodialysis or in ELDERLY over 75 years, consider initial dose of 75 mg once daily); CHILD not recommended

Aprovel® (Bristol-Myers Squibb, Sanofi-Aventis) PoM

Tablets, f/c, irbesartan 75 mg, net price 28-tab pack = £9.69; 150 mg, 28-tab pack = £11.84; 300 mg, 28-tab pack = £15.93

With diuretic

Note For hypertension not adequately controlled with irbesartan alone. For prescribing information on thiazides, see section 2.2.1

CoAprovel® (Bristol-Myers Squibb, Sanofi-Aventis) PoM

Tablets, f/c, irbesartan 150 mg, hydrochlorothiazide 12.5 mg (peach), net price 28-tab pack = £11.84; irbesartan 300 mg, hydrochlorothiazide 12.5 mg (peach), 28-tab pack = £15.93; irbesartan 300 mg, hydrochlorothiazide 25 mg (pink), 28-tab pack = £15.93

LOSARTAN POTASSIUM

Indications hypertension (including reduction of stroke risk in hypertension with left ventricular hypertrophy); chronic heart failure when ACE inhibitors are unsuitable or contra-indicated; diabetic nephropathy in type 2 diabetes mellitus (see also notes above)

Cautions see notes above; severe heart failure

Hepatic impairment consider dose reduction in mild to moderate impairment; manufacturer advises avoid in severe impairment—no information available

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; asthenia, fatigue, vertigo; *less commonly* gastro-intestinal disturbances, angina, palpitation, oedema, dyspnoea, headache, sleep disorders, urticaria, pruritus, rash; *rarely* hepatitis, atrial fibrillation, cerebrovascular accident, syncope, paraesthesia; also reported pancreatitis, anaphylaxis, cough, depression, erectile dysfunction, anaemia, thrombocytopenia, hyponatraemia, arthralgia, myalgia, rhabdomyolysis, tinnitus, photosensitivity, and vasculitis (including Henoch-Schönlein purpura)

Dose

- Hypertension, diabetic nephropathy in type 2 diabetes mellitus, usually 50 mg once daily (intravascular volume depletion, initially 25 mg once daily); if

necessary increased after several weeks to 100 mg once daily; ELDERLY over 75 years initially 25 mg daily

- Chronic heart failure, 12.5 mg once daily, increased at weekly intervals to 50 mg once daily if tolerated

Losartan Potassium (Non-proprietary)

Tablets, losartan potassium 12.5 mg, net price 28-tab pack = £7.70; 25 mg, 28-tab pack = £2.64; 50 mg, 28-tab pack = £2.38; 100 mg, 28-tab pack = £2.84

Cozaar® (MSD) ▼ PoM

Tablets, f/c, losartan potassium 12.5 mg (blue), net price 28-tab pack = £8.09; 25 mg (white), net price 28-tab pack = £16.18; 50 mg (white, scored), 28-tab pack = £12.80; 100 mg (white), 28-tab pack = £16.18

Oral suspension, losartan potassium 12.5 mg/5 mL when reconstituted with solvent provided, net price 200-mL (berry-citrus flavour) = £53.68

With diuretic

Note For hypertension not adequately controlled with losartan alone. For prescribing information on thiazides, see section 2.2.1

Cozaar-Comp® (MSD) PoM

Tablets 50/12.5, yellow, f/c, losartan potassium 50 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £12.80

Tablets 100/12.5, white, f/c, losartan potassium 100 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £16.18

Tablets 100/25, yellow, f/c, losartan potassium 100 mg, hydrochlorothiazide 25 mg, net price 28-tab pack = £16.18

OLMESARTAN MEDOXOMIL

Indications hypertension (see also notes above)

Cautions see notes above

Contra-indications biliary obstruction

Hepatic impairment dose should not exceed 20 mg daily in moderate impairment; manufacturer advises avoid in severe impairment—no information available

Renal impairment max. 20 mg daily if eGFR 20–60 mL/minute/1.73 m^2; avoid if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also gastro-intestinal disturbances; chest pain, peripheral oedema, hypertriglyceridaemia; fatigue; influenza-like symptoms, cough, pharyngitis, rhinitis; urinary-tract infection; haematuria, hyperuricaemia; arthritis, musculoskeletal pain; *less commonly* angina, vertigo, rash; *very rarely* headache, thrombocytopenia, myalgia, pruritus, urticaria

Dose

- Initially 10 mg once daily; if necessary increased to 20 mg once daily; max. 40 mg daily

Olmetec® (Daiichi Sankyo) PoM

Tablets, f/c, olmesartan medoxomil 10 mg, net price 28-tab pack = £10.95; 20 mg, 28-tab pack = £12.95; 40 mg, 28-tab pack = £17.50

With calcium-channel blocker

Note For hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on amlodipine, see section 2.6.2

Sevikar® (Daiichi Sankyo) ▼ PoM

Tablets 20/5, white, f/c, olmesartan medoxomil 20 mg, amlodipine (as besilate) 5 mg, net price 28-tab pack = £16.95

Tablets 40/5, ivory, f/c, olmesartan medoxomil 40 mg, amlodipine (as besilate) 5 mg, net price 28-tab pack = £16.95

Tablets 40/10, brownish-red, f/c, olmesartan medoxomil 40 mg, amlodipine (as besilate) 10 mg, net price 28-tab pack = £16.95

With diuretic

Note For hypertension not adequately controlled with olmesartan alone. For prescribing information on thiazides, see section 2.2.1

Olmetec Plus® (Daiichi Sankyo) ▼ PoM

Tablets, f/c, olmesartan medoxomil 20 mg, hydrochlorothiazide 12.5 mg (red-yellow), net price 28-tab pack = £12.95; olmesartan medoxomil 20 mg, hydrochlorothiazide 25 mg (pink), 28-tab pack = £12.95; olmesartan medoxomil 40 mg, hydrochlorothiazide 12.5 mg (red-yellow), 28-tab pack = £17.50

TELMISARTAN

Indications hypertension (see also notes above); prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease, or type 2 diabetes mellitus with target-organ damage

Cautions see notes above

Hepatic impairment 20–40 mg once daily in mild or moderate impairment; avoid in severe impairment or biliary obstruction

Renal impairment manufacturer advises initial dose of 20 mg once daily in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also gastro-intestinal disturbances; chest pain; influenza-like symptoms including pharyngitis and sinusitis; urinary-tract infection; arthralgia, myalgia, back pain, leg cramps; eczema; *less commonly* dry mouth, flatulence, anxiety, vertigo, tendinitis-like symptoms, abnormal vision, increased sweating; *rarely* bradycardia, tachycardia, dyspnoea, insomnia, depression, blood disorders, increase in uric acid, eosinophilia, rash, and pruritus; syncope and asthenia also reported

Dose

- Hypertension, usually 40 mg once daily (but 20 mg may be sufficient), increased if necessary after at least 4 weeks, to max. 80 mg once daily
- Prevention of cardiovascular events, 80 mg once daily

Micardis® (Boehringer Ingelheim) ▼ PoM

Tablets, telmisartan 20 mg, net price 28-tab pack = £8.00; 40 mg, 28-tab pack = £12.50; 80 mg, 28-tab pack = £17.00

With diuretic

Note For patients with hypertension not adequately controlled by telmisartan alone. For prescribing information on thiazides, see section 2.2.1

Micardis Plus® (Boehringer Ingelheim) PoM

Tablets 40/12.5, red/white, telmisartan 40 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £12.50

Tablets 80/12.5, red/white, telmisartan 80 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £17.00

Tablets 80/25, yellow/white, telmisartan 80 mg, hydrochlorothiazide 25 mg, net price 28-tab pack = £17.00

VALSARTAN

Indications hypertension; heart failure when ACE inhibitors cannot be used, or in conjunction with an ACE inhibitor when a beta-blocker cannot be used (see also section 2.5.5); myocardial infarction with left ventricular failure or left ventricular systolic dysfunction (adjunct—see section 2.5.5 and section 2.10.1)

Cautions see notes above

Contra-indications biliary cirrhosis, cholestasis

Hepatic impairment max. dose 80 mg daily in mild to moderate impairment; avoid if severe

Renal impairment use with caution if eGFR less than 10 mL/minute/1.73 m^2—no information available

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; renal impairment; *less commonly* gastro-intestinal disturbance, syncope, fatigue, cough, headache, acute renal failure; neutropenia, thrombocytopenia, myalgia, and hypersensitivity reactions (including rash, pruritus, vasculitis, and serum sickness) also reported

Dose

- Hypertension, usually 80 mg once daily (initially 40 mg once daily in intravascular volume depletion); if necessary increased at intervals of 4 weeks up to max. 320 mg daily
- Heart failure, initially 40 mg twice daily increased at intervals of at least 2 weeks up to max. 160 mg twice daily
- Myocardial infarction, initially 20 mg twice daily increased over several weeks to 160 mg twice daily if tolerated

Diovan® (Novartis) ▼ PoM

Capsules, valsartan 40 mg (grey), net price 28-cap pack = £13.97; 80 mg (grey/pink), 28-cap pack = £13.97; 160 mg (dark grey/pink), 28-cap pack = £18.41

Tablets, f/c, valsartan 40 mg (yellow, scored), net price 7-tab pack = £3.49; 320 mg (dark grey-violet), 28-tab pack = £20.23

With diuretic

Note For hypertension not adequately controlled by valsartan alone. For prescribing information on thiazides, see section 2.2.1

Co-Diovan® (Novartis) PoM

Tablets 80/12.5, orange, f/c, valsartan 80 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £13.97

Tablets 160/12.5, red, f/c, valsartan 160 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £18.41

Tablets 160/25, brown-orange, f/c, valsartan 160 mg, hydrochlorothiazide 25 mg, net price 28-tab pack = £18.41

2.5.5.3 Renin inhibitors

Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I. **Aliskiren** is licensed for the treatment of hypertension, either alone or in combination with other antihypertensives. The *Scottish Medicines Consortium* (p. 4) has advised (January 2010) that aliskiren (*Rasilez®*) is **not** recommended for use within NHS Scotland.

ALISKIREN

Indications essential hypertension

Cautions patients taking concomitant diuretics, on a low-sodium diet, or who are dehydrated (first doses may cause hypotension—initiate with care); renal artery stenosis; patients at risk of renal impairment; monitor plasma-potassium concentration and renal function in diabetes mellitus and heart failure; **interactions:** Appendix 1 (aliskiren)

Renal impairment caution in renal artery stenosis or if eGFR less than 30 mL/minute/1.73 m^2—no information available; monitor plasma-potassium concentration

Pregnancy manufacturer advises avoid—no information available; other drugs acting on the renin-angiotensin system have been associated with fetal malformations and neonatal death

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid

Side-effects diarrhoea; *less commonly* rash; *rarely* angioedema; acute renal failure (reversible on discontinuation of treatment), anaemia, and hyperkalaemia also reported

Dose

- ADULT over 18 years, 150 mg once daily, increased if necessary to 300 mg once daily

Rasilez® (Novartis) ▼ PoM

Tablets, f/c, aliskiren (as hemifumarate) 150 mg (pink), net price 28-tab pack = £19.80; 300 mg (red), net price 28-tab pack = £23.80. Label: 21

2.6 Nitrates, calcium-channel blockers, and other antianginal drugs

2.6.1 Nitrates
2.6.2 Calcium-channel blockers
2.6.3 Other antianginal drugs
2.6.4 Peripheral vasodilators and related drugs

Nitrates, calcium-channel blockers, and potassium-channel activators have vasodilating effects. Vasodilators can act in heart failure by arteriolar dilatation which reduces both peripheral vascular resistance and

left ventricular pressure during systole resulting in improved cardiac output. They can also cause venous dilatation which results in dilatation of capacitance vessels, increase of venous pooling, and diminution of venous return to the heart (decreasing left ventricular end-diastolic pressure).

For details on the management of stable angina and acute coronary syndromes, see section 2.10.1.

2.6.1 Nitrates

Nitrates have a useful role in *angina* (for details on the management of stable and unstable angina, see section 2.10.1). Although they are potent coronary vasodilators, their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates.

Sublingual **glyceryl trinitrate** is one of the most effective drugs for providing rapid symptomatic relief of angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The *aerosol spray* provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by *modified-release* and *transdermal* preparations (but tolerance may develop, see below).

Isosorbide dinitrate is active *sublingually* and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for *modified-release* preparations. The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate. **Isosorbide mononitrate** itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available.

Glyceryl trinitrate or isosorbide dinitrate may be tried by *intravenous injection* when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of congestive heart failure.

Tolerance Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 8 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for several consecutive hours in each 24 hours; in the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses should be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used; modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

GLYCERYL TRINITRATE

Indications anal fissure (section 1.7.4); extravasation (section 10.3)

Sublingual: prophylaxis and treatment of angina

Buccal: prophylaxis and treatment of angina; adjunct in unstable angina; acute and congestive heart failure

Injection: control of hypertension and myocardial ischaemia during and after cardiac surgery; induction of controlled hypotension during surgery; congestive heart failure; unstable angina

Transdermal: see under preparations below

Cautions hypothyroidism; malnutrition; hypothermia; recent history of myocardial infarction; heart failure due to obstruction; hypoxaemia or other ventilation and perfusion abnormalities; susceptibility to angle-closure glaucoma; metal-containing transdermal systems should be removed before magnetic resonance imaging procedures, cardioversion, or diathermy; avoid abrupt withdrawal; monitor blood pressure and heart rate during intravenous infusion; tolerance (see notes above); **interactions:** Appendix 1 (nitrates)

Contra-indications hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy; aortic stenosis; cardiac tamponade; constrictive pericarditis; mitral stenosis; toxic pulmonary oedema; head trauma; cerebral haemorrhage; cerebrovascular disease; marked anaemia

Hepatic impairment caution in severe impairment

Renal impairment manufacturers advise use with caution in severe impairment

Pregnancy not known to be harmful

Breast-feeding no information available—manufacturers advise use only if potential benefit outweighs risk

Side-effects postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache, dizziness; *less commonly* nausea, vomiting, heartburn, flushing, syncope, temporary hypoxaemia, rash, application site reactions with transdermal patches; *very rarely* angle-closure glaucoma

Injection Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, diaphoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain; prolonged administration has been associated with methaemoglobinaemia

Dose

- Sublingually, 0.3–1 mg, repeated as required; see also under preparations
- By buccal administration, see under preparation
- By intravenous infusion, 10–200 micrograms/minute, adjusted according to response; max. 400 micrograms/minute; consult product literature for recommended starting doses specific to indication
- By transdermal application, see under preparations

Short-acting tablets and sprays

Glyceryl Trinitrate (Non-proprietary)

Sublingual tablets, glyceryl trinitrate 300 micrograms, net price 100 = £2.71; 500 micrograms, 100 = £3.27; 600 micrograms, 100 = £12.31. Label: 16

Note Glyceryl trinitrate tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, and containing no cotton wool wadding; they should be discarded after 8 weeks in use

Aerosol spray, glyceryl trinitrate 400 micrograms/metered dose, net price 200-dose unit = £3.13

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Coro-Nitro Pump Spray® (Ayrton Saunders)
Aerosol spray, glyceryl trinitrate 400 micrograms/metered dose, net price 200-dose unit = £3.13
Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Glytrin Spray® (Sanofi-Aventis)
Aerosol spray, glyceryl trinitrate 400 micrograms/metered dose, net price 200-dose unit = £3.29
Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth
Cautions flammable

GTN 300 mcg (Martindale)
Sublingual tablets, glyceryl trinitrate 300 micrograms, net price 100 = £2.71. Label: 16

Nitrolingual Pumpspray® (Merck Serono)
Aerosol spray, glyceryl trinitrate 400 micrograms/metered dose, net price 200-dose unit = £3.44
Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Nitromin® (Egis)
Aerosol spray, glyceryl trinitrate 400 micrograms/metered dose, net price 180-dose unit = £2.63, 200-dose unit = £2.71
Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Longer-acting tablets

Suscard® (Forest)
Buccal tablets, m/r, glyceryl trinitrate 2 mg, net price 100-tab pack = £12.70; 3 mg, 100-tab pack = £18.33; 5 mg, 100-tab pack = £24.96. Counselling, see below
Dose treatment of angina, 2 mg as required, increased to 3 mg if necessary; prophylaxis 2–3 mg 3 times daily; 5 mg in severe angina
Unstable angina (adjunct), up to 5 mg with ECG monitoring
Congestive heart failure, 5 mg 3 times daily, increased to 10 mg 3 times daily in severe cases
Acute heart failure, 5 mg repeated until symptoms abate
Counselling Tablets have rapid onset of effect; they are placed between upper lip and gum, and left to dissolve; vary site to reduce risk of dental caries

Parenteral preparations

Note Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used

Glyceryl Trinitrate (Non-proprietary) PoM
Injection, glyceryl trinitrate 1 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 50-mL vial = £15.90
Injection, glyceryl trinitrate 5 mg/mL. To be diluted before use. Net price 5-mL amp = £6.49; 10-mL amp = £12.98
Excipients may include ethanol, propylene glycol (see Excipients, p. 2)

Nitrocine® (UCB Pharma) PoM
Injection, glyceryl trinitrate 1 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 10-mL amp = £5.88; 50-mL bottle = £13.77
Excipients include propylene glycol (see Excipients, p. 2)

Nitronal® (Merck Serono) PoM
Injection, glyceryl trinitrate 1 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 5-mL vial = £1.80; 50-mL vial = £14.76

Transdermal preparations

Deponit® (UCB Pharma)
Patches, self-adhesive, transparent, glyceryl trinitrate, *'5' patch* (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £12.77; *'10' patch* (releasing approx.10 mg/24 hours), 28 = £14.06
Dose prophylaxis of angina, apply one '5' or one '10' patch to lateral chest wall, upper arm, thigh, abdomen, or shoulder; increase to two '10' patches every 24 hours if necessary; replace every 24 hours, siting replacement patch on different area; see also notes above (Tolerance)

Minitran® (Meda)
Patches, self-adhesive, transparent, glyceryl trinitrate, *'5' patch* (releasing approx. 5 mg/24 hours when in contact with skin), net price 30 = £11.62; *'10' patch* (releasing approx. 10 mg/24 hours), 30 = £12.87; *'15' patch* (releasing approx. 15 mg/24 hours), 30 = £14.19
Dose prophylaxis of angina, apply one '5' patch to chest or upper arm; replace every 24 hours, siting replacement patch on different area; adjust dose according to response; see also notes above (Tolerance)
Maintenance of venous patency ('5' patch only), consult product literature

Nitro-Dur® (Schering-Plough)
Patches, self-adhesive, buff, glyceryl trinitrate, *'0.2 mg/h' patch* (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £10.59; *'0.4 mg/h' patch* (releasing approx. 10 mg/24 hours), 28 = £11.72; *'0.6 mg/h' patch* (releasing approx.15 mg/24 hours), 28 = £12.90
Dose prophylaxis of angina, apply one '0.2 mg/h' patch to chest or outer upper arm; replace every 24 hours, siting replacement patch on different area: adjust dose according to response; max. 15 mg in 24 hours; see also notes above (Tolerance)

Percutol® (Aspire)
Ointment, glyceryl trinitrate 2%, net price 60 g = £59.65. Counselling, see administration below
Excipients include wool fat
Dose prophylaxis of angina, usual dose 1–2 inches of ointment measured on to *Applirule®*, and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, every 3–4 hours as required; to determine dose, ½ inch on first day then increased by ½ inch/day until headache occurs, then reduced by ½ inch
Note Approx. 800 micrograms/hour absorbed from 1 inch of ointment

Transiderm-Nitro® (Novartis)
Patches, self-adhesive, pink, glyceryl trinitrate, *'5' patch* (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £17.05; *'10' patch* (releasing approx. 10 mg/24 hours), 28 = £18.74
Dose prophylaxis of angina, apply one '5' or one '10' patch to lateral chest wall; replace every 24 hours, siting replacement patch on different area; max. two '10' patches daily; see also notes above (Tolerance)
Prophylaxis of phlebitis and extravasation ('5' patch only), consult product literature

ISOSORBIDE DINITRATE

Indications prophylaxis and treatment of angina; left ventricular failure
Cautions see under Glyceryl Trinitrate
Contra-indications see under Glyceryl Trinitrate
Hepatic impairment see under Glyceryl Trinitrate
Renal impairment see under Glyceryl Trinitrate
Pregnancy may cross placenta—manufacturers advise avoid unless potential benefit outweighs risk
Breast-feeding see under Glyceryl Trinitrate

Side-effects see under Glyceryl Trinitrate

Dose

- By mouth, daily in divided doses, angina 30–120 mg, left ventricular failure 40–160 mg, up to 240 mg if required
- By intravenous infusion, 2–10 mg/hour; higher doses up to 20 mg/hour may be required

Short-acting tablets and sprays

Isosorbide Dinitrate (Non-proprietary)

Tablets, isosorbide dinitrate 10 mg, net price 56-tab pack = £12.24; 20 mg, 56-tab pack = £13.50

Angitak® (LPC)

Aerosol spray, isosorbide dinitrate 1.25 mg/metered dose, net price 200-dose unit = £3.95

Dose treatment or prophylaxis of angina, spray 1–3 doses under tongue whilst holding breath; allow 30 second interval between each dose

Modified-release preparations

Isoket Retard® (UCB Pharma)

Retard-20 tablets, m/r, scored, isosorbide dinitrate 20 mg, net price 56-tab pack = £2.58. Label: 25

Retard-40 tablets, m/r, scored, isosorbide dinitrate 40 mg, net price 56-tab pack = £6.36. Label: 25

Dose prophylaxis of angina, 40 mg daily in 1–2 divided doses, increased if necessary to 60–80 mg daily in 2–3 divided doses

Parenteral preparations

Isoket® (UCB Pharma) PoM

Injection 0.1%, isosorbide dinitrate 1 mg/mL. To be diluted before use. Net price 10-mL amp = £2.69

Note Glass or polyethylene infusion apparatus is preferable; loss of potency if PVC used

ISOSORBIDE MONONITRATE

Indications prophylaxis of angina; adjunct in congestive heart failure

Cautions see under Glyceryl Trinitrate

Contra-indications see under Glyceryl Trinitrate

Hepatic impairment see under Glyceryl Trinitrate

Renal impairment see under Glyceryl Trinitrate

Pregnancy manufacturers advise avoid unless potential benefit outweighs risk

Breast-feeding see under Glyceryl Trinitrate

Side-effects see under Glyceryl Trinitrate

Dose

- Initially 20 mg 2–3 times daily *or* 40 mg twice daily (10 mg twice daily in those who have not previously received nitrates); up to 120 mg daily in divided doses if required

Isosorbide Mononitrate (Non-proprietary)

Tablets, isosorbide mononitrate 10 mg, net price 56 = £1.05; 20 mg, 56 = £1.08; 40 mg, 56 = £1.40. Label: 25

Brands include *Angeze®*

Elantan® (UCB Pharma)

Elantan 10 tablets, scored, isosorbide mononitrate 10 mg, net price 56-tab pack = £1.32; 84-tab pack = £4.97. Label: 25

Elantan 20 tablets, scored, isosorbide mononitrate 20 mg, net price 56-tab pack = £1.73; 84-tab pack = £6.13. Label: 25

Elantan 40 tablets, scored, isosorbide mononitrate 40 mg, net price 56-tab pack = £2.81; 84-tab pack = £10.56. Label: 25

Ismo® (Riemser)

Ismo 10 tablets, isosorbide mononitrate 10 mg, net price 60-tab pack = £3.31. Label: 25

Ismo 20 tablets, scored, isosorbide mononitrate 20 mg, net price 60-tab pack = £4.85. Label: 25

Modified release

Chemydur® 60XL (Sovereign) PoM

Tablets, m/r, scored, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £3.99. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets

Elantan LA® (UCB Pharma)

Elantan LA 25 capsules, m/r, brown/white, enclosing white micropellets, isosorbide mononitrate 25 mg, net price 28-cap pack = £2.64. Label: 25

Dose prophylaxis of angina, 1 capsule in the morning, increased if necessary to 2 capsules

Elantan LA 50 capsules, m/r, brown/pink, enclosing white micropellets, isosorbide mononitrate 50 mg, net price 28-cap pack = £3.69. Label: 25

Dose prophylaxis of angina, 1 capsule daily in the morning, increased if necessary to 2 capsules

Imdur® (AstraZeneca)

Durules® (= tablets m/r), yellow, f/c, scored, isosorbide mononitrate 60 mg, net price 28-tab pack = £10.50. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet if headache occurs), increased to 2 tablets in the morning if required

Isib 60XL® (Ranbaxy)

Tablets, m/r, scored, yellow, isosorbide mononitrate 60 mg, net price 28-tab pack = £8.15. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for 2–4 days if headache occurs), increased if necessary to 2 tablets

Note Also available as Cibral 60XL®, Xismox 60XL®

Ismo Retard® (Riemser)

Tablets, m/r, s/c, isosorbide mononitrate 40 mg, net price 30-tab pack = £10.71. Label: 25

Dose prophylaxis of angina, 1 tablet daily in morning

Isodur® (Galen)

Isodur 25XL capsules, m/r, brown/white, isosorbide mononitrate 25 mg, net price 28-cap pack = £5.50. Label: 25

Isodur 50XL capsules, m/r, brown/red, isosorbide mononitrate 50 mg, net price 28-cap pack = £6.50. Label: 25

Dose prophylaxis of angina, 25–50 mg daily in the morning, increased if necessary to 50–100 mg once daily

Isotard® (ProStrakan)

Isotard 25XL tablets, m/r, ivory, isosorbide mononitrate 25 mg, net price 28-tab pack = £5.95. Label: 25

Isotard 40XL tablets, m/r, ivory, isosorbide mononitrate 40 mg, net price 28-tab pack = £6.78. Label: 25

Isotard 50XL tablets, m/r, ivory, isosorbide mononitrate 50 mg, net price 28-tab pack = £6.78. Label: 25

Isotard 60XL tablets, m/r, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £5.75. Label: 25

Dose prophylaxis of angina, 25–60 mg daily in the morning (if headache occurs with 60-mg tablet, half a 60-mg tablet may be given for 2–4 days), increased if necessary to 50–120 mg daily

Modisal XL® (Sandoz)

Tablets, m/r, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £10.36. Label: 25

Dose prophylaxis of angina, 1 tablet daily in the morning (half a tablet for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets once daily

Monomax® (Chiesi)

Monomax® SR, capsules, m/r, isosorbide mononitrate 40 mg, net price 28-cap pack = £6.52; 60 mg, 28-cap pack = £8.86. Label: 25

Dose prophylaxis of angina, 40–60 mg daily in the morning, increased if necessary to 120 mg daily

Note Also available as *Angeze SR®*

Monomax® XL tablets, m/r, isosorbide mononitrate 60 mg, net price 28-tab pack = £5.25. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets

Monomil XL® (TEVA UK) PoM

Tablets, m/r, isosorbide mononitrate 60 mg, net price 28-tab pack = £3.98. Label: 25

Dose prophylaxis of angina, 1 tablet daily in the morning (half a tablet daily for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets once daily

Monosorb XL 60® (Dexcel) PoM

Tablets, m/r, f/c, isosorbide mononitrate 60 mg, net price 28-tab pack = £16.66. Label: 25

Dose prophylaxis of angina, 1 tablet daily in the morning (half a tablet for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets

Zemon® (Neolab)

Zemon 40XL tablets, m/r, ivory, isosorbide mononitrate 40 mg, net price 28-tab pack = £14.25. Label: 25

Zemon 60XL tablets, scored, m/r, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £11.14. Label: 25

Dose prophylaxis of angina, 40–60 mg daily in the morning (half a 60-mg tablet may be given for 2–4 days to minimise possibility of headache), increased if necessary to 80–120 mg once daily

2.6.2 Calcium-channel blockers

Calcium-channel blockers (less correctly called 'calcium-antagonists') interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important differences between verapamil, diltiazem, and the dihydropyridine calcium-channel blockers (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nimodipine). Verapamil and diltiazem should usually be **avoided** in heart failure because they may further depress cardiac function and cause clinically significant deterioration.

Verapamil is used for the treatment of angina (section 2.10.1), hypertension (section 2.5), and arrhythmias (section 2.3.2). It is a highly negatively inotropic calcium channel-blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should **not** be used with beta-blockers (see p. 133). Constipation is the most common side-effect.

Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil, and unlike verapamil has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work. Short-acting formulations of nifedipine are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia. **Nicardipine** has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. **Amlodipine** and **felodipine** also resemble nifedipine and nicardipine in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure. They have a longer duration of action and can be given once daily. Nifedipine, nicardipine, amlodipine, and felodipine are used for the treatment of angina (section 2.10.1) or hypertension. All are valuable in forms of angina associated with coronary vasospasm. Side-effects associated with vasodilatation such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

Isradipine, **lacidipine**, and **lercanidipine** have similar effects to those of nifedipine and nicardipine; they are indicated for hypertension only.

Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

Diltiazem is effective in most forms of angina (section 2.10.1); the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.

Unstable angina Calcium-channel blockers do not reduce the risk of myocardial infarction in unstable angina. The use of diltiazem or verapamil should be reserved for patients resistant to treatment with beta-blockers.

Withdrawal There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of angina.

AMLODIPINE

Indications hypertension, prophylaxis of angina

Cautions acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock, unstable angina, significant aortic stenosis

Hepatic impairment may need dose reduction—half-life prolonged

Pregnancy no information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, nausea; palpitation, flushing, oedema; headache, dizziness, sleep disturbances, fatigue; *less commonly* gastro-intestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, asthenia, tremor, paraesthesia, urinary disturbances, impotence, gynaecomastia, weight changes, myalgia, muscle cramps, back pain, arthralgia, visual disturbances, tinnitus, pruritus, rashes (including isolated reports of erythema multiforme), sweating, alopecia, purpura, and skin discolouration; *very rarely* gastritis, pancreatitis, hepatitis, jaundice, cholestasis, gingival hyperplasia, myocardial infarction, arrhythmias, tachycardia, vasculitis, coughing, peripheral neuropathy, hyperglycaemia, thrombocytopenia, angioedema, and urticaria

Dose

- Hypertension or angina, initially 5 mg once daily; max. 10 mg once daily

Note Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable

Amlodipine (Non-proprietary) PoM

Tablets, amlodipine (as maleate or as mesilate) 5 mg, net price 28-tab pack = £1.05; 10 mg, 28-tab pack = £1.20

Brands include *Amlostin®*

Istin® (Pfizer) PoM

Tablets, amlodipine (as besilate) 5 mg, net price 28-tab pack = £11.08; 10 mg, 28-tab pack = £16.55

With valsartan

Note For hypertension in patients stabilised on the individual components in the same proportions. For prescribing information on valsartan, see section 2.5.5.2

Exforge® (Novartis) ▼ PoM

Tablets 5/80, f/c, dark yellow, amlodipine 5 mg, valsartan 80 mg, net price 28-tab pack = £13.97

Tablets 5/160, f/c, dark yellow, amlodipine 5 mg, valsartan 160 mg, net price 28-tab pack = £18.41

Tablets 10/160, f/c, light yellow, amlodipine 10 mg, valsartan 160 mg, net price 28-tab pack = £18.41

DILTIAZEM HYDROCHLORIDE

Indications prophylaxis and treatment of angina; hypertension

Cautions heart failure or significantly impaired left ventricular function, bradycardia (avoid if severe), first degree AV block, or prolonged PR interval; **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications severe bradycardia, left ventricular failure with pulmonary congestion, second- or third-degree AV block (unless pacemaker fitted), sick sinus syndrome; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose

Renal impairment start with smaller dose

Pregnancy avoid

Breast-feeding significant amount present in milk—no evidence of harm but avoid unless no safer alternative

Side-effects bradycardia, sino-atrial block, AV block, palpitation, dizziness, hypotension, malaise, asthenia, headache, hot flushes, gastro-intestinal disturbances, oedema (notably of ankles); rarely rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis, gynaecomastia, gum hyperplasia, extrapyramidal symptoms, depression reported

Dose

- Angina, 60 mg 3 times daily (elderly initially twice daily); increased if necessary to 360 mg daily
- Longer-acting formulations, see under preparations below

Standard formulations

Note These formulations are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation 'modified-release' their duration of action corresponds to that of tablets requiring administration 3 times daily

Diltiazem (Non-proprietary) PoM

Tablets, m/r (but see note above), diltiazem hydrochloride 60 mg, net price 84 = £2.93. Label: 25

Brands include *Optil®*

Tildiem® (Sanofi-Aventis) PoM

Tablets, m/r (but see note above), off-white, diltiazem hydrochloride 60 mg, net price 90-tab pack = £7.96. Label: 25

Longer-acting formulations

Note Different versions of modified-release preparations containing more than 60 mg diltiazem hydrochloride may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed

Adizem-SR® (Napp) PoM

Capsules, m/r, diltiazem hydrochloride 90 mg (white), net price 56-cap pack = £8.45; 120 mg (brown/white), 56-cap pack = £9.40; 180 mg (brown/white), 56-cap pack = £14.08. Label: 25

Tablets, m/r, f/c, scored, diltiazem hydrochloride 120 mg, net price 56-tab pack = £14.72. Label: 25

Dose mild to moderate hypertension, usually 120 mg twice daily (dose form not appropriate for initial dose titration)

Angina, initially 90 mg twice daily (elderly, dose form not appropriate for initial dose titration); increased to 180 mg twice daily if required

Adizem-XL® (Napp) PoM

Capsules, m/r, diltiazem hydrochloride 120 mg (pink/blue), net price 28-cap pack = £9.09; 180 mg (dark pink/blue), 28-cap pack = £10.32; 200 mg (brown), 28-cap pack = £6.66; 240 mg (red/blue), 28-cap pack = £11.46; 300 mg (maroon/blue), 28-cap pack = £9.09. Label: 25

Dose angina and mild to moderate hypertension, initially 240 mg once daily, increased if necessary to 300 mg once daily; in elderly and in hepatic or renal impairment, initially 120 mg daily

Angitil SR® (Chiesi) PoM

Capsules, m/r, diltiazem hydrochloride 90 mg (white), net price 56-cap pack = £7.03; 120 mg (brown), 56-cap pack = £6.91; 180 mg (brown), 56-cap pack = £13.27. Label: 25

Dose angina and mild to moderate hypertension, initially 90 mg twice daily; increased if necessary to 120 mg or 180 mg twice daily

Angitil XL® (Chiesi) PoM

Capsules, m/r, diltiazem hydrochloride 240 mg (white), net price 28-cap pack = £7.94; 300 mg (yellow), 28-cap pack = £6.98. Label: 25

Dose angina and mild to moderate hypertension, initially 240 mg once daily (elderly and in hepatic and renal impairment, dose form not appropriate for initial dose titration); increased if necessary to 300 mg once daily

Calcicard CR® (IVAX) PoM

Tablets, m/r, both f/c, diltiazem hydrochloride 90 mg, net price 56-tab pack = £6.33; 120 mg, 56-tab pack = £7.04. Label: 25

Dose mild to moderate hypertension, initially 90 mg or 120 mg twice daily; up to 360 mg daily may be required: ELDERLY and in hepatic and renal impairment, initially 120 mg once daily; up to 240 mg daily may be required

Angina, initially 90 mg or 120 mg twice daily; up to 480 mg daily in divided doses may be required; ELDERLY and in hepatic and renal impairment, dose form not appropriate for initial dose titration; up to 240 mg daily may be required

Dilcardia SR® (Generics) PoM

Capsules, m/r, diltiazem hydrochloride 60 mg (pink/white), net price 56-cap pack = £6.03; 90 mg (pink/yellow), 56-cap pack = £10.33; 120 mg (pink/orange), 56-cap pack = £11.49. Label: 25

Dose angina and mild to moderate hypertension, initially 90 mg twice daily; increased if necessary to 180 mg twice daily; ELDERLY and in hepatic or renal impairment, initially 60 mg twice daily, max. 90 mg twice daily

Dilzem SR® (Cephalon) PoM

Capsules, m/r, all beige, diltiazem hydrochloride 60 mg, net price 56-cap pack = £6.03; 90 mg, 56-cap pack = £11.29; 120 mg, 56-cap pack = £12.89. Label: 25

Dose angina and mild to moderate hypertension, initially 90 mg twice daily (elderly 60 mg twice daily); up to 180 mg twice daily may be required

Dilzem XL® (Cephalon) PoM

Capsules, m/r, diltiazem hydrochloride 120 mg, net price 28-cap pack = £7.78; 180 mg, 28-cap pack = £11.55; 240 mg, 28-cap pack = £11.03. Label: 25

Dose angina and mild to moderate hypertension, initially 180 mg once daily (elderly and in hepatic and renal impairment, 120 mg once daily); if necessary may be increased to 360 mg once daily

Slozem® (Merck Serono) PoM

Capsules, m/r, diltiazem hydrochloride 120 mg (pink/clear), net price 28-cap pack = £7.00; 180 mg (pink/clear), 28-cap pack = £7.80; 240 mg (red/clear), 28-cap pack = £8.20; 300 mg (red/white), 28-cap pack = £8.50. Label: 25

Dose angina and mild to moderate hypertension, initially 240 mg once daily (elderly and in hepatic and renal impairment, 120 mg once daily); if necessary may be increased to 360 mg once daily

Tildiem LA® (Sanofi-Aventis) PoM

Capsules, m/r, diltiazem hydrochloride 200 mg (pink/grey, containing white pellets), net price 28-cap pack = £6.27; 300 mg (white/yellow, containing white pellets), 28-cap pack = £7.22. Label: 25

Dose angina and mild to moderate hypertension, initially 200 mg once daily before or with food, increased if necessary to 300–400 mg daily, max. 500 mg daily; ELDERLY and in hepatic or renal impairment, initially 200 mg daily, increased if necessary to 300 mg daily

Tildiem Retard® (Sanofi-Aventis) PoM

Tablets, m/r, diltiazem hydrochloride 90 mg, net price 56-tab pack = £7.27; 120 mg, 56-tab pack = £7.15. Label: 25

Counselling Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy

Dose mild to moderate hypertension, initially 90 mg or 120 mg twice daily; increased if necessary to 360 mg daily in divided doses; ELDERLY and in hepatic or renal impairment, initially 120 mg once daily; increased if necessary to 120 mg twice daily

Angina, initially 90 mg or 120 mg twice daily; increased if necessary to 480 mg daily in divided doses; ELDERLY and in hepatic or renal impairment, dose form not appropriate for initial titration; up to 120 mg twice daily may be required

Viazem XL® (Genus) PoM

Capsules, m/r, diltiazem hydrochloride 120 mg (lavender), net price 28-cap pack = £6.60; 180 mg (white/blue-green), 28-cap pack = £7.36; 240 mg (blue-green/lavender), 28-cap pack = £7.74; 300 mg (white/lavender), 28-cap pack = £8.03; 360 mg (blue-green), 28-cap pack = £13.85. Label: 25

Dose angina and mild to moderate hypertension, initially 180 mg once daily, adjusted according to response to 240 mg once daily; max. 360 mg once daily; ELDERLY and in hepatic or renal impairment, initially 120 mg once daily, adjusted according to response

Zemtard® (Galen) PoM

Zemtard 120XL capsules, m/r, brown/orange, diltiazem hydrochloride 120 mg, net price 28-cap pack = £6.10. Label: 25

Zemtard 180XL capsules, m/r, grey/pink, diltiazem hydrochloride 180 mg, net price 28-cap pack = £6.20 Label: 25

Zemtard 240XL capsules, m/r, blue, diltiazem hydrochloride 240 mg, net price 28-cap pack = £6.30. Label: 25

Zemtard 300XL capsules, m/r, white/blue, diltiazem hydrochloride 300 mg, net price 28-cap pack = £6.70. Label: 25

Dose angina and mild to moderate hypertension, 180–300 mg once daily, increased if necessary to 360 mg once daily in hypertension and to 480 mg once daily in angina; ELDERLY and in hepatic or renal impairment, initially 120 mg once daily

FELODIPINE

Indications hypertension, prophylaxis of angina

Cautions withdraw if ischaemic pain occurs or existing pain worsens shortly after initiating treatment or if cardiogenic shock develops; severe left ventricular dysfunction; avoid grapefruit juice (may affect metabolism); acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications unstable angina, uncontrolled heart failure; significant aortic stenosis; within 1 month of myocardial infarction

Hepatic impairment reduce dose

Pregnancy avoid; toxicity in *animal* studies; may inhibit labour

Breast-feeding present in milk

Side-effects flushing, headache, palpitation, dizziness, fatigue, gravitational oedema; rarely rash, pruritus, cutaneous vasculitis, gum hyperplasia, urinary frequency, impotence, fever

Dose

- Hypertension, initially 5 mg (elderly 2.5 mg) daily in the morning; usual maintenance 5–10 mg once daily; doses above 20 mg daily rarely needed
- Angina, initially 5 mg daily in the morning, increased if necessary to 10 mg once daily

Felodipine (Non-proprietary) PoM

Tablets, m/r, felodipine 2.5 mg, net price 28-tab pack = £6.31; 5 mg, 28-tab pack = £4.21; 10 mg, 28-tab pack = £5.66, 30-tab pack = £12.87. Label: 25

Brands include *Cardioplen XL®*, *Felogen XL®*, *Felotens XL®*, *Keloc SR®*, *Neofel XL®*, *Parmid XL®*, *Vascalpha®*

Plendil® (AstraZeneca) PoM

Tablets, m/r, f/c, felodipine 2.5 mg (yellow), net price 28-tab pack = £6.31; 5 mg (pink), 28-tab pack = £4.21; 10 mg (brown), 28-tab pack = £5.66. Label: 25

ISRADIPINE

Indications hypertension

Cautions sick sinus syndrome (if pacemaker not fitted); avoid grapefruit juice (may affect metabolism); poor cardiac reserve; **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock; symptomatic or tight aortic stenosis; during or within 1 month of myocardial infarction; unstable angina; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose

Renal impairment reduce dose

Pregnancy may inhibit labour; risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects abdominal discomfort; tachycardia, palpitation, flushing, peripheral oedema; dyspnoea; headache, fatigue, dizziness; polyuria; rash; *less commonly* hypotension, weight gain; *very rarely* vomiting, nausea, gum hyperplasia, anorexia, drowsiness, arrhythmia, bradycardia, heart failure, cough, depression, paraesthesia, anxiety, erectile dysfunction, blood disorders (such as thrombocytopenia, leucopenia, anaemia), arthralgia, visual disturbance, hypersensitivity reactions; hepatitis and gynaecomastia also reported

Dose

- 2.5 mg twice daily, increased if necessary after 3–4 weeks to 5 mg twice daily (exceptionally up to 10 mg twice daily); ELDERLY (or in hepatic or renal impairment) 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response, maintenance dose of 2.5 mg or 5 mg once daily may be sufficient

Prescal® (Novartis) PoM
Tablets, yellow, scored, isradipine 2.5 mg, net price 56-tab pack = £16.54

LACIDIPINE

Indications hypertension

Cautions cardiac conduction abnormalities; poor cardiac reserve; avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock, unstable angina, aortic stenosis; avoid within 1 month of myocardial infarction; acute porphyria (section 9.8.2)

Hepatic impairment antihypertensive effect possibly increased

Pregnancy manufacturer advises avoid; may inhibit labour

Breast-feeding manufacturer advises avoid—no information available

Side-effects flushing, palpitation, oedema; headache, dizziness; *rarely* gastro-intestinal disturbances, gum hyperplasia, aggravation of angina, mood disturbances, asthenia, polyuria, muscle cramps, skin rash (including pruritus and erythema)

Dose

- Initially 2 mg as a single daily dose, preferably in the morning; increased after 3–4 weeks to 4 mg daily, then if necessary to 6 mg daily

Motens® (Boehringer Ingelheim) PoM
Tablets, both f/c, lacidipine 2 mg, net price 28-tab pack = £2.95; 4 mg (scored), 28-tab pack = £3.10

LERCANIDIPINE HYDROCHLORIDE

Indications mild to moderate hypertension

Cautions left ventricular dysfunction; sick sinus syndrome (if pacemaker not fitted); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications aortic stenosis; unstable angina, uncontrolled heart failure; within 1 month of myocardial infarction; acute porphyria (section 9.8.2)

Hepatic impairment avoid in severe disease

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid

Side-effects *less commonly* flushing, peripheral oedema, palpitation, tachycardia, headache, dizziness; *rarely* gastro-intestinal disturbances, angina, asthenia, drowsiness, polyuria, myalgia, rash; *very rarely* gingival hyperplasia, myocardial infarction, hypotension

Dose

- Initially 10 mg once daily; increased, if necessary, after at least 2 weeks to 20 mg daily

Lercanidipine Hydrochloride (Non-proprietary) PoM
Tablets, lercanidipine hydrochloride 10 mg, net price 28-tab pack = £5.32; 20 mg, 28-tab pack = £8.56. Label: 22

Zanidip® (Recordati) PoM
Tablets, f/c, lercanidipine hydrochloride 10 mg (yellow), net price 28-tab pack = £5.70; 20 mg (pink), 28-tab pack = £10.82. Label: 22

NICARDIPINE HYDROCHLORIDE

Indications prophylaxis of angina; mild to moderate hypertension

Cautions withdraw if ischaemic pain occurs or existing pain worsens within 30 minutes of initiating treatment or increasing dose; congestive heart failure or significantly impaired left ventricular function; elderly; avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock; advanced aortic stenosis; unstable or acute attacks of angina; avoid within 1 month of myocardial infarction; acute porphyria (section 9.8.2)

Hepatic impairment half-life prolonged in severe impairment—may need dose reduction

Renal impairment start with small dose

Pregnancy may inhibit labour; toxicity in *animal* studies; manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding manufacturer advises avoid—no information available

Side-effects dizziness, headache, peripheral oedema, flushing, palpitation, nausea; also gastro-intestinal disturbances, drowsiness, insomnia, tinnitus, hypotension, rashes, dyspnoea, paraesthesia, frequency of micturition; thrombocytopenia, depression and impotence reported

Dose

- Initially 20 mg 3 times daily, increased, after at least three days, to 30 mg 3 times daily (usual range 60–120 mg daily)

Nicardipine (Non-proprietary) PoM

Capsules, nicardipine hydrochloride 20 mg, net price 56-cap pack = £4.03; 30 mg, 56-cap pack = £5.16

Cardene® (Astellas) PoM

Capsules, nicardipine hydrochloride 20 mg (blue/white), net price 56-cap pack = £6.00; 30 mg (blue/pale blue), 56-cap pack = £6.96

Modified release

Cardene SR® (Astellas) PoM

Capsules, m/r, nicardipine hydrochloride 30 mg, net price 56-cap pack = £7.15; 45 mg (blue), 56-cap pack = £10.40. Label: 25

Dose mild to moderate hypertension, initially 30 mg twice daily; usual effective dose 45 mg twice daily (range 30–60 mg twice daily)

NIFEDIPINE

Indications prophylaxis of angina; hypertension; Raynaud's phenomenon

Cautions see notes above; also withdraw if ischaemic pain occurs or existing pain worsens shortly after initiating treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function (heart failure deterioration observed); severe hypotension; elderly; diabetes mellitus; avoid grapefruit juice (may affect metabolism); acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina

Hepatic impairment dose reduction may be required in severe liver disease

Pregnancy may inhibit labour; manufacturer advises avoid before week 20; risk to fetus should be balanced against risk of uncontrolled maternal hypertension; use only if other treatment options are not indicated or have failed

Breast-feeding amount too small to be harmful but manufacturers advise avoid

Side-effects gastro-intestinal disturbance; hypotension, oedema, vasodilatation, palpitation; headache, dizziness, lethargy, asthenia; *less commonly* tachycardia, syncope, chills, nasal congestion, dyspnoea, anxiety, sleep disturbance, vertigo, migraine, paraesthesia, tremor, polyuria, dysuria, nocturia, erectile dysfunction, epistaxis, myalgia, joint swelling, visual disturbance, sweating, hypersensitivity reactions (including angioedema, jaundice, pruritus, urticaria, and rash); *rarely* anorexia, gum hyperplasia, mood disturbances, hyperglycaemia, male infertility, purpura, and photosensitivity reactions; also reported dysphagia, intestinal obstruction, intestinal ulcer, bezoar formation (with some modified-release preparations), gynaecomastia, agranulocytosis, and anaphylaxis

Dose

- See preparations below

Nifedipine (Non-proprietary) PoM

Capsules, nifedipine 5 mg, net price 84-cap pack = £2.97; 10 mg, 84-cap pack = £4.00

Dose angina prophylaxis (but not recommended, see notes above) and Raynaud's phenomenon, initially 5 mg 3 times daily, adjusted according to response to 20 mg 3 times daily

Hypertension, not recommended therefore no dose stated

Adalat® (Bayer Schering) PoM

Capsules, orange, nifedipine 5 mg, net price 90-cap pack = £5.73; 10 mg, 90-cap pack = £7.30

Dose angina prophylaxis (but not recommended, see notes above) and Raynaud's phenomenon, initially 5 mg 3 times daily, adjusted according to response to max. 20 mg 3 times daily

Hypertension, not recommended therefore no dose stated

Modified release

Note Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed. Modified-release formulations may not be suitable for dose titration in hepatic disease

Adalat® LA (Bayer Schering) PoM

LA 20 tablets, m/r, f/c, pink, nifedipine 20 mg, net price 28-tab pack = £4.97. Label: 25

LA 30 tablets, m/r, f/c, pink, nifedipine 30 mg, net price 28-tab pack = £6.85. Label: 25

LA 60 tablets, m/r, f/c, pink, nifedipine 60 mg, net price 28-tab pack = £9.03. Label: 25

Counselling Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy

Cautions dose form not appropriate for use in hepatic impairment or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease (including Crohn's disease)

Dose hypertension, 20–30 mg once daily, increased if necessary to max. 90 mg once daily

Angina prophylaxis, 30 mg once daily, increased if necessary to max. 90 mg once daily

Adalat® Retard (Bayer Schering) PoM

Retard 10 tablets, m/r, f/c, grey-pink, nifedipine 10 mg, net price 56-tab pack = £7.34. Label: 25

Retard 20 tablets, m/r, f/c, grey-pink, nifedipine 20 mg, net price 56-tab pack = £8.81. Label: 25

Dose hypertension and angina prophylaxis, 10 mg twice daily, adjusted according to response to 40 mg twice daily

Adipine® MR (Chiesi) PoM

Tablets, m/r, nifedipine 10 mg (pink), net price 56-tab pack = £3.73; 20 mg (pink), 56-tab pack = £5.21. Label: 25

Dose hypertension and angina prophylaxis, 10 mg twice daily, adjusted according to response to 40 mg twice daily

Adipine® XL (Chiesi) PoM

Tablets, m/r, red, nifedipine 30 mg, net price 28-tab pack = £4.70; 60 mg, 28-tab pack = £7.10. Label: 25

Dose hypertension and angina prophylaxis, 30 mg once daily, increased if necessary; max. 90 mg once daily

Coracten SR® (UCB Pharma) PoM

Capsules, m/r, nifedipine 10 mg (grey/pink, enclosing yellow pellets), net price 60-cap pack = £3.90; 20 mg (pink/brown, enclosing yellow pellets), 60-cap pack = £5.41. Label: 25

Dose hypertension and angina prophylaxis, initially 10 mg twice daily, increased if necessary to max. 40 mg twice daily

Coracten XL® (UCB Pharma) PoM

Capsules, m/r, nifedipine 30 mg (brown), net price 28-cap pack = £4.89; 60 mg (orange), 28-cap pack = £7.34. Label: 25

Dose hypertension and angina prophylaxis, 30 mg once daily, increased if necessary; max. 90 mg once daily

Fortipine LA 40® (Goldshield) PoM

Tablets, m/r, red, nifedipine 40 mg, net price 30-tab pack = £9.60. Label: 21, 25

Dose hypertension and angina prophylaxis, 40 mg once daily, increased if necessary to 80 mg daily in 1–2 divided doses

Hypolar® Retard 20 (Sandoz) PoM

Tablets, m/r, red, f/c, nifedipine 20 mg, net price 56-tab pack = £5.75. Label: 25

Dose hypertension and angina prophylaxis, 20 mg twice daily, increased if necessary to 40 mg twice daily

Nifedipress® MR (Dexcel) PoM

Tablets, m/r, pink, nifedipine 10 mg, net price 56-tab pack = £9.23; 20 mg, 56-tab pack = £10.06. Label: 25

Dose hypertension and angina prophylaxis, initially 10 mg twice daily adjusted according to response to 40 mg twice daily

Note Also available as *Calchan® MR*, *Kentipine® MR*

Tensipine MR® (Genus) PoM

Tablets, m/r, pink-grey, nifedipine 10 mg, net price 56-tab pack = £4.30; 20 mg, 56-tab pack = £5.49. Label: 21, 25

Dose hypertension and angina prophylaxis, initially 10 mg twice daily adjusted according to response to 40 mg twice daily

Valni XL® (Winthrop) PoM

Tablets, m/r, red, nifedipine 30 mg, net price 28-tab pack = £7.29; 60 mg, 28-tab pack = £9.13. Label: 25

Cautions dose form not appropriate for use in hepatic impairment, or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, inflammatory bowel disease, or ileostomy after proctocolectomy

Dose severe hypertension and prophylaxis of angina, 30 mg once daily, increased if necessary to max. 90 mg once daily

With atenolol

Section 2.4

NIMODIPINE

Indications prevention and treatment of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage

Cautions cerebral oedema or severely raised intracranial pressure; hypotension; avoid concomitant administration of nimodipine tablets and infusion, other calcium-channel blockers, or beta-blockers; concomitant nephrotoxic drugs; avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers, alcohol (infusion only))

Contra-indications within 1 month of myocardial infarction; unstable angina; acute porphyria (section 9.8.2)

Hepatic impairment elimination reduced in cirrhosis—monitor blood pressure

Renal impairment manufacturer advises monitor renal function closely with intravenous administration

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in milk

Side-effects hypotension, variation in heart-rate, flushing, headache, gastro-intestinal disorders, nausea, sweating and feeling of warmth; thrombocytopenia and ileus reported

Dose

- Prevention, by mouth, 60 mg every 4 hours, starting within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days
- Treatment, by intravenous infusion via central catheter, initially 1 mg/hour (up to 500 micrograms/hour if body-weight less than 70 kg or if blood pressure unstable), increased after 2 hours to 2 mg/hour if no severe fall in blood pressure; continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days

Nimotop® (Bayer Schering) PoM

Tablets, yellow, f/c, nimodipine 30 mg, net price 100-tab pack = £33.60

Intravenous infusion, nimodipine 200 micrograms/mL; also contains ethanol 20% and macrogol '400' 17%. Net price 50-mL vial (with polyethylene infusion catheter) = £11.46

Note Polyethylene, polypropylene, or glass apparatus should be used; PVC should be avoided

VERAPAMIL HYDROCHLORIDE

Indications see under Dose and preparations

Cautions first-degree AV block; acute phase of myocardial infarction (avoid if bradycardia, hypotension, left ventricular failure); patients taking beta-blockers (**important:** see below); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers)

Verapamil and beta-blockers **Verapamil** injection should not be given to patients recently treated with beta-blockers because of the risk of hypotension and asystole. The suggestion that when verapamil injection has been given first, an interval of 30 minutes before giving a beta-blocker is sufficient has not been confirmed.

It may also be hazardous to give verapamil and a beta-blocker together by mouth (should only be contemplated if myocardial function well preserved).

Contra-indications hypotension, bradycardia, second- and third-degree AV block, sick sinus syndrome, cardiogenic shock, sino-atrial block; history of heart failure or significantly impaired left ventricular function, even if controlled by therapy; atrial flutter or fibrillation associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome); acute porphyria (section 9.8.2)

Hepatic impairment oral dose may need to be reduced

Pregnancy may reduce uterine blood flow with fetal hypoxia; manufacturer advises avoid in first trimester unless absolutely necessary; may inhibit labour

Breast-feeding amount too small to be harmful

Side-effects constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; rarely gynaecomastia and gingival hyperplasia after long-term treatment; after intravenous administration or high doses, hypotension, heart failure, bradycardia, heart block, and asystole

Dose

- By mouth, supraventricular arrhythmias (but see also Contra-indications), 40–120 mg 3 times daily

  Angina, 80–120 mg 3 times daily

  Hypertension, 240–480 mg daily in 2–3 divided doses

Prophylaxis of cluster headache [unlicensed] (under specialist supervision), 240–960 mg daily in 3–4 divided doses

- By slow intravenous injection over 2 minutes (3 minutes in elderly), supraventricular arrhythmias (but see also Contra-indications), 5–10 mg (preferably with ECG monitoring); in paroxysmal tachyarrhythmias a further 5 mg after 5–10 minutes if required

Verapamil (Non-proprietary) PoM

Tablets, coated, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.55; 80 mg, 84-tab pack = £1.91; 120 mg, 28-tab pack = £1.54; 160 mg, 56-tab pack = £28.20

Oral solution, verapamil hydrochloride 40 mg/5 mL, net price 150 mL = £36.90

Brands include *Zolvera®*

Cordilox® (Dexcel) PoM

Tablets, yellow, f/c, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.50; 80 mg, 84-tab pack = £2.05; 120 mg, 28-tab pack = £1.15; 160 mg, 56-tab pack = £2.80

Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.11

Securon® (Abbott) PoM

Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.08

Modified release

Half Securon SR® (Abbott) PoM

Tablets, m/r, f/c, verapamil hydrochloride 120 mg, net price 28-tab pack = £7.71. Label: 25

Dose see *Securon SR®*

Securon SR® (Abbott) PoM

Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £5.00. Label: 25

Dose hypertension, 240 mg daily (new patients initially 120 mg), increased if necessary to max. 480 mg daily (doses above 240 mg daily as 2 divided doses)

Angina, 240 mg twice daily (may sometimes be reduced to once daily)

Prophylaxis after myocardial infarction where beta-blockers not appropriate (started at least 1 week after infarction), 360 mg daily in divided doses, given as 240 mg in the morning and 120 mg in the evening *or* 120 mg 3 times daily

Univer® (Cephalon) PoM

Capsules, m/r, verapamil hydrochloride 120 mg (yellow/dark blue), net price 28-cap pack = £4.86; 180 mg (yellow), 56-cap pack = £11.38; 240 mg (yellow/dark blue), 28-cap pack = £7.67. Label: 25

Dose hypertension, 240 mg daily, max. 480 mg daily (new patients, initial dose 120 mg); angina, 360 mg daily, max. 480 mg daily

Verapress MR® (Dexcel) PoM

Tablets, m/r, pale green, f/c, verapamil hydrochloride 240 mg, net price 28-tab pack = £6.04. Label: 25

Dose hypertension, 1 tablet daily, increased to twice daily if necessary; angina, 1 tablet twice daily (may sometimes be reduced to once daily)

Note Also available as *Cordilox® MR*

Vertab® SR 240 (Chiesi) PoM

Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £5.45. Label: 25

Dose mild to moderate hypertension, 240 mg daily, increased to twice daily if necessary; angina, 240 mg twice daily (may sometimes be reduced to once daily)

2.6.3 Other antianginal drugs

Nicorandil, a potassium-channel activator with a nitrate component, has both arterial and venous vasodilating properties and is licensed for the prevention and long-term treatment of angina (section 2.10.1). Nicorandil has similar efficacy to other antianginal drugs in controlling symptoms; it may produce additional symptomatic benefit in combination with other antianginal drugs [unlicensed indication].

Ivabradine lowers the heart rate by its action on the sinus node. It is licensed for the treatment of angina in patients in normal sinus rhythm in combination with a beta-blocker, or when beta-blockers are contra-indicated or not tolerated.

Ranolazine is licensed as adjunctive therapy in patients who are inadequately controlled or intolerant of first-line antianginal drugs.

IVABRADINE

Indications treatment of angina in patients in normal sinus rhythm (see notes above)

Cautions mild heart failure including asymptomatic left ventricular dysfunction; monitor for atrial fibrillation or other arrhythmias (treatment ineffective); hypotension (avoid if severe); retinitis pigmentosa; elderly; **interactions**: Appendix 1 (ivabradine)

Contra-indications severe bradycardia (not to be initiated if heart rate below 60 beats per minute); cardiogenic shock; acute myocardial infarction; immediately after cerebrovascular accident; sick-sinus syndrome; sino-atrial block; moderate to severe heart failure; patients with pacemaker; unstable angina; second- and third-degree heart block; congenital QT syndrome

Hepatic impairment manufacturer advises caution in moderate impairment; avoid in severe impairment

Renal impairment manufacturer advises use with caution if eGFR less than 15 mL/minute/1.73 m^2—no information available

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid

Side-effects bradycardia, first-degree heart block, ventricular extrasystoles; headache, dizziness; visual disturbances including phosphenes and blurred vision; *less commonly* nausea, constipation, diarrhoea, palpitations, supraventricular extrasystoles, dyspnoea, vertigo, muscle cramps, eosinophilia, hyperuricaemia, and raised plasma-creatinine concentration

Dose

- Initially 5 mg twice daily, increased if necessary after 3–4 weeks to 7.5 mg twice daily (if not tolerated reduce dose to 2.5–5 mg twice daily); ELDERLY initially 2.5 mg twice daily

Note Ventricular rate at rest should not be allowed to fall below 50 beats per minute

Procoralan® (Servier) ▼ PoM

Tablets, pink, f/c, ivabradine (as hydrochloride) 5 mg (scored), net price 56-tab pack = £39.00; 7.5 mg, 56-tab pack = £39.00

NICORANDIL

Indications prophylaxis and treatment of angina

Cautions hypovolaemia; low systolic blood pressure; acute pulmonary oedema; acute myocardial infarction with acute left ventricular failure and low filling pressures; **interactions:** Appendix 1 (nicorandil)

Driving Patients should be warned not to drive or operate machinery until it is established that their performance is unimpaired

Contra-indications cardiogenic shock; left ventricular failure with low filling pressures; hypotension

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding no information available—manufacturer advises avoid

Side-effects headache (especially on initiation, usually transitory); cutaneous vasodilatation with flushing; nausea, vomiting, dizziness, weakness also reported; *rarely* oral ulceration, myalgia, and rash; at high dosage, reduction in blood pressure and/or increase in heart rate; angioedema, hepatic dysfunction, and anal ulceration also reported

Dose

- Initially 10 mg twice daily (if susceptible to headache 5 mg twice daily); usual dose 10–20 mg twice daily; up to 30 mg twice daily may be used

Ikorel® (Sanofi-Aventis) PoM

Tablets, scored, nicorandil 10 mg, net price 60-tab pack = £7.71; 20 mg, 60-tab pack = £14.64

RANOLAZINE

Indications as adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line antianginal therapies

Cautions moderate to severe congestive heart failure; QT interval prolongation; elderly; body-weight less than 60 kg; **interactions:** Appendix 1 (ranolazine)

Hepatic impairment use with caution in mild impairment; avoid in moderate and severe impairment

Renal impairment use with caution if eGFR 30–80 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects constipation, nausea, vomiting; dizziness, headache, asthenia; *less commonly* abdominal pain, weight loss, dry mouth, dyspepsia, flatulence; hot flush, hypotension, syncope, prolonged QT interval, peripheral oedema; dysponea, cough, epistaxis; lethargy, hypoaesthesia, drowsiness, tremor, anxiety, insomnia, anorexia; dysuria, haematuria, chromaturia; dehydration; pain in extremities, muscle cramp, joint swelling; visual disturbance; tinnitus; pruritus, sweating; *rarely* pancreatitis, erosive duodenitis; cold extremities; throat tightness; amnesia, loss of consciousness, disorientation; erectile dysfunction; parosmia, impaired hearing; allergic dermatitis, urticaria, rash

Dose

- ADULT over 18 years, initially 375 mg twice daily, increased after 2–4 weeks to 500 mg twice daily and then adjusted according to response to max. 750 mg twice daily (reduce dose to 375–500 mg twice daily if not tolerated)

Ranexa® (Menarini) ▼ PoM

Tablets, m/r, ranolazine 375 mg (blue), net price 60-tab pack = £48.98; 500 mg (orange), 60-tab pack = £48.98; 750 mg (green), 60-tab pack = £48.98.

Label: 25, patient alert card

2.6.4 Peripheral vasodilators and related drugs

Peripheral vascular disease can be either occlusive (e.g. *intermittent claudication*) in which occlusion of the peripheral arteries is caused by atherosclerosis, or vasospastic (e.g. *Raynaud's syndrome*).

Peripheral arterial occlusive disease is associated with an increased risk of cardiovascular events; this risk is reduced by measures such as smoking cessation (section 4.10.2), effective control of blood pressure (section 2.5), regulating blood lipids (section 2.12), optimising glycaemic control in diabetes (section 6.1), taking aspirin in a dose of 75 mg daily (section 2.9), and possibly weight reduction in obesity (section 4.5). Exercise training, treatment with cilostazol or naftidrofuryl (see below), and possibly statin therapy can improve symptoms of intermittent claudication.

Cilostazol is licensed for use in intermittent claudication to improve walking distance in patients without peripheral tissue necrosis who do not have pain at rest. Patients receiving cilostazol should be assessed for improvement after 3 months. The *Scottish Medicines Consortium* (p. 4) has advised (October 2005) that cilostazol is not recommended for the treatment of intermittent claudication within NHS Scotland.

Naftidrofuryl can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl should be assessed for improvement after 3–6 months.

Inositol nicotinate, pentoxifylline, and cinnarizine are not established as being effective for the treatment of intermittent claudication.

Management of *Raynaud's syndrome* includes avoidance of exposure to cold and stopping smoking. More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud's syndrome. **Nifedipine** (section 2.6.2) is useful for reducing the frequency and severity of vasospastic attacks. Alternatively, **naftidrofuryl** may produce symptomatic improvement; **inositol nicotinate** (a nicotinic acid derivative) may also be considered. Cinnarizine, pentoxifylline, prazosin, and moxisylyte are not established as being effective for the treatment of Raynaud's syndrome.

Vasodilator therapy is not established as being effective for *chilblains* (section 13.13).

CILOSTAZOL

Indications intermittent claudication in patients without rest pain and no peripheral tissue necrosis

Cautions atrial or ventricular ectopy, atrial fibrillation, atrial flutter; diabetes mellitus (higher risk of intraocular bleeding); concomitant drugs that increase risk of bleeding; **interactions:** Appendix 1 (cilostazol)

Contra-indications predisposition to bleeding (e.g. active peptic ulcer, haemorrhagic stroke in previous 6 months, surgery in previous 3 months, proliferative diabetic retinopathy, poorly controlled hypertension);

history of ventricular tachycardia, of ventricular fibrillation and of multifocal ventricular ectopics, prolongation of QT interval, congestive heart failure

Hepatic impairment avoid in moderate or severe liver disease

Renal impairment avoid if eGFR less than 25 mL/minute/1.73 m^2

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid

Side-effects gastro-intestinal disturbances; tachycardia, palpitation, angina, arrhythmia, chest pain, oedema; rhinitis; dizziness, headache; asthenia; rash, pruritus, ecchymosis; *less commonly* gastritis, congestive heart failure, postural hypotension, dyspnoea, pneumonia, cough, insomnia, abnormal dreams, anxiety, hyperglycaemia, diabetes mellitus, anaemia, haemorrhage, myalgia, hypersensitivity reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis in rare cases); *rarely* anorexia, hypertension, paresis, increased urinary frequency, bleeding disorders, renal impairment, conjunctivitis, tinnitus, and jaundice

Dose

- 100 mg twice daily (30 minutes before or 2 hours after food)

Pletal® (Otsuka) PoM

Tablets, cilostazol 50 mg, net price 56-tab pack = £35.31; 100 mg, 56-tab pack = £35.31

INOSITOL NICOTINATE

Indications peripheral vascular disease; hyperlipidaemia (section 2.12)

Cautions cerebrovascular insufficiency, unstable angina

Contra-indications recent myocardial infarction, acute phase of a cerebrovascular accident

Pregnancy no information available—manufacturer advises avoid unless potential benefit outweighs risk

Side-effects nausea, vomiting, hypotension, flushing, syncope, oedema, headache, dizziness, paraesthesia, rash

Dose

- 3 g daily in 2–3 divided doses; max. 4 g daily

Hexopal® (Genus)

Tablets, scored, inositol nicotinate 500 mg, net price 100 = £30.76

Tablets forte, scored, inositol nicotinate 750 mg, net price 112-tab pack = £51.03

MOXISYLYTE
(Thymoxamine)

Indications primary Raynaud's syndrome (short-term treatment)

Cautions diabetes mellitus

Contra-indications active liver disease

Pregnancy manufacturer advises avoid

Side-effects nausea, diarrhoea, flushing, headache, dizziness; hepatic reactions including cholestatic jaundice and hepatitis reported to CSM

Dose

- Initially 40 mg 4 times daily, increased to 80 mg 4 times daily if poor initial response; discontinue after 2 weeks if no response

Opilon® (Archimedes) PoM

Tablets, yellow, f/c, moxisylyte 40 mg (as hydrochloride), net price 112-tab pack = £75.18. Label: 21

NAFTIDROFURYL OXALATE

Indications see under Dose

Side-effects nausea, epigastric pain, rash, hepatitis, hepatic failure

Dose

- Peripheral vascular disease (see notes above), 100–200 mg 3 times daily
- Cerebral vascular disease, 100 mg 3 times daily

Naftidrofuryl (Non-proprietary) PoM

Capsules, naftidrofuryl oxalate 100 mg, net price 84-cap pack = £4.52. Label: 25, 27

Praxilene® (Merck Serono) PoM

Capsules, pink, naftidrofuryl oxalate 100 mg, net price 84-cap pack = £8.10. Label: 25, 27

PENTOXIFYLLINE
(Oxpentifylline)

Indications peripheral vascular disease; venous leg ulcers [unlicensed indication] (Appendix A8.2.5)

Cautions hypotension, coronary artery disease; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (pentoxifylline)

Contra-indications cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction

Hepatic impairment manufacturer advises reduce dose in severe impairment

Renal impairment reduce dose by 30–50% if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—no information available

Breast-feeding present in milk—manufacturer advises use only if potential benefit outweighs risk

Side-effects gastro-intestinal disturbances, dizziness, agitation, sleep disturbances, headache; rarely flushing, tachycardia, angina, hypotension, thrombocytopenia, intrahepatic cholestasis, hypersensitivity reactions including rash, pruritus and bronchospasm

Dose

- 400 mg 2–3 times daily

Trental® (Sanofi-Aventis) PoM

Tablets, m/r, pink, s/c, pentoxifylline 400 mg, net price 90-tab pack = £19.68. Label: 21, 25

Other preparations used in peripheral vascular disease

Rutosides (oxerutins, *Paroven®*) are not vasodilators and are not generally regarded as effective preparations as capillary sealants or for the treatment of cramps; side-effects include headache, flushing, rashes, mild gastro-intestinal disturbances.

Paroven® (Novartis Consumer Health)

Capsules, yellow, oxerutins 250 mg, net price 120-cap pack = £13.05

Dose relief of symptoms of oedema associated with chronic venous insufficiency, 500 mg twice daily

2.7 Sympathomimetics

2.7.1 Inotropic sympathomimetics
2.7.2 Vasoconstrictor sympathomimetics
2.7.3 Cardiopulmonary resuscitation

The properties of sympathomimetics vary according to whether they act on alpha or on beta adrenergic receptors. Adrenaline (epinephrine) (section 2.7.3) acts on both alpha and beta receptors and increases both heart rate and contractility (beta$_1$ effects); it can cause peripheral vasodilation (a beta$_2$ effect) or vasoconstriction (an alpha effect).

2.7.1 Inotropic sympathomimetics

The cardiac stimulants **dobutamine** and **dopamine** act on beta$_1$ receptors in cardiac muscle, and increase contractility with little effect on rate.

Dopexamine acts on beta$_2$ receptors in cardiac muscle to produce its positive inotropic effect; and on peripheral dopamine receptors to increase renal perfusion; it is reported not to induce vasoconstriction.

Isoprenaline injection is available from 'special-order' manufacturers or specialist importing companies, see p. 988.

Shock Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis, or myocardial insufficiency should be corrected. The profound hypotension of shock must be treated promptly to prevent tissue hypoxia and organ failure. Volume replacement is essential to correct the hypovolaemia associated with haemorrhage and sepsis but may be detrimental in cardiogenic shock. Depending on haemodynamic status, cardiac output may be improved by the use of sympathomimetic inotropes such as adrenaline (epinephrine), dobutamine or dopamine (see notes above). In septic shock, when fluid replacement and inotropic support fail to maintain blood pressure, the vasoconstrictor noradrenaline (norepinephrine) (section 2.7.2) may be considered. In cardiogenic shock peripheral resistance is frequently high and to raise it further may worsen myocardial performance and exacerbate tissue ischaemia.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

For advice on the management of anaphylactic shock, see section 3.4.3.

DOBUTAMINE

Indications inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, and cardiogenic shock; cardiac stress testing (consult product literature)

Cautions arrhythmias, acute myocardial infarction, acute heart failure, severe hypotension, marked obstruction of cardiac ejection (such as idiopathic hypertrophic subaortic stenosis); correct hypovolaemia before starting treatment; tolerance may develop with continuous infusions longer than 72 hours; hyperthyroidism; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications phaeochromocytoma

Pregnancy no evidence of harm in *animal* studies—manufacturers advise use only if potential benefit outweighs risk

Breast-feeding manufacturers advise avoid—no information available

Side-effects nausea; hypotension, hypertension (marked increase in systolic blood pressure indicates overdose), arrhythmias, palpitations, chest pain; dyspnoea, bronchospasm; headache; fever; increased urinary urgency; eosinophilia; rash, phlebitis; *very rarely* myocardial infarction, hypokalaemia; coronary artery spasm and thrombocytopenia also reported

Dose

- By intravenous infusion, 2.5–10 micrograms/kg/minute, adjusted according to response

Dobutamine (Non-proprietary) PoM

Injection, dobutamine (as hydrochloride) 5 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 50-mL vial = £7.50
Excipients may include sulphites

Concentrate for intravenous infusion, dobutamine (as hydrochloride) 12.5 mg/mL. To be diluted before use. Net price 20-mL amp = £5.20
Excipients may include sulphites

DOPAMINE HYDROCHLORIDE

Indications cardiogenic shock in infarction or cardiac surgery

Cautions correct hypovolaemia; low dose in shock due to acute myocardial infarction—see notes above; hyperthyroidism; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications tachyarrhythmia, phaeochromocytoma

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Side-effects nausea and vomiting, peripheral vasoconstriction, hypotension, hypertension, tachycardia

Dose

- By intravenous infusion, 2–5 micrograms/kg/minute initially (see notes above)

Dopamine (Non-proprietary) PoM

Concentrate for intravenous infusion, dopamine hydrochloride 40 mg/mL, net price 5-mL amp = 90p; 160 mg/mL, 5-mL amp = £3.40. To be diluted before use

Intravenous infusion, dopamine hydrochloride 1.6 mg/mL in glucose 5% intravenous infusion, net price 250-mL container (400 mg) = £11.69. Available from 'special-order' manufacturers or specialist importing companies, see p. 988

DOPEXAMINE HYDROCHLORIDE

Indications inotropic support and vasodilator in exacerbations of chronic heart failure and in heart failure associated with cardiac surgery

Cautions myocardial infarction, recent angina, hypokalaemia, hyperglycaemia; correct hypovolaemia before starting and during treatment, monitor blood pressure, pulse, plasma potassium, and blood glucose; hyperthyroidism; avoid abrupt withdrawal; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications left ventricular outlet obstruction such as hypertrophic cardiomyopathy or aortic stenosis; phaeochromocytoma, thrombocytopenia

Pregnancy no information available—manufacturer advises avoid

Side-effects nausea, vomiting; tachycardia, bradycardia, arrhythmias, angina, myocardial infarction; tremor, headache; dyspnoea; reversible thrombocytopenia; sweating

Dose

- By intravenous infusion into central or large peripheral vein, 500 nanograms/kg/minute, may be increased to 1 microgram/kg/minute and further increased up to 6 micrograms/kg/minute in increments of 0.5–1 microgram/kg/minute at intervals of not less than 15 minutes

Dopacard® (Cephalon) PoM

Concentrate for intravenous infusion, dopexamine hydrochloride 10 mg/mL (1%). To be diluted before use. Net price 5-mL amp = £19.80

Note Contact with metal in infusion apparatus should be minimised

2.7.2 Vasoconstrictor sympathomimetics

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed (see also section 2.7.1).

The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney.

Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension. Management may include intravenous fluids (which are usually given prophylactically), oxygen (section 3.6), elevation of the legs, and injection of a pressor drug such as ephedrine. As well as constricting peripheral vessels **ephedrine** also accelerates the heart rate (by acting on beta receptors). Use is made of this dual action of ephedrine to manage associated bradycardia (although intravenous injection of atropine sulphate 400 to 600 micrograms may also be required if bradycardia persists).

EPHEDRINE HYDROCHLORIDE

Indications see under Dose

Cautions hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, susceptibility to angle-closure glaucoma, elderly; may cause acute urine retention in prostatic hypertrophy; **interactions:** Appendix 1 (sympathomimetics)

Renal impairment use with caution

Pregnancy increased fetal heart rate reported with parenteral ephedrine

Breast-feeding irritability and disturbed sleep reported

Side-effects nausea, vomiting, anorexia; tachycardia (sometimes bradycardia), arrhythmias, anginal pain, vasoconstriction with hypertension, vasodilation with hypotension, dizziness and flushing; dyspnoea; headache, anxiety, restlessness, confusion, psychoses, insomnia, tremor; difficulty in micturition, urine retention; sweating, hypersalivation; changes in blood-glucose concentration; *very rarely* angle-closure glaucoma

Dose

- Reversal of hypotension from spinal or epidural anaesthesia, by slow intravenous injection of a solution containing ephedrine hydrochloride 3 mg/mL, 3–6 mg (max. 9 mg) repeated every 3–4 minutes according to response to max. 30 mg

Ephedrine Hydrochloride (Non-proprietary) PoM

Injection, ephedrine hydrochloride 3 mg/mL, net price 10-mL amp = £3.25; 30 mg/mL, net price 1-mL amp = 41p

METARAMINOL

Indications acute hypotension (see notes above); priapism (section 7.4.5) [unlicensed indication]

Cautions see under Noradrenaline Acid Tartrate; longer duration of action than noradrenaline (norepinephrine), see below; cirrhosis

Hypertensive response Metaraminol has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Contra-indications see under Noradrenaline Acid Tartrate

Pregnancy may reduce placental perfusion—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises caution—no information available

Side-effects see under Noradrenaline Acid Tartrate; tachycardia; fatal ventricular arrhythmia reported in Laennec's cirrhosis

Dose

- By intravenous infusion, 15–100 mg, adjusted according to response
- In emergency, by intravenous injection, 0.5–5 mg then by intravenous infusion, 15–100 mg, adjusted according to response

Metaraminol (Non-proprietary) PoM

Injection, metaraminol 10 mg (as tartrate)/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

NORADRENALINE ACID TARTRATE/ NOREPINEPHRINE BITARTRATE

Indications see under dose

Cautions coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction, Prinzmetal's variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypovolaemia; elderly; extravasation at injection site may cause necrosis; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications hypertension (monitor blood pressure and rate of flow frequently)

Pregnancy avoid—may reduce placental perfusion

Side-effects hypertension, headache, bradycardia, arrhythmias, peripheral ischaemia

Dose

- Acute hypotension, by intravenous infusion, via central venous catheter, of a solution containing noradrenaline acid tartrate 80 micrograms/mL (equivalent to noradrenaline base 40 micrograms/mL) at an initial rate of 0.16–0.33 mL/minute, adjusted according to response

- Cardiac arrest, by rapid intravenous *or* intracardiac injection, 0.5–0.75 mL of a solution containing noradrenaline acid tartrate 200 micrograms/mL (equivalent to noradrenaline base 100 micrograms/mL)

Noradrenaline/Norepinephrine (Non-proprietary) PoM
Injection, noradrenaline acid tartrate 2 mg/mL (equivalent to noradrenaline base 1 mg/mL). For dilution before use. Net price 2-mL amp = £2.40, 4-mL amp = £4.40, 20-mL amp = £6.35

PHENYLEPHRINE HYDROCHLORIDE

Indications acute hypotension (see notes above); priapism (section 7.4.5) [unlicensed indication]

Cautions see under Noradrenaline Acid Tartrate; longer duration of action than noradrenaline (norepinephrine), see below; coronary disease
Hypertensive response Phenylephrine has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Contra-indications see under Noradrenaline Acid Tartrate; severe hyperthyroidism

Pregnancy avoid if possible; malformations reported following use in first trimester; fetal hypoxia and bradycardia reported in late pregnancy and labour

Side-effects see under Noradrenaline Acid Tartrate; tachycardia or reflex bradycardia

Dose

- By subcutaneous *or* intramuscular injection, 2–5 mg, followed if necessary by further doses of 1–10 mg
- By slow intravenous injection of a 1 mg/mL solution, 100–500 micrograms repeated as necessary after at least 15 minutes
- By intravenous infusion, initial rate up to 180 micrograms/minute reduced to 30–60 micrograms/minute according to response

Phenylephrine (Sovereign) PoM
Injection, phenylephrine hydrochloride 10 mg/mL (1%), net price 1-mL amp = £5.50

2.7.3 Cardiopulmonary resuscitation

The algorithm for cardiopulmonary resuscitation (see inside back cover) reflects the most recent recommendations of the Resuscitation Council (UK). These guidelines are available at www.resus.org.uk.

Cardiac arrest can be associated with ventricular fibrillation, pulseless ventricular tachycardia, asystole, and pulseless electrical activity (electromechanical dissociation). **Adrenaline (epinephrine)** 1 in 10 000 (100 micrograms/mL) is recommended in a dose of 1 mg (10 mL) by intravenous injection repeated every 3–5 minutes if necessary. Administration through a central line results in a faster response than peripheral administration, however placement of a central line must not interfere with chest compressions; drugs administered peripherally must be followed by a flush of at least 20 mL Sodium Chloride 0.9% injection to aid entry into the central circulation. Intravenous injection of **amiodarone** 300 mg (from a prefilled syringe *or* diluted in 20 mL Glucose 5%) should be considered after adrenaline to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. An additional dose of amiodarone 150 mg can be given by intravenous injection if necessary, followed by an intravenous infusion of amiodarone 900 mg over 24 hours. **Lidocaine**, in a dose of 1 mg/kg, is an alternative if amiodarone is not available; a total dose of 3 mg/kg lidocaine should not be exceeded during the first hour. **Atropine** is no longer recommended in the treatment of asystole or pulseless electrical activity.

During cardiopulmonary arrest if intravenous access cannot be obtained, the intraosseous route can be used instead. Drug administration via the endotracheal route is no longer recommended.

For the management of acute anaphylaxis see section 3.4.3.

ADRENALINE/EPINEPHRINE

Indications see notes above

Cautions ischaemic heart disease, severe angina, obstructive cardiomyopathy, hypertension, arrhythmias, cerebrovascular disease, occlusive vascular disease, arteriosclerosis, monitor blood pressure and ECG; cor pulmonale; organic brain damage, psychoneurosis; diabetes mellitus, hyperthyroidism, phaeochromocytoma; prostate disorders; hypokalaemia, hypercalcaemia; susceptibility to angle-closure glaucoma; elderly; **interactions:** Appendix 1 (sympathomimetics)

Renal impairment manufacturers advise use with caution in severe impairment

Pregnancy may reduce placental perfusion and can delay second stage of labour; manufacturers advise use only if benefit outweighs risk

Breast-feeding present in milk but unlikely to be harmful as poor oral bioavailability

Side-effects nausea, vomiting, dry mouth, hypersalavation; arrhythmias, syncope, angina, pallor, palpitation, cold extremities, hypertension (risk of cerebral haemorrhage); dyspnoea, pulmonary oedema (on excessive dosage or extreme sensitivity); anxiety, tremor, restlessness, headache, weakness, dizziness, hallucinations; hyperglycaemia; urinary retention, difficulty in micturition; metabolic acidosis; hypokalaemia; tissue necrosis at injection site and of extremities, liver and kidneys; mydriasis, angle-closure glaucoma, and sweating

Dose

- See notes above

Adrenaline/Epinephrine 1 in 10 000, Dilute (Non-proprietary) PoM
Injection, adrenaline (as acid tartrate) 100 micrograms/mL. 10-mL amp.
Brands include *Minijet® Adrenaline*

2.8 Anticoagulants and protamine

2.8.1 Parenteral anticoagulants
2.8.2 Oral anticoagulants
2.8.3 Protamine sulphate

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the

thrombus consists of a fibrin web enmeshed with platelets and red cells.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.

For the uses of anticoagulants see Parenteral anticoagulants, below and Oral anticoagulants, p. 146

Venous thromboembolism

Venous thromboembolism includes deep-vein thrombosis and pulmonary embolism, and occurs as a result of thrombus formation in a vein.

Prophylaxis of venous thromboembolism All patients admitted to hospital should undergo a risk assessment for venous thromboembolism on admission. Patients considered to be at high risk include those anticipated to have a substantial reduction in mobility, those with obesity, malignant disease, history of venous thromboembolism, thrombophilic disorder, or patients over 60 years. Patients with risk factors for bleeding (e.g. acute stroke, thrombocytopenia, acquired or untreated inherited bleeding disorders) should only receive pharmacological prophylaxis when the risk of bleeding does not outweigh the risk of venous thromboembolism. A NICE Guideline[1] provides a full list of risk factors, and gives recommendations for prophylaxis. A venous thromboembolism risk assessment checklist is also available from the Department of Health (www.dh.gov.uk).

Patients scheduled for surgery should be offered mechanical prophylaxis (e.g. anti-embolism stockings) on admission if appropriate; prophylaxis should continue until the patient is sufficiently mobile. Choice of mechanical prophylaxis will depend on factors such as the type of surgery, suitability for the patient, and their condition.

Patients undergoing general or orthopaedic surgery, who are considered to be at high risk of venous thromboembolism (see above), should be offered pharmacological prophylaxis. Choice of prophylaxis will depend on the type of surgery, suitability for the patient, and local policy. A low molecular weight heparin is suitable in all types of general and orthopaedic surgery; unfractionated heparin is preferred for patients in renal failure. Fondaparinux is an option for patients undergoing hip or knee replacement surgery, hip fracture surgery, gastro-intestinal, bariatric, or day surgery procedures. The oral anticoagulants dabigatran etexilate and rivaroxaban are indicated for thromboprophylaxis following hip or knee replacement surgery (see section 2.8.2). Pharmacological prophylaxis in general surgery should usually continue for 5–7 days, or until sufficient mobility has been re-established. Pharmacological prophylaxis should be extended to 28 days after major cancer surgery in the abdomen or pelvis. Hip or knee replacement surgery, and hip fracture surgery, require an extended duration of pharmacological prophylaxis, depending on the preparation used (consult product literature).

General medical patients who are considered to be at high risk of venous thromboembolism (see above) should be offered pharmacological prophylaxis on admission. Choice of prophylaxis will depend on the medical condition, suitability for the patient, and local policy. Patients should receive either a low molecular weight heparin, unfractionated heparin (if patient in renal failure), or fondaparinux. Prophylaxis should continue until the patient is no longer considered to be at significant risk of venous thromboembolism. Mechanical prophylaxis (e.g. anti-embolism stockings) can be offered to medical patients in whom pharmacological prophylaxis is contra-indicated, and continued until the patient is sufficiently mobile.

1. NICE clinical guideline 92 (January 2010). Venous thromboembolism: reducing the risk

2.8.1 Parenteral anticoagulants

Heparin

Heparin initiates anticoagulation rapidly but has a short duration of action. It is often referred to as '**standard**' or '**unfractionated heparin**' to distinguish it from the **low molecular weight heparins** (see p. 141), which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, unfractionated heparin can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.

Treatment For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used; alternatively, unfractionated heparin is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. Intermittent intravenous injection of unfractionated heparin is no longer recommended. An oral anticoagulant (usually warfarin, section 2.8.2) is started at the same time as unfractionated or low molecular weight heparin (the heparin needs to be continued for at least 5 days and until the INR has been in the therapeutic range for 2 consecutive days). Laboratory monitoring for unfractionated heparin, preferably on a daily basis, is essential; determination of the activated partial thromboplastin time (APTT) is the most widely used measure (for unfractionated heparin). A low molecular weight heparin or, in some circumstances, unfractionated heparin is also used in regimens for the management of myocardial infarction and unstable angina (section 2.10.1).

Prophylaxis For details on the use of heparins in the prophylaxis of venous thromboembolism see section 2.8.

Pregnancy Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin, enoxaparin, and tinzaparin; see also under individual drugs. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

Extracorporeal circuits Unfractionated heparin is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Haemorrhage If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulphate (section 2.8.3) is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

HEPARIN

Indications see under Dose

Cautions see notes above; also elderly; concomitant use of drugs that increase risk of bleeding; **interactions**: Appendix 1 (heparin)

Heparin-induced thrombocytopenia Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis. Platelet counts should be measured just before treatment with unfractionated or low molecular weight heparin, and regular monitoring of platelet counts is recommended if given for longer than 4 days. Signs of heparin-induced thrombocytopenia include a 50% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be **stopped** and an alternative anticoagulant, such as lepirudin or danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin

Hyperkalaemia Inhibition of aldosterone secretion by unfractionated or low molecular weight heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy, and plasma-potassium concentration should be measured in patients at risk of hyperkalaemia before starting the heparin and monitored regularly thereafter, particularly if treatment is to be continued for longer than 7 days

Contra-indications haemophilia and other haemorrhagic disorders, thrombocytopenia (including history of heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension; peptic ulcer; after major trauma or recent surgery to eye or nervous system; acute bacterial endocarditis; spinal or epidural anaesthesia with treatment doses of unfractionated or low molecular weight heparin; hypersensitivity to unfractionated or low molecular weight heparin

Hepatic impairment risk of bleeding increased—reduce dose or avoid in severe impairment (including oesophageal varices)

Renal impairment risk of bleeding increased in severe impairment—dose may need to be reduced

Pregnancy does not cross the placenta; maternal osteoporosis reported after prolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid; see also notes above

Breast-feeding not excreted into milk due to high molecular weight

Side-effects haemorrhage (see notes above), thrombocytopenia (see Cautions), *rarely* rebound hyperlipidaemia following unfractionated heparin withdrawal, priapism, hyperkalaemia (see Cautions), osteoporosis (risk lower with low molecular weight heparins), alopecia on prolonged use, injection-site reactions, skin necrosis, and hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis)

Dose

- Treatment of deep-vein thrombosis, pulmonary embolism, unstable angina, and acute peripheral arterial occlusion, by intravenous injection, loading dose of 5000 units *or* 75 units/kg (10 000 units in severe pulmonary embolism), followed by continuous intravenous infusion of 18 units/kg/hour *or* treatment of deep-vein thrombosis, by subcutaneous injection of 15 000 units every 12 hours (laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly); CHILD under 18 years *see* BNF for Children
- Prophylaxis in surgery (see also notes above), by subcutaneous injection, 5000 units 2 hours before surgery, then every 8–12 hours (monitoring not needed); during pregnancy (with monitoring), 5000–10 000 units every 12 hours (**important:** prevention of prosthetic heart-valve thrombosis in pregnancy calls for **specialist management**)
- Haemodialysis by intravenous injection initially 1000–5000 units, followed by continuous intravenous infusion of 250–1000 units/hour
- Myocardial infarction, see section 2.10.1
- Prevention of clotting in extracorporeal circuits, consult product literature

Doses above reflect the guidelines of the British Society for Haematology; for doses of the low molecular weight heparins, see below

Heparin Sodium (Non-proprietary) PoM

Injection, heparin sodium 1000 units/mL, net price 1-mL amp = 99p, 5-mL amp = £2.50, 5-mL vial = £2.50, 10-mL amp = £4.31, 20-mL amp = £7.09; 5000 units/mL, 1-mL amp = £1.94, 5-mL amp = £5.06, 5-mL vial = £5.64; 25 000 units/mL, 0.2-mL amp = £2.49, 1-mL amp = £5.13, 5-mL vial = £11.11

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Heparin Calcium (Non-proprietary) PoM

Injection, heparin calcium 25 000 units/mL, net price 0.2-mL amp = £2.61

Low molecular weight heparins

Low molecular weight heparins (**bemiparin**, **dalteparin**, **enoxaparin**, and **tinzaparin**) are usually preferred over unfractionated heparin in the *prevention* of venous thromboembolism because they are as effective and they have a lower risk of heparin-induced thrombocytopenia; see Prophylaxis of Venous Thromboembolism, p. 140. The standard prophylactic regimen does not require monitoring. The duration of action of low molecular weight heparins is longer than that of unfractionated heparin and *once-daily subcutaneous* administration is possible for some indications, making them convenient to use.

Low molecular weight heparins are also used in the *treatment* of deep-vein thrombosis, pulmonary embolism (see also Treatment, above), myocardial infarction (section 2.10.1), unstable coronary artery disease (section 2.10.1) and for the prevention of clotting in extracorporeal circuits.

Dalteparin is also licensed for the extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours; treatment is recommended for a duration of 6 months.

Routine monitoring of anti-Factor Xa activity is not usually required during treatment with low molecular weight heparins, but may be necessary in patients at

increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

Haemorrhage See under Heparin.

Pregnancy See under Heparin.

BEMIPARIN SODIUM

Indications see notes above and under preparations
Cautions see under Heparin and notes above
Contra-indications see under Heparin
Hepatic impairment manufacturer advises use with caution and avoid in severe impairment
Renal impairment risk of bleeding may be increased—use with caution; monitoring of anti-Factor Xa may be required; use of unfractionated heparin may be preferable
Pregnancy manufacturer advises avoid unless essential—no information available; see also Pregnancy, p. 140
Breast-feeding manufacturer advises avoid—no information available
Side-effects see under Heparin
Dose

- See under preparations below

Zibor® (Archimedes) ▼ PoM

Injection, bemiparin sodium 12 500 units/mL, net price 2500-unit (0.2-mL) prefilled syringe = £1.86; 17 500 units/mL, 3500-unit (0.2-mL) prefilled syringe = £2.75

Dose prophylaxis of deep-vein thrombosis, by subcutaneous injection, moderate risk, 2500 units 2 hours before or 6 hours after surgery then 2500 units every 24 hours; high risk, 3500 units 2 hours before or 6 hours after surgery then 3500 units every 24 hours

Prevention of clotting in extracorporeal circuits, consult product literature

Injection, bemiparin sodium 25 000 units/mL, net price 0.2-mL (5000-unit) prefilled syringe = £4.22, 0.3-mL (7500-unit) prefilled syringe = £5.34, 0.4-mL (10 000-unit) prefilled syringe = £4.39

Dose treatment of deep-vein thrombosis (with or without pulmonary embolism), by subcutaneous injection, 115 units/kg every 24 hours until adequate oral anticoagulation established

DALTEPARIN SODIUM

Indications see notes above and under preparations
Cautions see under Heparin and notes above
Contra-indications see under Heparin
Hepatic impairment dose reduction may be required in severe impairment
Renal impairment risk of bleeding may be increased—dose reduction, and monitoring of anti-Factor Xa, may be required; use of unfractionated heparin may be preferable
Pregnancy not known to be harmful; multidose vial contains benzyl alcohol—manufacturer advises avoid; see also Pregnancy, p. 140
Breast-feeding no information available
Side-effects see under Heparin
Dose

- See under preparations below

Fragmin® (Pharmacia) ▼ PoM

Injection (single-dose syringe), dalteparin sodium 12 500 units/mL, net price 2500-unit (0.2-mL) syringe = £1.86; 25 000 units/mL, 5000-unit (0.2-mL) syringe = £2.82, 7500-unit (0.3-mL) syringe = £4.23, 10 000-unit (0.4-mL) syringe = £5.65, 12 500-unit (0.5-mL) syringe = £7.06, 15 000-unit (0.6-mL) syringe = £8.47, 18 000-unit (0.72-mL) syringe = £10.16

Dose prophylaxis of deep-vein thrombosis, in surgical patients, by subcutaneous injection, moderate risk, 2500 units 1–2 hours before surgery then 2500 units every 24 hours; high risk, 2500 units 1–2 hours before surgery, then 2500 units 8–12 hours later (*or* 5000 units on the evening before surgery, then 5000 units on the following evening), then 5000 units every 24 hours

Prophylaxis of deep-vein thrombosis in medical patients, by subcutaneous injection, 5000 units every 24 hours

Treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, as a single daily dose, ADULT body-weight under 46 kg, 7500 units daily; body-weight 46–56 kg, 10 000 units daily; body-weight 57–68 kg, 12 500 units daily; body-weight 69–82 kg, 15 000 units daily; body-weight 83 kg and over, 18 000 units daily, with oral anticoagulant treatment until adequate oral anticoagulation established; monitoring of anti-Factor Xa not usually required; for patients at increased risk of haemorrhage, see below

Treatment of venous thromboembolism in pregnancy [unlicensed indication], by subcutaneous injection, early pregnancy body-weight under 50 kg, 5000 units twice daily; body-weight 50–70 kg, 6000 units twice daily; body-weight 70–90 kg, 8000 units twice daily; body-weight over 90 kg, 10 000 units twice daily

Extended treatment and prophylaxis of venous thromboembolism in patients with solid tumours, by subcutaneous injection, once daily for 30 days, ADULT body-weight 40–45 kg, 7500 units daily; body-weight 46–56 kg, 10 000 units daily; body-weight 57–68 kg, 12 500 units daily; body-weight 69–82 kg, 15 000 units daily; body-weight 83 kg and over, 18 000 units daily; *then* once daily for a further 5 months, by subcutaneous injection, ADULT body-weight 40–56 kg, 7500 units daily; body-weight 57–68 kg, 10 000 units daily; body-weight 69–82 kg, 12 500 units daily; body-weight 83–98 kg, 15 000 units daily; body-weight 99 kg and over, 18 000 units daily; interrupt treatment or reduce dose in chemotherapy-induced thrombocytopenia—consult product literature

Injection, dalteparin sodium 2500 units/mL (for subcutaneous or intravenous use), net price 4-mL (10 000-unit) amp = £5.12; 10 000-units/mL (for subcutaneous or intravenous use), 1-mL (10 000-unit) amp = £5.12; 25 000 units/mL (for subcutaneous use only), 4-mL (100 000-unit) vial = £48.66

Excipients include benzyl alcohol (in 100 000-unit/4 mL multidose vial) (avoid in neonates, see Excipients, p. 2)

Dose treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, 200 units/kg (max. 18 000 units) as a single daily dose (*or* 100 units/kg twice daily if increased risk of haemorrhage) until adequate oral anticoagulation established

Note For monitoring, blood should be taken 3–4 hours after a dose (recommended plasma concentration of anti-Factor Xa 0.5–1 unit/mL); monitoring not required for once-daily treatment regimen and not generally necessary for twice-daily regimen

Unstable coronary artery disease, by subcutaneous injection, 120 units/kg every 12 hours (max. 10 000 units twice daily) for 5–8 days

Prevention of clotting in extracorporeal circuits, consult product literature

Injection (graduated syringe), dalteparin sodium 10 000 units/mL, net price 1-mL (10 000-unit) syringe = £5.65

Dose unstable coronary artery disease (including non-ST-segment-elevation myocardial infarction), by subcutaneous injection, 120 units/kg every 12 hours (max. 10 000 units twice daily) for up to 8 days; beyond 8 days (if awaiting angiography or revascularisation) women body-weight less than 80 kg and men less than 70 kg, 5000 units every 12 hours, women body-weight greater than 80 kg and men greater than 70 kg, 7500 units every 12 hours, until day of procedure (max. 45 days)

ENOXAPARIN SODIUM

Indications see notes above and under preparations
Cautions see under Heparin and notes above; low body-weight (increased risk of bleeding)
Contra-indications see under Heparin

Hepatic impairment manufacturer advises caution—no information available

Renal impairment risk of bleeding increased; reduce dose if eGFR less than 30 mL/minute/1.73 m^2—consult product literature for details; monitoring of anti-factor Xa may be required; use of unfractionated heparin may be preferable

Pregnancy not known to be harmful; see also Pregnancy, p. 140

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Heparin

Dose

- See under preparation below

Clexane® (Sanofi-Aventis) PoM

Injection, enoxaparin sodium 100 mg/mL, net price 20-mg (0.2-mL, 2000-units) syringe = £3.03, 40-mg (0.4-mL, 4000-units) syringe = £4.04, 60-mg (0.6-mL, 6000-units) syringe = £4.57, 80-mg (0.8-mL, 8000-units) syringe = £6.49, 100-mg (1-mL, 10 000-units) syringe = £8.04; 300 mg (3-mL, 30 000-units) vial (*Clexane® Multidose*) = £21.33; 150 mg/mL (*Clexane® Forte*), 120-mg (0.8-mL, 12 000-units) syringe = £9.77, 150-mg (1-mL, 15 000-units) syringe = £11.10

Excipients include benzyl alcohol (in 300 mg multidose vials) (avoid in neonates, see Excipients, p. 2)

Dose prophylaxis of deep-vein thrombosis especially in surgical patients, by subcutaneous injection, *moderate risk*, 20 mg (2000 units) approx. 2 hours before surgery then 20 mg (2000 units) every 24 hours; *high risk* (e.g. orthopaedic surgery), 40 mg (4000 units) 12 hours before surgery then 40 mg (4000 units) every 24 hours

Prophylaxis of deep-vein thrombosis in medical patients, by subcutaneous injection, 40 mg (4000 units) every 24 hours

Treatment of deep-vein thrombosis or pulmonary embolism, by subcutaneous injection, 1.5 mg/kg (150 units/kg) every 24 hours until adequate oral anticoagulation established

Treatment of acute ST-segment elevation myocardial infarction, ADULT under 75 years, by intravenous injection, 30 mg (3000 units) followed by subcutaneous injection, 1 mg/kg (100 units/kg), then by subcutaneous injection, 1 mg/kg every 12 hours for up to 8 days (max. 100 mg (10 000 units) for first two subcutaneous doses only); ELDERLY over 75 years, by subcutaneous injection *only*, 750 micrograms/kg (75 units/kg) every 12 hours (max. 75 mg (7500 units) for first two doses only); patients undergoing percutaneous coronary intervention, additional dose, by intravenous injection, 300 micrograms/kg (30 units/kg) at time of procedure if last subcutaneous dose given more than 8 hours previously

Note When administered in conjunction with a thrombolytic, enoxaparin should be given between 15 minutes before and 30 minutes after the start of thrombolytic therapy

Unstable angina and non-ST-segment-elevation myocardial infarction, by subcutaneous injection, 1 mg/kg (100 units/kg) every 12 hours usually for 2–8 days (minimum 2 days)

Prevention of clotting in extracorporeal circuits, consult product literature

Treatment of venous thromboembolism in pregnancy [unlicensed indication], by subcutaneous injection, early pregnancy body-weight under 50 kg, 40 mg (4000 units) twice daily; body-weight 50–70 kg, 60 mg (6000 units) twice daily; body-weight 70–90 kg, 80 mg (8000 units) twice daily; body-weight over 90 kg, 100 mg (10 000 units) twice daily

TINZAPARIN SODIUM

Indications see notes above and under preparations

Cautions see under Heparin and notes above

Contra-indications see under Heparin

Hepatic impairment manufacturer advises avoid in severe impairment

Renal impairment risk of bleeding may be increased—dose reduction, and monitoring of anti-Factor Xa may be required; use with caution in elderly and avoid if age over 90 years; unfractionated heparin may be preferable

Pregnancy not known to be harmful; vials contain benzyl alcohol—manufacturer advises avoid; see also Pregnancy, p. 140

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Heparin

Dose

- See under preparations below

Innohep® (LEO) PoM

Injection, tinzaparin sodium 10 000 units/mL, net price 2500-unit (0.25-mL) syringe = £1.98, 3500-unit (0.35-mL) syringe = £2.77, 4500-unit (0.45-mL) syringe = £3.56, 20 000-unit (2-mL) vial = £10.56

Excipients include benzyl alcohol (in vial) (avoid in neonates, see Excipients, p. 2)

Dose prophylaxis of deep-vein thrombosis, by subcutaneous injection, general surgery, 3500 units 2 hours before surgery, then 3500 units every 24 hours; orthopaedic surgery, 50 units/kg 2 hours before surgery, then 50 units/kg every 24 hours *or* 4500 units 12 hours before surgery, then 4500 units every 24 hours

Prevention of clotting in extracorporeal circuits, consult product literature

Injection, tinzaparin sodium 20 000 units/mL, net price 0.5-mL (10 000-unit) syringe = £8.46, 0.7-mL (14 000-unit) syringe = £11.85, 0.9-mL (18 000-unit) syringe = £15.23, 2-mL (40 000-unit) vial = £34.20

Excipients include benzyl alcohol (in vial) (avoid in neonates, see Excipients, p. 2), sulphites (in 20 000 units/mL vial and syringe)

Dose treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, 175 units/kg once daily until adequate oral anticoagulation established

Treatment of venous thromboembolism in pregnancy [unlicensed indication], by subcutaneous injection, 175 units/kg once daily (based on early pregnancy body-weight)

Note Treatment regimens do not require anticoagulation monitoring

Heparinoids

Danaparoid is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery. Providing there is no evidence of cross-reactivity, it also has a role in patients who develop heparin-induced thrombocytopenia.

DANAPAROID SODIUM

Indications prevention of deep-vein thrombosis in general or orthopaedic surgery; thromboembolic disease in patients with history of heparin-induced thrombocytopenia

Cautions recent bleeding or risk of bleeding; concomitant use of drugs that increase risk of bleeding; antibodies to heparins (risk of antibody-induced thrombocytopenia); body-weight over 90 kg (monitor anti factor Xa activity)

Contra-indications haemophilia and other haemorrhagic disorders, thrombocytopenia (unless patient has heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension, active peptic ulcer (unless this is the reason for operation), diabetic retinopathy, acute bacterial endocarditis, spinal or epidural anaesthesia with treatment doses of danaparoid

Hepatic impairment caution in moderate impairment (increased risk of bleeding); avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available

Renal impairment caution in moderate impairment; increased risk of bleeding (monitor anti-Factor Xa activity); avoid in severe impairment unless patient has heparin-induced thrombocytopenia and no alternative available

Pregnancy manufacturer advises avoid—limited information available but not known to be harmful

Breast-feeding amount probably too small to be harmful but manufacturer advises avoid

Side-effects bleeding; hypersensitivity reactions (including rash)

Dose

- Prevention of deep-vein thrombosis, by subcutaneous injection, 750 units twice daily for 7–10 days; initiate treatment before operation (with last preoperative dose 1–4 hours before surgery)
- Thromboembolic disease in patients with history of heparin-induced thrombocytopenia, by intravenous injection, 2500 units (1250 units if body-weight under 55 kg, 3750 units if over 90 kg), followed by intravenous infusion of 400 units/hour for 2 hours, *then* 300 units/hour for 2 hours, *then* 200 units/hour for 5 days

Orgaran® (Organon) PoM
Injection, danaparoid sodium 1250 units/mL, net price 0.6-mL amp (750 units) = £26.68

Hirudins

Lepirudin, a recombinant hirudin, is licensed for anticoagulation in patients with Type II (immune) heparin-induced thrombocytopenia who require parenteral antithrombotic treatment. The dose of lepirudin is adjusted according to activated partial thromboplastin time (APTT). **Bivalirudin**, a hirudin analogue, is a thrombin inhibitor which is licensed for acute coronary syndromes in patients planned for urgent or early intervention, and as an anticoagulant for patients undergoing percutaneous coronary intervention (see also section 2.10.1); bivalirudin should be administered in combination with aspirin and clopidogrel. The *Scottish Medicines Consortium* (p. 4) has advised (November 2008) that bivalirudin (*Angiox®*) is accepted for restricted use within NHS Scotland for patients with acute coronary syndromes planned for urgent or early intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone. The *Scottish Medicines Consortium* (p. 4) has advised (August 2010) that bivalirudin (*Angiox®*) is accepted for restricted use within NHS Scotland as an anticoagulant in patients undergoing percutaneous coronary intervention who would have been considered for treatment with unfractionated heparin in combination with a glycoprotein IIb/IIIa inhibitor; it should not be used as an alternative to heparin alone.

BIVALIRUDIN

Indications acute coronary syndromes in patients planned for urgent or early intervention; anticoagulation for patients undergoing percutaneous coronary intervention (PCI)

Cautions exposure to lepirudin (theoretical risk from lepirudin antibodies); brachytherapy procedures; concomitant use of drugs that increase risk of bleeding

Contra-indications severe hypertension; subacute bacterial endocarditis; active bleeding; bleeding disorders

Renal impairment for *percutaneous coronary intervention*, reduce rate of infusion to 1.4 mg/kg/hour if eGFR 30–60 mL/minute/1.73 m^2 and monitor blood clotting parameters; for *acute coronary syndromes* and *percutaneous coronary intervention*, avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises caution—no information available

Side-effects bleeding (discontinue), thrombosis, ecchymosis; *less commonly* nausea, vomiting, tachycardia, bradycardia, hypotension, angina, dyspnoea, allergic reactions (including isolated reports of anaphylaxis), headache, thrombocytopenia, anaemia, back and chest pain, and injection-site reactions

Dose

- Acute coronary syndromes (in addition to aspirin and clopidogrel), initially by intravenous injection, 100 micrograms/kg then by intravenous infusion 250 micrograms/kg/hour (for up to 72 hours in medically managed patients); patients proceeding to percutaneous coronary intervention or coronary artery bypass surgery *without* cardiopulmonary bypass, additional bolus dose by intravenous injection 500 micrograms/kg, then by intravenous infusion 1.75 mg/kg/hour for duration of procedure; following percutaneous coronary intervention, reduce infusion rate to 250 micrograms/kg/hour for 4–12 hours as necessary; patients proceeding to coronary artery bypass surgery *with* cardiopulmonary bypass, discontinue intravenous infusion 1 hour before procedure and treat with unfractionated heparin
- Anticoagulation in patients undergoing percutaneous coronary intervention (in addition to aspirin and clopidogrel), initially by intravenous injection, 750 micrograms/kg then by intravenous infusion 1.75 mg/kg/hour for up to 4 hours after procedure; a reduced infusion rate of 250 micrograms/kg/hour may be continued for a further 4–12 hours if necessary

Angiox® (The Medicines Company) ▼ PoM
Injection, powder for reconstitution, bivalirudin, net price 250-mg vial = £310.00

LEPIRUDIN

Indications thromboembolic disease requiring parenteral anticoagulation in patients with heparin-induced thrombocytopenia type II

Cautions recent bleeding or risk of bleeding including recent puncture of large vessels, organ biopsy, recent major surgery, stroke, bleeding disorders, severe hypertension, bacterial endocarditis; concomitant use of drugs that increase risk of bleeding; determine activated partial thromboplastin time 4 hours after start of treatment (or after infusion rate altered) and at least once daily thereafter

Hepatic impairment no information—manufacturer advises that cirrhosis may affect renal excretion

Renal impairment reduce initial intravenous injection dose to 200 micrograms/kg and reduce subsequent infusion dose by 50–85% if eGFR less than 60 mL/

minute/1.73 m^2, but avoid or stop infusion if eGFR less than 15 mL/minute/1.73 m^2 (consult product literature)

Pregnancy avoid

Breast-feeding avoid

Side-effects bleeding; reduced haemoglobin concentration without obvious source of bleeding; fever, hypersensitivity reactions (including rash); injection-site reactions

Dose

- Initially by slow intravenous injection (of 5 mg/mL solution), 400 micrograms/kg followed by continuous intravenous infusion of 150 micrograms/kg/hour (max. 16.5 mg/hour), adjusted according to activated partial thromboplastin time, for 2–10 days (longer if necessary)

Refludan® (Celgene) PoM

Injection, powder for reconstitution, lepirudin, net price 50-mg vial = £57.00

Heparin flushes

The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride injection 0.9% is as effective as heparin flushes. The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Heparin Sodium (Non-proprietary) PoM

Solution, heparin sodium 10 units/mL, net price 5-mL amp = £1.00; 100 units/mL, 2-mL amp = £1.05

Dose to maintain patency of catheters, cannulas, etc. 10–200 units flushed through every 4–8 hours. Not for therapeutic use

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Epoprostenol

Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatment, usually with oral anticoagulation. Since its half-life is only about 3 minutes it must be given by continuous intravenous infusion. It is a potent vasodilator and therefore its side-effects include flushing, headache, and hypotension.

EPOPROSTENOL

Indications see notes above

Cautions anticoagulant monitoring required when given with anticoagulants; haemorrhagic diathesis; dose titration for pulmonary hypertension should be in hospital (risk of pulmonary oedema); concomitant use of drugs that increase risk of bleeding

Contra-indications severe left ventricular dysfunction

Pregnancy manufacturer advises caution—no information available

Side-effects see notes above; also bradycardia, tachycardia, pallor, sweating with higher doses; gastro-intestinal disturbances; lassitude, anxiety, agitation; dry mouth, jaw pain, chest pain; also reported, hyperglycaemia and injection-site reactions

Dose

- See product literature

Flolan® (GSK) PoM

Infusion, powder for reconstitution, epoprostenol (as sodium salt), net price 500-microgram vial (with diluent) = £62.05; 1.5-mg vial (▼) (with diluent) = £125.00

Fondaparinux

Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

For details on the use of fondaparinux in the prophylaxis of venous thromboembolism, see section 2.8, p. 140.

FONDAPARINUX SODIUM

Indications prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness, and patients undergoing major orthopaedic surgery of the hip or leg, or abdominal surgery; treatment of deep-vein thrombosis, superficial-vein thrombosis, and pulmonary embolism; treatment of unstable angina or non-ST-segment elevation myocardial infarction; treatment of ST-segment elevation myocardial infarction

Cautions bleeding disorders, active gastro-intestinal ulcer disease; recent intracranial haemorrhage; brain, spinal, or ophthalmic surgery; spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses); risk of catheter thrombus during percutaneous coronary intervention; low body-weight; elderly patients; concomitant use of drugs that increase risk of bleeding

Contra-indications active bleeding; bacterial endocarditis

Hepatic impairment caution in severe impairment (increased risk of bleeding)

Renal impairment increased risk of bleeding; for *treatment of acute coronary syndromes* avoid if eGFR less than 20 mL/minute/1.73 m^2; for *treatment of venous thromboembolism* use with caution if eGFR 30–50 mL/minute/1.73 m^2, avoid if eGFR less than 30 mL/minute/1.73 m^2; for *prophylaxis of venous thromboembolism* and *treatment of superficial-vein thrombosis* reduce dose to 1.5 mg daily if eGFR 20–50 mL/minute/1.73 m^2, avoid if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless potential benefit outweighs possible risk—no information available

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid

Side-effects bleeding, purpura, anaemia; *less commonly* gastro-intestinal disturbances, oedema, hepatic impairment, chest pain, dyspnoea, thrombocytopenia, thrombocythaemia, rash, pruritus; *rarely* hypotension, flushing, cough, vertigo, dizziness, anxiety, drowsiness, confusion, headache, hypokalaemia, hyperbilirubinaemia, injection-site reactions; also reported atrial fibrillation, tachycardia, and pyrexia

Dose

- Prophylaxis of venous thromboembolism after surgery, by subcutaneous injection, 2.5 mg 6 hours after surgery then 2.5 mg once daily; CHILD under 17 years not recommended

- Prophylaxis of venous thromboembolism in medical patients, by subcutaneous injection, 2.5 mg once daily; CHILD under 17 years not recommended
- Treatment of superficial-vein thrombosis, by subcutaneous injection, ADULT body-weight over 50 kg, 2.5 mg once daily for at least 30 days (max. 45 days if high risk of thromboembolic complications); treatment should be stopped 24 hours before surgery and restarted at least 6 hours post operatively; CHILD under 17 years not recommended
- Unstable angina and non-ST-segment elevation myocardial infarction, by subcutaneous injection, 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner); treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively; CHILD under 17 years not recommended
- ST-segment elevation myocardial infarction, initially by intravenous injection or infusion, 2.5 mg for first day, thereafter by subcutaneous injection 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner); treatment should be stopped 24 hours before coronary artery bypass graft surgery (where possible) and restarted 48 hours post operatively; CHILD under 17 years not recommended
- Treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, ADULT body-weight under 50 kg, 5 mg every 24 hours; body-weight 50–100 kg, 7.5 mg every 24 hours; body-weight over 100 kg, 10 mg every 24 hours; continue until adequate oral anticoagulation established; CHILD under 17 years not recommended

Arixtra® (GSK) ▼ PoM

Injection, fondaparinux sodium 5 mg/mL, net price 0.3-mL (1.5-mg) prefilled syringe = £6.28; 0.5-mL (2.5-mg) prefilled syringe = £6.28

Injection, fondaparinux sodium 12.5 mg/mL, net price 0.4-mL (5-mg) prefilled syringe = £11.66, 0.6-mL (7.5-mg) prefilled syringe = £11.66, 0.8-mL (10-mg) prefilled syringe = £11.66

2.8.2 Oral anticoagulants

Coumarins and phenindione

The oral anticoagulants **warfarin**, **acenocoumarol** and **phenindione**, antagonise the effects of vitamin K, and take at least 48 to 72 hours for the anticoagulant effect to develop fully; warfarin is the drug of choice. If an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly.

Uses Indications for these oral anticoagulants include *deep-vein thrombosis*, *pulmonary embolism*, *atrial fibrillation* in those who are at risk of embolisation (see also section 2.3.1), and *mechanical prosthetic heart valves* (to prevent emboli developing on the valves).

These oral anticoagulants should not be used in cerebral artery thrombosis or peripheral artery occlusion as first-line therapy; aspirin is more appropriate for reduction of risk in transient ischaemic attacks (see p. 151). Unfractionated or a low molecular weight heparin (section 2.8.1) is usually preferred for the prophylaxis of venous thromboembolism in patients undergoing surgery; alternatively, warfarin can be continued in selected patients currently taking long-term warfarin and who are at high risk of thromboembolism (seek expert advice).

Dose The base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.

For patients who require rapid anticoagulation the usual adult induction dose of warfarin is 5–10 mg[1] on the first day; subsequent doses depend upon the prothrombin time, reported as INR (international normalised ratio). For patients who do not require rapid anticoagulation, a lower loading dose can be used over 3–4 weeks. The daily maintenance dose of warfarin is usually 3–9 mg (taken at the **same time** each day). The following indications and target INRs[2] take into account recommendations of the British Society for Haematology[3]:

- INR 2.5 for treatment of deep-vein thrombosis and pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin), for atrial fibrillation, cardioversion (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR; anticoagulation should continue for at least 4 weeks following the procedure), dilated cardiomyopathy, mural thrombus, symptomatic inherited thrombophilia, coronary artery thrombosis (if anticoagulated), and paroxysmal nocturnal haemoglobinuria;
- INR 3.5 for recurrent deep-vein thrombosis and pulmonary embolism (in patients currently receiving warfarin with INR above 2);
- For mechanical prosthetic heart valves, the recommended target INR depends on the type and location of the valve. Generally, a target INR of 3 is recommended for mechanical aortic valves, and 3.5 for mechanical mitral valves.

Monitoring It is essential that the INR be determined daily or on alternate days in early days of treatment, *then* at longer intervals (depending on response[4]) *then* up to every 12 weeks.

Haemorrhage The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The following recommendations are based on the result of the INR and whether there is major or

1. First dose reduced if base-line prothrombin time prolonged, if liver-function tests abnormal, or if patient in cardiac failure, on parenteral feeding, less than average body weight, elderly, or receiving other drugs known to potentiate oral anticoagulants.
2. An INR which is within 0.5 units of the target value is generally satisfactory; larger deviations require dosage adjustment. Target values (rather than ranges) are now recommended.
3. Guidelines on Oral Anticoagulation (warfarin): third edition—2005 update. *Br J Haematol* 2005; **132**: 277–285.
4. Change in patient's clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. See also **interactions**, Appendix 1 (warfarin). Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect warfarin control.

minor bleeding; the recommendations apply to patients taking warfarin:

- Major bleeding—stop warfarin; give phytomenadione (vitamin K_1) 5–10 mg by slow intravenous injection; give dried prothrombin complex (factors II, VII, IX, and X—section 2.11) 30–50 units/kg (if dried prothrombin complex unavailable, fresh frozen plasma 15 mL/kg can be given but is less effective)
- INR > 8.0, no bleeding or minor bleeding—stop warfarin and give phytomenadione (vitamin K_1) 2.5–5 mg by mouth using the intravenous preparation orally [unlicensed use], or 0.5–1 mg by slow intravenous injection (if complete reversal required 5–10 mg by slow intravenous injection); repeat dose of phytomenadione if INR still too high after 24 hours; restart warfarin when INR <5.0
- INR 5.0–8.0, no bleeding—stop warfarin; minor bleeding—stop warfarin and give phytomenadione (vitamin K_1) 1–2.5 mg by mouth using the intravenous preparation orally [unlicensed use]; restart warfarin when INR <5.0
- Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

Hepatic impairment Warfarin, acenocoumarol, and phenindione should be avoided in severe impairment, especially if prothrombin time is already prolonged.

Renal impairment Warfarin, acenocoumarol, and phenindione should be used with caution in mild to moderate impairment and avoided in severe impairment.

Pregnancy Warfarin, acenocoumarol, and phenindione are teratogenic and should not be given in the first trimester of pregnancy. Women of child-bearing age should be warned of this danger since stopping these drugs before the sixth week of gestation may largely avoid the risk of fetal abnormality. These oral anticoagulants cross the placenta with risk of congenital malformations, and placental, fetal, or neonatal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, they should be avoided in pregnancy, especially in the first and third trimesters. Difficult decisions may have to be made, particularly in women with prosthetic heart valves, atrial fibrillation, or with a history of recurrent venous thrombosis or pulmonary embolism.

Breast-feeding With warfarin, acenocoumarol, and phenindione there is a risk of haemorrhage which is increased by vitamin-K deficiency. Warfarin is not present in milk in significant amounts, and appears safe, but phenindione should be avoided; the manufacturer of acenocoumarol recommends prophylactic vitamin K for the infant (consult product literature).

Treatment booklets Anticoagulant treatment booklets should be issued to patients, and are available for distribution to local healthcare professionals from Health Authorities and from:

3M Security Printing and Systems Limited
Gorse Street
Chadderton
Oldham, OL9 9QH
Tel: 0845 610 1112
nhsforms@spsl.uk.com

These booklets include advice for patients on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording of INR results and dosage information. Electronic copies and further advice are also available at www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant.

WARFARIN SODIUM

Indications prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks

Cautions see notes above; also recent surgery; recent ischaemic stroke; history of gastro-intestinal bleeding; peptic ulcer; concomitant use of drugs that increase risk of bleeding; bacterial endocarditis (increased risk of bleeding; use only if warfarin otherwise indicated); avoid cranberry juice; **interactions:** Appendix 1 (coumarins)

Contra-indications haemorrhagic stroke; significant bleeding; avoid use within 48 hours postpartum

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects haemorrhage—see notes above; also nausea, vomiting, diarrhoea, jaundice, hepatic dysfunction, pancreatitis, pyrexia, alopecia, purpura, rash, 'purple toes', skin necrosis (increased risk in patients with protein C or protein S deficiency)

Dose

- See notes above

Warfarin (Non-proprietary) PoM

Tablets, warfarin sodium 500 micrograms (white), net price 28-tab pack = £1.49; 1 mg (brown), 28-tab pack = 93p; 3 mg (blue), 28-tab pack = 95p; 5 mg (pink), 28-tab pack = £1.03. Label: 10, anticoagulant card
Brands include *Marevan®*

Oral suspension, warfarin sodium 5 mg/5 mL, net price 150 mL = £90.00. Label: 10, anticoagulant card

ACENOCOUMAROL

(Nicoumalone)

Indications see under Warfarin Sodium

Cautions see under Warfarin Sodium

Contra-indications see under Warfarin Sodium

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Warfarin Sodium

Dose

- 4 mg on first day, 4–8 mg on second day; maintenance dose usually 1–8 mg daily adjusted according to response

Sinthrome® (Alliance) PoM

Tablets, acenocoumarol 1 mg, net price 100-tab pack = £4.27. Label: 10, anticoagulant card

PHENINDIONE

Indications prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism

Cautions see under Warfarin Sodium; **interactions**: Appendix 1 (phenindione)

Contra-indications see under Warfarin Sodium

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Warfarin Sodium; also hypersensitivity reactions including exfoliative dermatitis, exanthema, fever, leucopenia, agranulocytosis, eosinophilia, and renal damage; micro-adenopathy and urine coloured pink or orange

Dose

- 200 mg on day 1; 100 mg on day 2, then adjusted according to response; maintenance dose usually 50–150 mg daily

Phenindione (Non-proprietary) PoM

Tablets, phenindione 10 mg, net price 28-tab pack = £21.10; 25 mg, 28-tab pack = £27.36; 50 mg, 28-tab pack = £32.33. Label: 10, anticoagulant card, 14, (urine pink or orange)

Dabigatran etexilate

Dabigatran etexilate, a direct thrombin inhibitor, is given orally for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery; see Prophylaxis of Venous Thromboembolism, p. 140. Dabigatran etexilate has a rapid onset of action and does not require therapeutic monitoring. The most common side-effect is haemorrhage and patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

NICE guidance

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (September 2008)

Dabigatran etexilate is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery.

DABIGATRAN ETEXILATE

Indications see notes above

Cautions see notes above; also elderly; body-weight less than 50 kg; recent surgery; anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—give initial dose at least 2 hours after catheter removal and monitor neurological signs); bacterial endocarditis (increased risk of bleeding); bleeding disorders; active gastro-intestinal ulceration; concomitant use of drugs that increase risk of bleeding; **interactions**: Appendix 1 (dabigatran etexilate)

Contra-indications active bleeding; impaired haemostasis

Hepatic impairment avoid in severe liver disease, especially if prothrombin time already prolonged

Renal impairment reduce initial dose to 75 mg and subsequent doses to 150 mg once daily if eGFR 30–50 mL/minute/1.73 m^2; reduce dose to 75 mg once daily if eGFR 30–50 mL/minute/1.73 m^2 and patient receiving concomitant treatment with verapamil; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects haemorrhage—see notes above; *less commonly* hepatobiliary disorders

Dose

- Prophylaxis of venous thromboembolism following total knee replacement surgery, ADULT over 18 years, 110 mg (ELDERLY over 75 years, 75 mg) 1–4 hours after surgery, *then* 220 mg (ELDERLY over 75 years, 150 mg) once daily for 9 days
- Prophylaxis of venous thromboembolism following total hip replacement surgery, ADULT over 18 years, 110 mg (ELDERLY over 75 years, 75 mg) 1–4 hours after surgery, *then* 220 mg (ELDERLY over 75 years, 150 mg) once daily for 27–34 days

Note Max. 150 mg daily with concomitant amiodarone or verapamil

Pradaxa® (Boehringer Ingelheim) ▼ PoM

Capsules, blue/ivory, dabigatran etexilate (as mesilate) 75 mg, net price 10-cap pack = £21.00, 60-cap pack = £126.00; 110 mg 10-cap pack = £21.00, 60-cap pack = £126.00. Label: 25

Rivaroxaban

Rivaroxaban, a direct inhibitor of activated factor X, is given orally for prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery; see Prophylaxis of Venous Thromboembolism, p. 140. Rivaroxaban does not require therapeutic monitoring. The common side-effects are nausea and haemorrhage, and patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

NICE guidance

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (April 2009)

Rivaroxaban is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery.

RIVAROXABAN

Indications see notes above

Cautions see notes above; also bleeding disorders; concomitant use of drugs that increase risk of bleeding; severe hypertension; active or recent gastro-intestinal ulceration; vascular retinopathy; anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal); recent surgery; **interactions**: Appendix 1 (rivaroxaban)

Contra-indications active bleeding

Hepatic impairment manufacturer advises caution in cirrhotic patients with moderate hepatic impairment; avoid in liver disease with coagulopathy

Renal impairment use with caution if eGFR 15–29 mL/minute/1.73 m^2 or if eGFR 30–49 mL/minute/1.73 m^2 and concomitant use of drugs that increase plasma-rivaroxaban concentration (consult product literature); avoid if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects nausea; haemorrhage (see notes above); *less commonly* constipation, diarrhoea, dyspepsia, dry mouth, vomiting, hypotension, oedema, tachycardia, thrombocythaemia, syncope, dizziness, headache, renal impairment, pain in extremities, pruritus, and rash; jaundice also reported

Dose

- Prophylaxis of venous thromboembolism following knee replacement surgery, ADULT over 18 years, 10 mg once daily for 2 weeks starting 6–10 hours after surgery
- Prophylaxis of venous thromboembolism following hip replacement surgery, ADULT over 18 years, 10 mg once daily for 5 weeks starting 6–10 hours after surgery

Xarelto® (Bayer Schering) ▼ PoM

Tablets, red, f/c, rivaroxaban 10 mg, net price 10-tab pack = £44.15, 30-tab pack = £132.44, 100-tab pack = £441.45

2.8.3 Protamine sulphate

Protamine sulphate is used to treat overdosage of unfractionated or low molecular weight heparin. The long half-life of low molecular weight heparins should be taken into consideration when determining the dose of protamine sulphate; the effects of low molecular weight heparins can persist for up to 24 hours after administration. Excessive doses of protamine sulphate can have an anticoagulant effect.

PROTAMINE SULPHATE
(Protamine Sulfate)

Indications see above

Cautions see above; also monitor activated partial thromboplastin time or other appropriate blood clotting parameters; increased risk of allergic reaction to protamine (including previous treatment with protamine or protamine insulin, allergy to fish, men who are infertile or who have had a vasectomy)

Side-effects nausea, vomiting, lassitude, flushing, hypotension, hypertension, bradycardia, dyspnoea, rebound bleeding, back pain; hypersensitivity reactions (including angioedema, anaphylaxis) and pulmonary oedema reported

Dose

- Overdosage with intravenous injection of unfractionated heparin, by intravenous injection (rate not exceeding 5 mg/minute), 1 mg neutralises 80–100 units heparin when given within 15 minutes of heparin; if longer than 15 minutes since heparin, less protamine required (consult product literature for details) as heparin rapidly excreted; max. 50 mg
- Overdosage with intravenous infusion of unfractionated heparin, by intravenous injection (rate not exceeding 5 mg/minute), 25–50 mg once heparin infusion stopped
- Overdosage with subcutaneous injection of unfractionated heparin, 1 mg neutralises 100 units heparin; give 25–50 mg by intravenous injection (rate not exceeding 5 mg/minute) then any remaining dose given by intravenous infusion over 8–16 hours; max. total dose 50 mg
- Overdosage with subcutaneous injection of low molecular weight heparin, by intermittent intravenous injection (rate not exceeding 5 mg/minute) or by continuous intravenous infusion, 1 mg neutralises approx. 100 units low molecular weight heparin (consult product literature of low molecular weight heparin for details); max. 50 mg

Protamine Sulphate (Non-proprietary) PoM

Injection, protamine sulphate 10 mg /mL, net price 5-mL amp = £1.43, 10-mL amp = £4.15

2.9 Antiplatelet drugs

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.

Use of **aspirin** in primary prevention of cardiovascular events, in patients with or without diabetes, is of unproven benefit. Long-term use of aspirin, in a dose of 75 mg daily, is of benefit in established cardiovascular disease (secondary prevention); unduly high blood pressure must be controlled before aspirin is given. If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor (section 1.3.5) can be added.

Aspirin in a dose of 75–300 mg daily is given following coronary bypass surgery. For details on the use of aspirin in atrial fibrillation see section 2.3.1; for intermittent claudication see section 2.6.4; for stable angina and acute coronary syndromes see section 2.10.1; for use following placement of coronary stents see below; for use in stroke see also below.

Clopidogrel is licensed for the prevention of ischaemic events in patients with a history of symptomatic ischaemic disease. Clopidogrel, in combination with low-dose aspirin, is also licensed for acute coronary syndrome without ST-segment elevation (section 2.10.1); in these circumstances the combination is given for up to 12 months (most benefit occurs during the first 3 months; there is no evidence of benefit beyond 12 months). Clopidogrel, in combination with low-dose aspirin, is also licensed for acute myocardial infarction with ST-segment elevation (section 2.10.1); the combination is licensed for at least 4 weeks, but the optimum treatment duration has not been established. In patients undergoing percutaneous coronary intervention, clopidogrel is used as an adjunct with aspirin (see also below). Patients, who are not already taking clopidogrel, should receive a 300 mg loading dose prior to the procedure; alternatively, a 600 mg [unlicensed] loading dose may produce a greater and more rapid inhibition of platelet aggregation. Use of clopidogrel with aspirin increases the risk of bleeding. Clopidogrel monotherapy is an alternative when aspirin is contra-indi-

cated, for example in those with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor.

For details on the use of clopidogrel in stroke, see below.

The *Scottish Medicines Consortium* (p. 4) has advised (February 2004) that clopidogrel be accepted for restricted use for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. Clopidogrel should be initiated in hospital inpatients **only**. The *Scottish Medicines Consortium* has also advised (July 2007) that clopidogrel be accepted for restricted use for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only.

Dipyridamole is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks (see also Long-term Management, under Ischaemic Stroke, below).

NICE guidance

Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events (December 2010)

The guidance applies to patients who have had an occlusive vascular event, or who have established peripheral arterial disease. The guidance does **not** apply to patients who have had, or are at risk of, stroke associated with atrial fibrillation, or who need prophylaxis for occlusive events following coronary revascularisation or carotid artery procedures.

Clopidogrel monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:

- an ischaemic stroke, or who have peripheral arterial disease or multivascular disease, **or**
- a myocardial infarction, only if aspirin is contra-indicated or not tolerated.

Modified-release dipyridamole, in combination with aspirin, is recommended as an option to prevent occlusive vascular events in patients who have had:

- a transient ischaemic attack, **or**
- an ischaemic stroke, only if clopidogrel is contra-indicated or not tolerated.

Modified-release dipyridamole monotherapy is recommended as an option to prevent occlusive vascular events in patients who have had:

- an ischaemic stroke, only if aspirin and clopidogrel are contra-indicated or not tolerated, **or**
- a transient ischaemic attack, only if aspirin is contra-indicated or not tolerated.

Prasugrel, in combination with aspirin, is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention (section 2.10.1); the combination is usually given for up to 12 months.

The *Scottish Medicines Consortium* (p. 4) has advised (August 2009) that prasugrel (*Efient®*), in combination with aspirin, be accepted for restricted use within NHS Scotland for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention who are eligible to receive the 10 mg dose of prasugrel.

NICE guidance

Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention (October 2009)

Prasugrel, in combination with aspirin, is an option for the prevention of atherothrombotic events in patients with acute coronary syndromes undergoing percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention is necessary for ST-segment elevation myocardial infarction, **or**
- stent thrombosis occurred during treatment with clopidogrel, **or**
- the patient has diabetes mellitus.

Patients selected for percutaneous coronary intervention, with the placement of a coronary stent, will require dual antiplatelet therapy with aspirin and clopidogrel, or aspirin and prasugrel. Aspirin therapy should continue indefinitely. Clopidogrel is recommended for 1 month following elective percutaneous coronary intervention with placement of a bare-metal stent, and for 12 months if percutaneous coronary intervention with placement of a bare-metal stent was for an acute coronary syndrome; clopidogrel should be given for 12 months following placement of a drug-eluting stent. Clopidogrel should not be discontinued prematurely in patients with a drug-eluting stent—there is an increased risk of stent thrombosis as a result of the eluted drug slowing the re-endothelialisation process. Patients considered to be at high risk of developing late stent thrombosis with a drug-eluting stent may require a longer duration of treatment with clopidogrel. Prasugrel is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see notes above).

Glycoprotein IIb/IIIa inhibitors Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. **Abciximab** is a monoclonal antibody which binds to glycoprotein IIb/IIIa receptors and to other related sites; it is licensed as an adjunct to unfractionated heparin and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only (to avoid additional risk of thrombocytopenia). **Eptifibatide** and **tirofiban** also inhibit glycoprotein IIb/IIIa receptors; they are licensed for use with unfractionated heparin and aspirin to prevent early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction (section 2.10.1). Abciximab, eptifibatide and tirofiban should be used by specialists only.

For use of epoprostenol, see section 2.8.1.

Management of stroke

Stroke is associated with a significant risk of morbidity and mortality. Patients presenting with acute symptoms should be immediately transferred to hospital for accurate diagnosis of stroke type, and urgent initiation of appropriate treatment; patients should be managed by a specialist multidisciplinary stroke team.

The following notes give an overview of the initial and long-term management of transient ischaemic attack, ischaemic stroke, and intracerebral haemorrhage.

Transient ischaemic attack

Patients suspected of having a transient ischaemic attack should immediately receive aspirin 300 mg once daily (patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel 75 mg once daily [unlicensed use] as an alternative). Following a confirmed diagnosis, patients should receive treatment for secondary prevention (see Long-term Management, under Ischaemic Stroke, below).

Ischaemic stroke

Initial management **Alteplase** (section 2.10.2) is recommended in the treatment of acute ischaemic stroke if it can be administered within 3 hours of symptom onset; it should be given by medical staff experienced in the administration of thrombolytics and the treatment of acute stroke, preferably within a specialist stroke centre. Treatment with aspirin 300 mg once daily for 14 days should be initiated 24 hours after thrombolysis (or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis); patients with aspirin hypersensitivity, or those intolerant of aspirin despite the addition of a proton pump inhibitor, should receive clopidogrel 75 mg once daily [unlicensed use] as an alternative.

Anticoagulants are not recommended as an alternative to antiplatelet drugs in acute ischaemic stroke in patients who are in sinus rhythm. However, parenteral anticoagulants (section 2.8.1) may be indicated in patients who are symptomatic of, or at high risk of developing, deep vein thrombosis or pulmonary embolism; warfarin should not be commenced in the acute phase of ischaemic stroke.

Anticoagulants (section 2.8.2) should be considered after cardio-embolic ischaemic stroke in patients with atrial fibrillation, however patients presenting with atrial fibrillation following a disabling ischaemic stroke should receive aspirin 300 mg once daily for 14 days, before being considered for warfarin treatment. Patients already receiving anticoagulation for a prosthetic heart valve who experience a disabling ischaemic stroke and are at significant risk of haemorrhagic transformation, should have their anticoagulant treatment stopped for 7 days and substituted with aspirin 300 mg once daily.

Treatment of hypertension in the acute phase of ischaemic stroke can result in reduced cerebral perfusion, and should therefore only be instituted in the event of a hypertensive emergency (see section 2.5), or in those patients considered for thrombolysis.

Long-term management Patients should receive long-term treatment following a transient ischaemic attack or an ischaemic stroke to reduce the risk of further cardiovascular events. Following a transient ischaemic attack, long-term treatment with modified-release dipyridamole in combination with aspirin is recommended; if patients are intolerant of aspirin, or it is contra-indicated, then modified-release dipyridamole alone is recommended. Clopidogrel 75 mg once daily is recommended as long-term treatment following an ischaemic stroke (not associated with atrial fibrillation (see below)); if clopidogrel is contra-indicated or not tolerated, patients should receive modified-release dipyridamole in combination with aspirin; modified-release dipyridamole alone can be considered for patients with contra-indications to, or intolerance of, aspirin and clopidogrel. Patients with stroke associated with atrial fibrillation should be reviewed for long-term treatment with aspirin or warfarin (see Initial Management under Ischaemic Stroke, above, and section 2.3).

Anticoagulants are not routinely recommended in the long-term prevention of recurrent stroke, except in patients with atrial fibrillation (section 2.3).

A statin (section 2.12) should be initiated 48 hours after stroke symptom onset, irrespective of the patient's serum-cholesterol concentration.

Following the acute phase of ischaemic stroke, blood pressure should be measured and treatment initiated to achieve a target blood pressure of $<130/80$ mmHg (see section 2.5). Beta-blockers should not be used in the management of hypertension following a stroke, unless they are indicated for a co-existing condition.

All patients should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight, alcohol intake, and smoking.

Intracerebral haemorrhage

Initial management Surgical intervention may be required following intracerebral haemorrhage to remove the haematoma and relieve intracranial pressure. Patients taking anticoagulants should have this treatment stopped and reversed (see section 2.8.2); anticoagulant therapy has, however, been used in patients with intracerebral haemorrhage who are symptomatic of deep vein thrombosis or pulmonary embolism; placement of a caval filter is an alternative in this situation.

Long-term management Aspirin therapy should only be given to patients at a high risk of a cardiac ischaemic event. Blood pressure should be measured and treatment initiated where appropriate (see section 2.5), taking care to avoid hypoperfusion. Statins should be avoided following intracerebral haemorrhage, however they can be used with caution when the risk of a vascular event outweighs the risk of further haemorrhage.

ABCIXIMAB

Indications prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention; short-term prevention of myocardial infarction in patients with unstable angina not responding to conventional treatment and who are scheduled for percutaneous coronary intervention (use under specialist supervision)

Cautions measure baseline prothrombin time, activated clotting time, activated partial thromboplastin time, platelet count, haemoglobin and haematocrit; monitor haemoglobin and haematocrit 12 hours and 24 hours after start of treatment and platelet count 2–4 hours and 24 hours after start of treatment; concomitant use of drugs that increase risk of bleeding; discontinue if uncontrollable serious bleeding occurs or emergency cardiac surgery needed; consult product literature for details of procedures to minimise bleeding; elderly

Contra-indications active internal bleeding; major surgery, intracranial or intraspinal surgery or trauma within last 2 months; stroke within last 2 years; intracranial neoplasm, arteriovenous malformation or aneurysm, severe hypertension, haemorrhagic diathesis, thrombocytopenia, vasculitis, hypertensive retinopathy

Hepatic impairment avoid in severe liver disease—increased risk of bleeding

Renal impairment caution in severe impairment—increased risk of bleeding

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects bleeding manifestations; nausea, vomiting, hypotension, bradycardia, chest pain, back pain, headache, fever, puncture site pain, thrombocytopenia; *rarely* cardiac tamponade, adult respiratory distress, hypersensitivity reactions

Dose

- ADULT initially by intravenous injection over 1 minute, 250 micrograms/kg, then by intravenous infusion, 125 nanograms/kg/minute (max. 10 micrograms/minute); for prevention of ischaemic complications start 10–60 minutes before percutaneous coronary intervention and continue infusion for 12 hours; for unstable angina start up to 24 hours before possible percutaneous coronary intervention and continue infusion for 12 hours after intervention

ReoPro® (Lilly) PoM

Injection, abciximab 2 mg/mL, net price 5-mL vial = £250.24

ASPIRIN (antiplatelet)

(Acetylsalicylic Acid)

Indications secondary prevention of thrombotic cerebrovascular or cardiovascular disease, and following by-pass surgery (see also section 2.10.1 and notes above)

Cautions asthma; uncontrolled hypertension; previous peptic ulceration (but manufacturers may advise avoidance of low-dose aspirin in history of peptic ulceration); concomitant use of drugs that increase risk of bleeding; G6PD deficiency (section 9.1.5); **interactions:** Appendix 1 (aspirin)

Contra-indications use other than as an antiplatelet in children and adolescents under 16 years (Reye's syndrome, section 4.7.1); active peptic ulceration; haemophilia and other bleeding disorders

Hypersensitivity Aspirin and other NSAIDs are **contra-indicated** in history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID

Hepatic impairment avoid in severe impairment—increased risk of gastro-intestinal bleeding

Renal impairment use with caution; avoid in severe impairment; sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding

Pregnancy use with caution during third trimester; impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); with high doses, closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of newborn; kernicterus in jaundiced neonates

Breast-feeding avoid—possible risk of Reye's syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low

Side-effects bronchospasm; gastro-intestinal irritation, gastro-intestinal haemorrhage (occasionally major), also other haemorrhage (e.g. subconjunctival)

Dose

- See notes above

[1]Aspirin (Non-proprietary) PoM

Dispersible tablets, aspirin 75 mg, net price 28 = 83p; 300 mg, see section 4.7.1. Label: 13, 21, 32

Tablets, e/c, aspirin 75 mg, net price 28-tab pack = 93p; 56-tab pack = £1.03; 300 mg, see section 4.7.1. Label: 5, 25, 32

Brands include *Micropirin®*

Caprin® (Pinewood) PoM

Tablets, e/c, pink, aspirin 75 mg, net price 28-tab pack = £1.51, 56-tab pack = £2.52, 100-tab pack = £5.24; 300 mg, see section 4.7.1. Label: 5, 25, 32

Nu-Seals® Aspirin (Alliance) PoM

Tablets, e/c, aspirin 75 mg, net price 56-tab pack = £3.12; 300 mg, see section 4.7.1. Label: 5, 25, 32

Note Tablets may be chewed at diagnosis for rapid absorption

CLOPIDOGREL

Indications prevention of atherosclerotic events in peripheral arterial disease, or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke; prevention of artherosclerotic events in acute coronary syndrome without ST-segment elevation (given with aspirin—see notes above) and in acute myocardial infarction with ST-segment elevation (given with aspirin—see notes above)

Cautions patients at risk of increased bleeding from trauma, surgery or other pathological conditions; concomitant use of drugs that increase risk of bleeding; discontinue 7 days before elective surgery if antiplatelet effect not desirable; **interactions:** Appendix 1 (clopidogrel)

Contra-indications active bleeding

Hepatic impairment manufacturer advises caution (risk of bleeding); avoid in severe impairment

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid

Side-effects dyspepsia, abdominal pain, diarrhoea; bleeding disorders (including gastro-intestinal and intracranial); *less commonly* nausea, vomiting, gastritis, flatulence, constipation, gastric and duodenal ulcers, headache, dizziness, paraesthesia, leucopenia, decreased platelets (very rarely severe thrombocytopenia), eosinophilia, rash, and pruritus; *rarely* vertigo; *very rarely* colitis, pancreatitis, hepatitis, acute liver failure, vasculitis, confusion, hallucinations, taste disturbance, stomatitis, bronchospasm, interstitial pneumonitis, blood disorders (including thrombocytopenic

1. Aspirin tablets 75 mg may be sold to the public in packs of up to 100 tablets; for details relating to other strengths see section 4.7.1 and *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

purpura, agranulocytosis and pancytopenia), and hypersensitivity-like reactions (including fever, glomerulonephritis, arthralgia, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus)

Dose

- Prevention of artherosclerotic events in peripheral arterial disease or after myocardial infarction or ischaemic stroke, 75 mg once daily
- Acute coronary syndrome (without ST-segment elevation), initially 300 mg then 75 mg daily (with aspirin—see notes above)
- Acute myocardial infarction (with ST-segment elevation), initially 300 mg then 75 mg daily (with aspirin—see notes above); initial dose omitted if patient over 75 years

Clopidogrel (Non-proprietary) PoM

Tablets, clopidogrel (as besilate or hydrochloride) 75 mg, net price 28-tab pack = £3.17, 30-tab pack = £3.40

Brands include *Grepid®*

Plavix® (Sanofi-Aventis) PoM

Tablets, pink, f/c, clopidogrel (as hydrogen sulphate) 75 mg, net price 30-tab pack = £35.64; 300 mg, 30-tab pack = £142.54

DIPYRIDAMOLE

Indications see notes above and under Dose

Cautions rapidly worsening angina, aortic stenosis, recent myocardial infarction, left ventricular outflow obstruction, heart failure; may exacerbate migraine; hypotension; myasthenia gravis (risk of exacerbation); coagulation disorders; concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (dipyridamole)

Pregnancy not known to be harmful

Breast-feeding manufacturers advise use only if essential—small amount present in milk

Side-effects gastro-intestinal effects, dizziness, myalgia, throbbing headache, hypotension, hot flushes and tachycardia; worsening symptoms of coronary heart disease; hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema; increased bleeding during or after surgery; thrombocytopenia reported

Dose

- By mouth, 300–600 mg daily in 3–4 divided doses
  Modified-release preparations, see under preparation below
- By intravenous injection, diagnostic only, consult product literature

Dipyridamole (Non-proprietary) PoM

Tablets, coated, dipyridamole 25 mg, net price 84 = £3.11; 100 mg, 84 = £2.80. Label: 22

Oral suspension, dipyridamole 50 mg/5 mL, net price 150 mL = £40.63

Persantin® (Boehringer Ingelheim) PoM

Tablets, s/c, dipyridamole 25 mg (orange), net price 84-tab pack = £1.49; 100 mg, 84-tab pack = £4.16. Label: 22

Injection, dipyridamole 5 mg/mL, net price 2-mL amp = 12p

Modified release

Persantin® Retard (Boehringer Ingelheim) PoM

Capsules, m/r, red/orange containing yellow pellets, dipyridamole 200 mg, net price 60-cap pack = £9.00. Label: 21, 25

Dose secondary prevention of ischaemic stroke and transient ischaemic attacks (used alone or with aspirin), adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves, 200 mg twice daily preferably with food

Note Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening

With aspirin

For prescribing information on aspirin, see under Aspirin, p. 152

Asasantin® Retard (Boehringer Ingelheim) PoM

Capsules, red/ivory, aspirin 25 mg, dipyridamole 200 mg (m/r), net price 60-cap pack = £7.79. Label: 21, 25

Dose secondary prevention of ischaemic stroke and transient ischaemic attacks, 1 capsule twice daily

Note Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening

EPTIFIBATIDE

Indications prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 24 hours (use under specialist supervision)

Cautions risk of bleeding, concomitant drugs that increase risk of bleeding—discontinue immediately if uncontrolled serious bleeding; measure baseline prothrombin time, activated partial thromboplastin time, platelet count, haemoglobin, haematocrit and serum creatinine; monitor haemoglobin, haematocrit and platelets within 6 hours after start of treatment then at least once daily; discontinue if thrombolytic therapy, intra-aortic balloon pump or emergency cardiac surgery necessary

Contra-indications abnormal bleeding within 30 days, major surgery or severe trauma within 6 weeks, stroke within last 30 days or any history of haemorrhagic stroke, intracranial disease (aneurysm, neoplasm or arteriovenous malformation), severe hypertension, haemorrhagic diathesis, increased prothrombin time or INR, thrombocytopenia

Hepatic impairment avoid in severe liver disease—increased risk of bleeding

Renal impairment reduce infusion to 1 microgram/kg/minute if eGFR 30–50 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects bleeding manifestations; *very rarely* anaphylaxis and rash

Dose

- Initially by intravenous injection, 180 micrograms/kg, then by intravenous infusion, 2 micrograms/kg/minute for up to 72 hours (up to 96 hours if percutaneous coronary intervention during treatment)

Integrilin® (GSK) PoM

Injection, eptifibatide 2 mg/mL, net price 10-mL (20-mg) vial = £13.61

Infusion, eptifibatide 750 micrograms/mL, net price 100-mL (75-mg) vial = £42.79

PRASUGREL

Indications in combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention

Cautions patients at increased risk of bleeding (e.g. from recent trauma, surgery, gastro-intestinal bleeding, or active peptic ulcer disease); concomitant use of drugs that increase risk of bleeding; discontinue at least 7 days before elective surgery if antiplatelet effect not desirable; elderly; body-weight less than 60 kg; **interactions:** Appendix 1 (prasugrel)

Contra-indications active bleeding; history of stroke or transient ischaemic attack

Hepatic impairment use with caution—increased risk of bleeding; avoid in severe impairment

Renal impairment use with caution—increased risk of bleeding

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—no information available

Side-effects haemorrhage (including gastro-intestinal and intracranial), haematoma; haematuria; anaemia; rash

Dose

- ADULT over 18 years, (with aspirin—see notes above) initially 60 mg as a single dose then body-weight over 60 kg, 10 mg once daily *or* body-weight under 60 kg or ELDERLY over 75 years, 5 mg once daily

Efient® (Lilly) ▼ PoM

Tablets, f/c, prasugrel (as hydrochloride) 5 mg (yellow), net price 28-tab pack = £47.56; 10 mg (beige), 28-tab pack = £47.56

TIROFIBAN

Indications prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 12 hours (use under specialist supervision)

Cautions major surgery or severe trauma within 3 months (avoid if within 6 weeks); traumatic or protracted cardiopulmonary resuscitation, organ biopsy or lithotripsy within last 2 weeks; risk of bleeding including active peptic ulcer within 3 months; acute pericarditis, aortic dissection, haemorrhagic retinopathy, vasculitis, haematuria, faecal occult blood; severe heart failure, cardiogenic shock, anaemia; puncture of non-compressible vessel within 24 hours; concomitant drugs that increase risk of bleeding (including within 48 hours of thrombolytic administration); monitor platelet count, haemoglobin and haematocrit before treatment, 2–6 hours after start of treatment and then at least once daily; discontinue if thrombolytic therapy, intra-aortic balloon pump or emergency cardiac surgery necessary; discontinue immediately if serious bleeding uncontrolled by pressure occurs; **interactions:** Appendix 1 (tirofiban)

Contra-indications abnormal bleeding within 30 days, stroke within 30 days or any history of haemorrhagic stroke, intracranial disease (aneurysm, neoplasm or arteriovenous malformation), severe hypertension, haemorrhagic diathesis, increased prothrombin time or INR, thrombocytopenia

Hepatic impairment caution in mild to moderate liver disease; avoid in severe liver disease—increased risk of bleeding

Renal impairment increased risk of bleeding; monitor carefully if eGFR less than 60 mL/minute/1.73 m^2; use half normal dose if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects bleeding manifestations; reversible thrombocytopenia

Dose

- By intravenous infusion, initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention); max. duration of treatment 108 hours

Aggrastat® (Chiesi) PoM

Concentrate for intravenous infusion, tirofiban (as hydrochloride) 250 micrograms/mL. For dilution before use, net price 50-mL (12.5-mg) vial = £146.11

Intravenous infusion, tirofiban (as hydrochloride) 50 micrograms/mL, net price 250-mL *Intravia®* bag = £160.72

2.10 Stable angina, acute coronary syndromes, and fibrinolysis

2.10.1 Management of stable angina and acute coronary syndromes
2.10.2 Fibrinolytic drugs

2.10.1 Management of stable angina and acute coronary syndromes

Stable angina

It is important to distinguish stable angina from unstable angina. *Stable angina* usually results from atherosclerotic plaques in the coronary arteries and is often precipitated by exertion and relieved by rest. Treatment involves management of acute anginal pain, and long-term management to prevent angina attacks and to reduce the risk of cardiovascular events.

Management of stable angina

Acute attacks of stable angina should be managed with sublingual **glyceryl trinitrate** (section 2.6.1); sublingual glyceryl trinitrate can also be taken before performing activities that are known to bring on an attack. If attacks occur more than twice a week, regular drug therapy is required and should be introduced in a step-wise manner according to response.

Patients with mild or moderate stable angina should be given a **beta-blocker** (section 2.4). In those with left-ventricular dysfunction, beta-blocker treatment should be started at a very low dose and titrated very slowly over a period of weeks or months (section 2.5.5).

For those patients in whom beta-blockers are not tolerated or are contra-indicated, a long-acting **nitrate** (section 2.6.1) or a rate-limiting **calcium-channel blocker** (diltiazem or verapamil, section 2.6.2) can be used; in patients with left-ventricular dysfunction, diltiazem and verapamil are contra-indicated because heart failure may be precipitated (**important**: see p. 128); however, a long-acting dihydropyridine calcium-channel blocker, such as amlodipine or felodipine, is suitable. Nicorandil or ivabradine (section 2.6.3) are alternatives.

When a single drug fails to control symptoms, combination treatment can be used. A calcium-channel blocker can be added to a beta-blocker, although combining verapamil with a beta-blocker should be avoided (see p. 133); combinations including diltiazem and a beta-blocker should be used with caution. Long-acting nitrates can also be used with a beta-blocker or a calcium-channel blocker, if appropriate. Combinations that include nicorandil or ranolazine (section 2.6.3) can also be considered.

Patients should be referred to a specialist if a combination of two drugs fails to control symptoms. Revascularisation procedures may be appropriate; see section 2.9 for the use of antiplatelet drugs in patients undergoing coronary stenting.

For long-term prevention of cardiovascular events, see Prevention of cardiovascular events, p. 156.

Acute coronary syndromes

Acute coronary syndromes encompass a spectrum of conditions which include unstable angina, and myocardial infarction with or without ST-segment elevation. Patients with different acute coronary syndromes may present similarly; definitive diagnosis is made on the basis of clinical presentation, ECG changes, and measurement of biochemical cardiac markers.

Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) are related acute coronary syndromes that fall between the classifications of stable angina and ST-segment elevation myocardial infarction (STEMI). They usually occur as a result of atheromatous plaque rupture, and are often characterised by stable angina that suddenly worsens, recurring or prolonged angina at rest, or new onset of severe angina. Patients with unstable angina have no evidence of myocardial necrosis, whereas in NSTEMI, myocardial necrosis (less significant than with STEMI) will be evident. There is a risk of progression to STEMI or sudden death, particularly in patients who experience pain at rest.

ST-segment elevation myocardial infarction (STEMI) is an acute coronary syndrome where atheromatous plaque rupture leads to thrombosis and myocardial ischaemia, with irreversible necrosis of the heart muscle, often leading to long-term complications. STEMI can also occasionally occur as a result of coronary spasm or embolism, arteritis, spontaneous thrombosis, or sudden severe elevation in blood pressure.

Management of unstable angina and non-ST-segment elevation myocardial infarction

These conditions are managed similarly; the aims of management are to provide supportive care and pain relief during the acute attack and to prevent further cardiac events and death. For advice on the management of patients with acute ST-segment elevation myocardial infarction (STEMI), see below.

Initial management **Oxygen** (section 3.6) should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hyperoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

Nitrates (section 2.6.1) are used to relieve ischaemic pain. If sublingual glyceryl trinitrate is not effective, intravenous or buccal glyceryl trinitrate or intravenous isosorbide dinitrate is given. If pain continues, **diamorphine** or **morphine** (section 4.7.2) can be given by slow intravenous injection; an antiemetic such as metoclopramide should also be given (section 4.6).

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect in a dose of 300 mg (section 2.9). If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. **Clopidogrel** in a dose of 300 mg (or 600 mg [unlicensed] if used prior to percutaneous coronary intervention) should also be given (see section 2.9). **Prasugrel**, in a dose of 60 mg, is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance, p. 150). Patients should also receive either unfractionated heparin, a **low molecular weight heparin**, or **fondaparinux** (section 2.8.1).

Patients without contra-indications should receive **beta-blockers** (section 2.4) which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, **diltiazem** or **verapamil** can be given (section 2.6.2).

The glycoprotein IIb/IIIa inhibitors **eptifibatide** and **tirofiban** (section 2.9) can be used (with aspirin and unfractionated heparin) for unstable angina or for non-ST-segment elevation myocardial infarction in patients at a high risk of either myocardial infarction or death.

In intermediate- and high-risk patients, abciximab, eptifibatide, or tirofiban can also be used with aspirin and unfractionated heparin in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion. In intermediate- and high-risk patients in whom early intervention is planned, bivalirudin (section 2.8.1) can be considered as an alternative to the combination of a glyocprotein IIb/IIIa inhibitor plus a heparin.

Revascularisation procedures are often appropriate for patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI); see section 2.9 for the use of antiplatelet drugs in patients undergoing coronary stenting.

Long-term management The need for long-term angina treatment or for coronary angiography should be assessed. Most patients will require standard angina treatment (see management of stable angina, above) to prevent recurrence of symptoms.

Prevention of cardiovascular events Patients with stable and unstable angina should be given advice and treatments to reduce their cardiovascular risk. The importance of life-style changes, especially stopping smoking, should be emphasised. Patients should take **aspirin** indefinitely in a dose of 75 mg daily. In patients with non-ST-segment elevation acute coronary syndrome, a combination of aspirin and clopidogrel (section 2.9) is given for up to 12 months; most benefit occurs during the first 3 months. An **ACE inhibitor** (section 2.5.5.1) and a **statin** (section 2.12) should also be given.

Management of ST-segment elevation myocardial infarction

Local guidelines for the management of myocardial infarction should be followed where they exist

These notes give an overview of the initial and long-term management of myocardial infarction with ST-segment elevation. For advice on the management of non-ST-segment elevation myocardial infarction and unstable angina, see above. The aims of management of ST-segment elevation myocardial infarction are to provide supportive care and pain relief, to promote reperfusion and to reduce mortality. Oxygen, nitrates, and diamorphine or morphine can provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolytics promote reperfusion; anticoagulants help to reduce re-occlusion and systemic embolisation; long-term use of aspirin, beta-blockers, ACE inhibitors, and statins help to reduce mortality further.

Initial management **Oxygen** (section 3.6) should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hyperoxia should be avoided and particular care is required in patients with chronic obstructive airways disease.

The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of **diamorphine** or **morphine** (section 4.7.2); an antiemetic such as metoclopramide (or, if left ventricular function is not compromised, cyclizine) by intravenous injection should also be given (section 4.6).

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect (section 2.9); a dose of 300 mg is suitable. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. **Clopidogrel**, in a dose of 300 mg (or 600 mg [unlicensed] if used prior to percutaneous coronary intervention), should also be given (section 2.9). **Prasugrel**, in a dose of 60 mg, is an alternative to clopidogrel in certain patients undergoing percutaneous coronary intervention (see NICE guidance, p. 150).

Patency of the occluded artery can be restored by percutaneous coronary intervention or by giving a **thrombolytic drug** (section 2.10.2), unless contra-indicated. Percutaneous coronary intervention is the preferred method; a **glycoprotein IIb/IIIa inhibitor** (section 2.9) can be used to reduce the risk of immediate vascular occlusion in intermediate- and high-risk patients. Patients undergoing percutaneous coronary intervention should also receive either unfractionated heparin or a low molecular weight heparin (e.g. enoxaparin); bivalirudin (section 2.8.1) is an alternative to the combination of a glycoprotein IIb/IIIa inhibitor plus a heparin. In patients who cannot be offered percutaneous coronary intervention within 90 minutes of diagnosis, a thrombolytic drug should be administered along with either unfractionated heparin (for maximum 2 days), a low molecular weight heparin (e.g. enoxaparin), or fondaparinux. See section 2.9 for the use of antiplatelet drugs in patients undergoing coronary stenting.

Patients who do not receive reperfusion therapy (with percutaneous coronary intervention or a thrombolytic) should be treated with either fondaparinux, enoxaparin, or unfractionated heparin. Prescribers should consult product literature and local protocols (where they exist) for details of anticoagulant dose and duration.

Nitrates (section 2.6.1) are used to relieve ischaemic pain. If sublingual glyceryl trinitrate is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate is given.

Early administration of some **beta-blockers** (section 2.4) has been shown to be of benefit and should be given to patients without contra-indications.

ACE inhibitors (section 2.5.5.1), and angiotensin-II receptor antagonists (section 2.5.5.2) if an ACE inhibitor cannot be used, are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor, or an angiotensin-II receptor antagonist, can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment).

All patients should be closely monitored for hyperglycaemia; those with diabetes or raised blood-glucose concentration should receive **insulin**.

Long-term management Long-term management following ST-segment elevation myocardial infarction involves the use of several drugs which should ideally be started before the patient is discharged from hospital.

Aspirin (section 2.9) should be given to all patients, unless contra-indicated, at a dose of 75 mg daily. The addition of **clopidogrel** (section 2.9) has been shown to reduce morbidity and mortality. For those intolerant of clopidogrel, and who are at low risk of bleeding, the combination of **warfarin** (section 2.8.2) and aspirin should be considered. In those intolerant of both aspirin and clopidogrel, warfarin alone can be used. Warfarin should be continued for those who are already being treated for another indication, such as atrial fibrillation, with the addition of aspirin if there is a low risk of bleeding. The combination of aspirin with clopidogrel or warfarin increases the risk of bleeding. See section 2.9 for details of antiplatelet drug duration following coronary stenting.

Beta-blockers (section 2.4) should be given to all patients in whom they are not contra-indicated. Acebutolol, metoprolol, propranolol, and timolol are suitable; for patients with left ventricular dysfunction, carvedilol, bisoprolol, or long-acting metoprolol may be appropriate (section 2.5.5).

Diltiazem [unlicensed] or **verapamil** (section 2.6.2) can be considered if a beta-blocker cannot be used; however, they are contra-indicated in those with left ventricular dysfunction. Other calcium-channel blockers have no place in routine long-term management after a myocardial infarction.

An **ACE inhibitor** (section 2.5.5.1) should be considered for all patients, especially those with evidence of left ventricular dysfunction. If an ACE inhibitor cannot be used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

Nitrates (section 2.6.1) are used for patients with angina.

Eplerenone (section 2.2.3) is licensed for use following a myocardial infarction in those with left ventricular dysfunction and evidence of heart failure.

For the role of **statins** in preventing recurrent cardiovascular events, see section 2.12.

2.10.2 Fibrinolytic drugs

Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

The value of thrombolytic drugs for the treatment of *myocardial infarction* has been established (section 2.10.1). **Streptokinase** and **alteplase** have been shown to reduce mortality. **Reteplase** and **tenecteplase** are also licensed for acute myocardial infarction. Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest in those with ECG changes that include ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients.

Alteplase, reteplase and streptokinase need to be given within 12 hours of symptom onset, ideally within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase, and **urokinase** can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke (see section 2.9).

Urokinase is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.

Cautions Thrombolytic drugs should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures. They should also be used with caution in external chest compression, elderly, hypertension, conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation), and recent or concurrent use of drugs that increase the risk of bleeding.

Contra-indications Thrombolytic drugs are contra-indicated in recent haemorrhage, trauma, or surgery (including dental extraction), coagulation defects, bleeding diatheses, aortic dissection, aneurysm, coma, history of cerebrovascular disease especially recent events or with any residual disability, recent symptoms of possible peptic ulceration, heavy vaginal bleeding, severe hypertension, active pulmonary disease with cavitation, acute pancreatitis, pericarditis, bacterial endocarditis, and oesophageal varices; also in the case of streptokinase, previous allergic reactions to either streptokinase or anistreplase (no longer available).

Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available) can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration of either streptokinase or anistreplase.

Hepatic impairment Thrombolytic drugs should be avoided in severe hepatic impairment as there is an increased risk of bleeding.

Pregnancy Thrombolytic drugs can possibly lead to premature separation of the placenta in the first 18 weeks of pregnancy. There is also a risk of maternal haemorrhage throughout pregnancy and post-partum, and also a theoretical risk of fetal haemorrhage throughout pregnancy.

Side-effects Side-effects of thrombolytics are mainly nausea and vomiting and bleeding. When thrombolytics are used in myocardial infarction, reperfusion arrhythmias and recurrent ischaemia and angina may occur. Reperfusion may also cause cerebral and pulmonary oedema. Hypotension can also occur and can usually be controlled by elevating the patient's legs, or by reducing the rate of infusion or stopping it temporarily. Back pain, fever, and convulsions have been reported. Bleeding is usually limited to the site of injection, but intracerebral haemorrhage or bleeding from other sites can occur. Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid). Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli). Thrombolytics can cause allergic reactions (including rash, flushing and uveitis) and anaphylaxis has been reported (for details of management see Allergic Emergencies, section 3.4.3). Guillain-Barré syndrome has been reported rarely after streptokinase treatment.

ALTEPLASE

(rt-PA, tissue-type plasminogen activator)

Indications acute myocardial infarction (see notes above and section 2.10.1); pulmonary embolism; acute ischaemic stroke (treatment under specialist neurology physician **only**)

Cautions see notes above; *in acute stroke*, monitor for intracranial haemorrhage, monitor blood pressure (antihypertensive recommended if systolic above 180 mmHg or diastolic above 105 mmHg)

Contra-indications see notes above; *in acute stroke*, convulsion accompanying stroke, severe stroke, history of stroke in patients with diabetes, stroke in last 3 months, hypoglycaemia, hyperglycaemia

Hepatic impairment see notes above

Pregnancy see notes above

Side-effects see notes above; also risk of cerebral bleeding increased in acute stroke

Dose

- Myocardial infarction, accelerated regimen (initiated within 6 hours of symptom onset), 15 mg by intravenous injection, followed by intravenous infusion of 50 mg over 30 minutes, then 35 mg over 60 minutes (total dose 100 mg over 90 minutes); in patients less than 65 kg, 15 mg by intravenous injection, followed by intravenous infusion of 0.75 mg/kg over 30 minutes, then 0.5 mg/kg over 60 minutes (max. total dose 100 mg over 90 minutes)
- Myocardial infarction, initiated within 6–12 hours of symptom onset, 10 mg by intravenous injection, followed by intravenous infusion of 50 mg over 60 minutes, then 4 infusions each of 10 mg over 30 minutes (total dose 100 mg over 3 hours; max. 1.5 mg/kg in patients less than 65 kg)
- Pulmonary embolism, 10 mg by intravenous injection over 1–2 minutes, followed by intravenous infusion of 90 mg over 2 hours; max. 1.5 mg/kg in patients less than 65 kg
- Acute stroke (treatment **must** begin within 3 hours of symptom onset), by intravenous administration over 60 minutes, 900 micrograms/kg (max. 90 mg); initial 10% of dose by intravenous injection, remainder by intravenous infusion; ELDERLY over 80 years not recommended

Actilyse® (Boehringer Ingelheim) PoM

Injection, powder for reconstitution, alteplase 10 mg (5.8 million units)/vial, net price per vial (with diluent) = £120.00; 20 mg (11.6 million units)/vial (with diluent and transfer device) = £180.00; 50 mg (29 million units)/vial (with diluent, transfer device, and infusion bag) = £300.00

RETEPLASE

Indications acute myocardial infarction (see notes above and section 2.10.1)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding manufacturer advises avoid breast-feeding for 24 hours after dose (express and discard milk during this time)

Side-effects see notes above

Dose

- By intravenous injection (initiated within 12 hours of symptom onset), 10 units over not more than 2 minutes, followed after 30 minutes by a further 10 units

Rapilysin® (Actavis) PoM

Injection, powder for reconstitution, reteplase 10 units/vial, net price pack of 2 vials (with 2 prefilled syringes of diluent and transfer device) = £627.97

STREPTOKINASE

Indications acute myocardial infarction (see notes above and section 2.10.1); deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism, and central retinal venous or arterial thrombosis

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Side-effects see notes above

Dose

- Myocardial infarction (initiated within 12 hours of symptom onset), by intravenous infusion, 1.5 million units over 60 minutes
- Deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism, central retinal venous or arterial thrombosis, by intravenous infusion, 250 000 units over 30 minutes, then 100 000 units every hour for up to 12–72 hours according to condition with monitoring of clotting parameters (consult product literature)

Streptase® (CSL Behring) PoM

Injection, powder for reconstitution, streptokinase, net price 250 000-unit vial = £15.91; 750 000-unit vial = £41.72; 1.5 million-unit vial = £83.44 (hosp. only)

TENECTEPLASE

Indications acute myocardial infarction (see notes above and section 2.10.1)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding manufacturer advises avoid breast-feeding for 24 hours after dose (express and discard milk during this time)

Side-effects see notes above

Dose

- By intravenous injection over 10 seconds (initiated within 6 hours of symptom onset), 30–50 mg according to body-weight—consult product literature; max. 50 mg

Metalyse® (Boehringer Ingelheim) PoM

Injection, powder for reconstitution, tenecteplase, net price 40-mg (8000-unit) vial = £502.25; 50-mg (10 000-unit) vial = £502.25 (both with prefilled syringe of water for injection)

UROKINASE

Indications thromboembolic occlusive vascular disease including deep-vein thrombosis, pulmonary embolism, and peripheral vascular occlusion; occluded intravenous catheters and cannulas blocked by fibrin clots

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above

Dose

- Deep-vein thrombosis, by intravenous infusion, initially 4400 units/kg in 15 mL sodium chloride 0.9% over 10 minutes, followed by 4400 units/kg/hour for 12–24 hours
- Pulmonary embolism, by intravenous infusion, initially 4400 units/kg in 15 mL sodium chloride 0.9% over 10 minutes, followed by 4400 units/kg/hour for 12 hours *or* by injection into pulmonary artery, initially 15 000 units/kg, subsequent doses adjusted according to response; max. 3 doses in 24 hours

- Peripheral vascular occlusion, consult product literature
- Occluded catheters and cannulas, by injection directly into catheter or cannula, 5000–25 000 units dissolved in suitable volume of sodium chloride 0.9% to fill the catheter or cannula lumen; leave for 20–60 minutes then aspirate the lysate; repeat if necessary

Syner-KINASE® (Syner-Med) PoM
Injection, powder for reconstitution, urokinase, net price 10 000-unit vial = £35.95; 25 000-unit vial = £45.95; 100 000-unit vial = £112.95
Note 50 000-unit vial and 250 000-unit vial also available from 'special-order' manufacturers or specialist importing companies, see p. 988

2.11 Antifibrinolytic drugs and haemostatics

Fibrin dissolution can be impaired by the administration of **tranexamic acid**, which inhibits fibrinolysis. It can be used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis (e.g. in prostatectomy, bladder surgery, in dental extraction in patients with haemophilia, in conisation of the cervix, and in traumatic hyphaema) and in the management of menorrhagia. Tranexamic acid may also be used in hereditary angioedema, epistaxis, and in thrombolytic overdose.

Desmopressin (section 6.5.2) is used in the management of mild to moderate haemophilia and von Willebrand's disease. It is also used for fibrinolytic response testing.

Etamsylate reduces capillary bleeding in the presence of a normal number of platelets; it does not act by fibrin stabilisation, but probably by correcting abnormal adhesion. Etamsylate is less effective than other treatments in the management of heavy menstrual bleeding and its use is no longer recommended.

ETAMSYLATE
(Ethamsylate)

Indications blood loss in menorrhagia
Cautions exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment
Contra-indications acute porphyria (see section 9.8.2)
Breast-feeding present in milk—manufacturer advises avoid
Side-effects nausea, vomiting, diarrhoea, fever (discontinue treatment), headache, rashes
Dose
- 500 mg 4 times daily during menstruation

Dicynene® (Sanofi-Aventis) PoM
Tablets, scored, etamsylate 500 mg, net price 100–tab pack = £8.44
Excipients include sulphites

TRANEXAMIC ACID

Indications see notes above
Cautions massive haematuria (avoid if risk of ureteric obstruction); not for use in disseminated intravascular coagulation; irregular menstrual bleeding (exclude structural or histological causes of menorrhagia, or fibroids causing distortion of the uterine cavity, before initiating treatment); regular liver function tests in long-term treatment of hereditary angioedema
Contra-indications thromboembolic disease
Renal impairment reduce dose—consult product literature for details
Pregnancy no evidence of teratogenicity in *animal* studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta
Breast-feeding small amount present in milk—antifibrinolytic effect in infant unlikely
Side-effects nausea, vomiting, diarrhoea (reduce dose); *rarely* disturbances in colour vision (discontinue), thromboembolic events, convulsions, allergic skin reactions; dizziness and hypotension on rapid intravenous injection
Dose
- By mouth, local fibrinolysis, 1–1.5 g (*or* 15–25 mg/kg) 2–3 times daily
  Menorrhagia (initiated when menstruation has started), 1 g 3 times daily for up to 4 days; max. 4 g daily
  Hereditary angioedema, 1–1.5 g 2–3 times daily
  Epistaxis, 1 g 3 times daily for 7 days
- By slow intravenous injection, local fibrinolysis, 0.5–1 g 3 times daily
- By continuous intravenous infusion, local fibrinolysis, following initial treatment by intravenous injection, 25–50 mg/kg over 24 hours

Tranexamic acid (Non-proprietary) PoM
Tablets, tranexamic acid 500 mg, net price 60-tab pack = £5.27

Cyklokapron® (Meda) PoM
Tablets, f/c, scored, tranexamic acid 500 mg, net price 60-tab pack = £14.30

Cyklokapron® (Pfizer) PoM
Injection, tranexamic acid 100 mg/mL, net price 5-mL amp = £1.55

Blood products

DRIED PROTHROMBIN COMPLEX
(Human Prothrombin Complex)

Dried prothrombin complex is prepared from human plasma by a suitable fractionation technique, and contains factor IX, together with variable amounts of factors II, VII, and X

Indications treatment and peri-operative prophylaxis of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available; treatment and peri-operative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment—see section 2.8.2)
Cautions risk of thrombosis; disseminated intravascular coagulation; history of myocardial infarction or coronary heart disease; postoperative use
Contra-indications angina; recent myocardial infarction (except in life-threatening haemorrhage following overdosage of oral anticoagulants, and before induction of fibrinolytic therapy); history of heparin-induced thrombocytopenia

Hepatic impairment monitor closely (risk of thromoembolic complications)

Side-effects thrombotic events (including disseminated intravascular coagulation); *rarely* headache; *very rarely* pyrexia, antibody formation, hypersensitivity reactions (including anaphylaxis); nephrotic syndrome also reported

Available from CSL Behring (*Beriplex® P/N*), Octapharma (*Octaplex®*)

DROTRECOGIN ALFA (ACTIVATED)

Recombinant activated protein C

Indications adjunctive treatment of severe sepsis with multiple organ failure—start treatment within 24 hours (and no later than 48 hours) after onset of organ failure

Cautions increased risk of bleeding, concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (drotrecogin alfa)

Contra-indications internal bleeding; intracranial neoplasm or cerebral herniation; thrombocytopenia; not recommended for use in children under 18 years or in single organ failure

Hepatic impairment avoid in chronic severe liver disease

Pregnancy manufacturer advises avoid unless benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects bleeding; headache; ecchymosis; pain

Available from Lilly (*Xigris®*)

NICE guidance

Drotrecogin alfa (activated) for severe sepsis (September 2004)

Drotrecogin alfa (activated) should be considered for adults with severe sepsis that has resulted in the failure of two or more major organs and who are receiving optimum intensive care support. Drotrecogin alfa (activated) should be initiated and supervised only by a specialist consultant with intensive care skills and experience in the care of patients with sepsis.

FACTOR VIIa (RECOMBINANT)

Eptacog alfa (activated)

Indications treatment and prophylaxis of haemorrhage in patients with haemophilia A or B with inhibitors to factors VIII or IX, acquired haemophilia, factor VII deficiency, or Glanzmann's thrombasthenia

Cautions risk of thrombosis or disseminated intravascular coagulation

Side-effects *very rarely* nausea, thrombotic events (including myocardial infarction and cerebrovascular accident), coagulation disorders, fever, pain, and allergic reactions including rash

Available from Novo Nordisk (*NovoSeven®* ▼)

FACTOR VIII FRACTION, DRIED

(Human Coagulation Factor VIII, Dried)

Dried factor VIII fraction is prepared from human plasma by a suitable fractionation technique

Indications treatment and prophylaxis of haemorrhage in congenital factor VIII deficiency (haemophilia A), acquired factor VIII deficiency, von Willebrand's disease

Cautions monitor for development of factor VIII inhibitors; intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB—less likely with high potency concentrates

Side-effects gastro-intestinal disturbances, taste disturbances; flushing, palpitation; dyspnoea, coughing; headache, dizziness, paraesthesia, drowsiness; blurred vision; antibody formation; hypersensitivity reactions including hypotension, angioedema, chills, fever, urticaria, and anaphylaxis

Available from Biotest UK (*Haemoctin®* ▼), CSL Behring (*Haemate® P*), BPL (*Optivate®*, High Purity Factor VIII and von Willebrand factor concentrate; *8Y®*), Grifols (*Alphanate®*; *Fanhdi®*), Octapharma (*Octanate®*; *Wilate®* ▼)

Note Preparation of recombinant human coagulation factor VIII (octocog alfa) available from CSL Behring (*Helixate® NexGen*), Baxter (*Advate®*), Bayer Schering (*Kogenate® Bayer*); preparation of recombinant human coagulation factor VIII (moroctocog alfa) available from Wyeth (*ReFacto AF®* ▼); octocog alfa and moroctocog alfa are not indicated for use in von Willebrand's disease

FACTOR VIII INHIBITOR BYPASSING FRACTION

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma

Indications treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors; treatment of haemorrhage in non-haemophiliac patients with acquired factor VIII inhibitors

Contra-indications disseminated intravascular coagulation

Side-effects thrombosis, disseminated intravascular coagulation, myocardial infarction; paraesthesia; pyrexia; hypersensitivity reactions including hypotension, flushing, urticaria, rash, and anaphylaxis

Available from Baxter (*FEIBA®*)

FACTOR IX FRACTION, DRIED

Dried factor IX fraction is prepared from human plasma by a suitable fractionation technique; it may also contain clotting factors II, VII, and X

Indications treatment and prophylaxis of haemorrhage in congenital factor IX deficiency (haemophilia B)

Cautions risk of thrombosis—principally with former low purity products

Contra-indications disseminated intravascular coagulation

Side-effects gastro-intestinal disturbances; headache, dizziness; allergic reactions, including chills, fever

Available from CSL Behring (*Mononine®*), BPL (*Replenine®-VF*, Dried Factor IX Fraction), Grifols (*AlphaNine®*)

Note Preparation of recombinant coagulation factor IX (nonacog alfa) available from Wyeth (*BeneFIX®*)

FACTOR XIII FRACTION, DRIED

(Human Fibrin-stabilising Factor, Dried)

Indications congenital factor XIII deficiency

Side-effects rarely, allergic reactions and fever

Available from CSL Behring (*Fibrogammin® P*)

FRESH FROZEN PLASMA

Fresh frozen plasma is prepared from the supernatant liquid obtained by centrifugation of one donation of whole blood

Indications to replace coagulation factors or other plasma proteins where their concentration or functional activity is critically reduced

Cautions need for compatibility

Contra-indications circulatory overload; avoid use as a volume expander

Side-effects allergic reactions including chills, fever, bronchospasm; adult respiratory distress syndrome

Available from Regional Blood Transfusion Services

Note A preparation of solvent/detergent treated human plasma (frozen) from pooled donors is available from Octapharma (*Octaplas®*)

PROTEIN C CONCENTRATE

Protein C is prepared from human plasma

Indications congenital protein C deficiency

Cautions hypersensitivity to heparins

Side-effects *very rarely* fever, bleeding, dizziness, and hypersensitivity reactions

Available from Baxter (*Ceprotin®*)

2.12 Lipid-regulating drugs

Preventative measures should be taken in individuals with a high risk of developing cardiovascular disease (primary prevention) and to prevent recurrence of events in those with established cardiovascular disease (secondary prevention).

Individuals at high risk include those who already have atherosclerotic disease, those with diabetes mellitus aged over 40 years, and those with familial hypercholesterolaemia. The risk also increases with age; those over 75 years are at particularly high risk, especially if they smoke or have hypertension.

Preventative measures are also required for other individuals who may be at high risk of developing atherosclerotic cardiovascular disease; those with a 10-year risk of cardiovascular disease[1] of 20% or more stand to benefit most from drug treatment. The risk is assessed on the basis of lipid concentration as well as smoking status, blood pressure, gender, and age; other risk factors, such as premature menopause, ethnicity, obesity, triglyceride concentration, chronic kidney disease, impaired glucose tolerance, and a family history of premature cardiovascular disease, should also be taken into account when assessing risk in individual patients.

Patients with hypothyroidism should receive adequate thyroid replacement therapy before assessing the requirement for lipid-regulating treatment because correcting hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

Lowering the concentration of low-density lipoprotein (LDL) cholesterol and raising high-density lipoprotein (HDL) cholesterol slows the progression of atherosclerosis and may even induce regression. All patients at high risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation. Lipid-regulating drug treatment must be combined with advice on diet and lifestyle measures, lowering of raised blood pressure (section 2.5), the use of low-dose aspirin (section 2.9), and management of diabetes (section 6.1).

A **statin** (see p. 162) reduces the risk of cardiovascular disease events, irrespective of serum cholesterol concentration, and is the drug of first choice for primary and secondary prevention of cardiovascular disease. If statins are contra-indicated or not tolerated, a **fibrate** (p. 166) or a **bile acid sequestrant** (p. 164) may be considered for *primary* or *secondary* prevention; **nicotinic acid** (p. 168) is also an option for *secondary* prevention. Fibrates, bile acid sequestrants, or nicotinic acid should not be used in combination with a statin for *primary* prevention of cardiovascular disease. In secondary prevention of cardiovascular events, if a total cholesterol concentration of less than 4 mmol/litre *or* a LDL-cholesterol concentration of less than 2 mmol/litre is not achieved with initial treatment, consider treating patients with a 'high-intensity' statin (e.g. simvastatin or atorvastatin)—a 'high-intensity' statin is one that produces a greater LDL-cholesterol reduction than simvastatin 40 mg; see also risk of Muscle Effects, p. 162. Patients with an acute coronary syndrome should also receive treatment with a 'high-intensity' statin where appropriate.

A statin is also the drug of first choice for treating hypercholesterolaemia and moderate hypertriglyceridaemia. Severe hyperlipidaemia not adequately controlled with a maximal dose of a statin may require the use of an additional lipid-regulating drug such as **ezetimibe** or **colestyramine**; such treatment should generally be supervised by a specialist.

A number of conditions, some familial, are characterised by very high LDL-cholesterol concentration, high triglyceride concentration, or both. **Fenofibrate** may be added to statin therapy if triglycerides remain high even after the LDL-cholesterol concentration has been reduced adequately; **nicotinic acid** may also be used to further lower triglyceride or LDL-cholesterol concentration.

Combination of a statin with a fibrate or with nicotinic acid carries an increased risk of side-effects (including rhabdomyolysis—see Muscle Effects below) and should be used under specialist supervision; monitoring of liver function and creatine kinase should also be considered. The concomitant administration of gemfibrozil with a statin increases the risk of rhabdomyolysis considerably—this combination should **not** be used.

A statin is recommended for all patients with familial hypercholesterolaemia. A 'high-intensity' statin (e.g. rosuvastatin (initiated by a specialist), simvastatin, or atorvastatin) should be considered in order to achieve the recommended reduction in LDL-cholesterol concentration of greater than 50% from baseline; a 'high-intensity' statin is one that produces a greater LDL-cholesterol reduction than simvastatin 40 mg—see also

1. Cardiovascular disease risk may be determined from the chart issued by the Joint British Societies (*Heart* 2005; **91** (Suppl V): v1–v52)—see inside back cover. The Joint British Societies' 'Cardiac Risk Assessor' computer programme may also be used to determine cardiovascular disease risk.

risk of Muscle Effects, below. Patients with heterozygous familial hypercholesterolaemia who have contra-indications to, or are intolerant of, statins should receive ezetimibe. The combination of a statin and ezetimibe can be considered if a statin alone fails to provide adequate control (or if intolerance limits dose titration), and when a switch to an alternative statin is being considered. Patients for whom statins and ezetimibe are inappropriate, should be referred to a specialist for the consideration of treatment with a bile acid sequestrant, nicotinic acid, or a fibrate.

The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken in a specialist centre.

Statins

The statins (**atorvastatin**, **fluvastatin**, **pravastatin**, **rosuvastatin**, and **simvastatin**) competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration.

Statins should be considered for all patients, including the elderly, with symptomatic cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non-haemorrhagic stroke, or transient ischaemic attacks).

In patients with diabetes mellitus, the risk of developing cardiovascular disease depends on the duration and complications of diabetes, age, and concomitant risk factors. Statin therapy should be considered for *all* patients over 40 years with diabetes mellitus (type 1 and 2). In younger patients with diabetes, treatment with a statin should be considered if there is target-organ damage, poor glycaemic control (HbA_{1c} greater than 9%), low HDL-cholesterol and raised triglyceride concentration, hypertension, or a family history of premature cardiovascular disease.

Statins are also used for the prevention of cardiovascular disease events in asymptomatic individuals who are at increased risk (see p. 161). Statin treatment should also be considered if the total cholesterol concentration to HDL-cholesterol ratio exceeds 6.

Cautions Hypothyroidism should be managed adequately before starting treatment with a statin (see p. 161). Statins should be used with caution in those with a history of liver disease or with a high alcohol intake—see also Hepatic impairment, below. There is little information available on a rational approach to liver-function monitoring; however, a NICE guideline[1] suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity. Those with serum transaminases that are raised, but less than 3 times the upper limit of the reference range, should **not** be routinely excluded from statin therapy. Those with serum transaminases of more than 3 times the upper limit of the reference range should discontinue statin therapy. Statins should be used with caution in those with risk factors for myopathy or rhabdomyolysis; patients should be advised to report unexplained muscle pain (see Muscle Effects below). Statins should be avoided in acute porphyria (section 9.8.2) but rosuvastatin is thought to be safe. **Interactions:** Appendix 1 (statins).

Hepatic impairment Statins should be used with caution in those with a history of liver disease and avoided in active liver disease or when there are unexplained persistent elevations in serum transaminases.

Pregnancy Statins should be avoided in pregnancy as congenital anomalies have been reported and the decreased synthesis of cholesterol possibly affects fetal development. Adequate contraception is required during treatment and for 1 month afterwards.

Breast-feeding The manufacturers of atorvastatin, fluvastatin, rosuvastatin, and simvastatin advise avoiding use in mothers who are breast-feeding as there is no information available. The manufacturers of pravastatin advise against use in breast-feeding mothers as a small amount of drug is present in breast milk.

Side-effects The statins can cause various muscular side-effects, including myositis, which can lead to rhabdomyolysis. Muscular effects are rare but often significant (see Muscle Effects below). Statins can cause gastro-intestinal disturbances, and very rarely pancreatitis. They can also cause altered liver function tests, and rarely hepatitis and jaundice; hepatic failure has been reported very rarely. Other side-effects include sleep disturbance, headache, dizziness, depression, paraesthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance, alopecia, and hypersensitivity reactions (including rash, pruritus, urticaria, and very rarely lupus erythematosus-like reactions). In very rare cases, statins can cause interstitial lung disease; if patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.

Muscle effects Myalgia, myositis, myopathy and rarely rhabdomyolysis have been reported with the statins; if myopathy is suspected and creatine kinase is markedly elevated (more than 5 times upper limit of normal), or muscular symptoms are severe, treatment should be discontinued; in patients at increased risk of muscle effects, a statin should not be started if creatine kinase is elevated. Patients at increased risk of myopathy include those with a personal or family history of muscular disorders, previous history of muscular toxicity, those with a high alcohol intake, renal impairment, hypothyroidism, women, and the elderly. There is also an increased incidence of myopathy if a statin is given at a high dose or given with a fibrate, with lipid-lowering doses of nicotinic acid, or with drugs that increase the plasma-statin concentration, such as ciclosporin; close monitoring of liver function and, if symptomatic, of creatine kinase is required in patients receiving these drugs. Rhabdomyolysis with acute renal impairment secondary to myoglobinuria has also been reported.

Counselling Advise patient to report promptly unexplained muscle pain, tenderness, or weakness.

1. NICE clinical guideline 67 (May 2008). Lipid Modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

ATORVASTATIN

Indications primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of cardiovascular events in patients with type 2 diabetes and at least one additional risk factor for cardiovascular disease

Cautions see notes above; also haemorrhagic stroke

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also chest pain; back pain; *less commonly* anorexia, malaise, weight gain, hypoglycaemia, hyperglycaemia, tinnitus; *rarely* cholestatic jaundice, peripheral oedema; *very rarely* taste disturbances, gynaecomastia, hearing loss, Stevens-Johnson Syndrome, and toxic epidermal necrolysis

Dose

- Primary hypercholesterolaemia and combined hyperlipidaemia, usually 10 mg once daily; if necessary, may be increased at intervals of at least 4 weeks to max. 80 mg once daily; CHILD 10–17 years usually 10 mg once daily (limited experience with doses above 20 mg daily)
- Familial hypercholesterolaemia, initially 10 mg daily, increased at intervals of at least 4 weeks to 40 mg once daily; if necessary, further increased to max. 80 mg once daily (or 40 mg once daily combined with anion-exchange resin in heterozygous familial hypercholesterolaemia); CHILD 10–17 years initially 10 mg daily, increased if necessary after at least 4 weeks to 20 mg once daily (limited experience with higher doses)
- Prevention of cardiovascular events in type 2 diabetes, 10 mg once daily

Note Max. 10 mg daily with concomitant ciclosporin; max. 20 mg daily (or temporarily discontinue atorvastatin) with concomitant clarithromycin; max. 40 mg daily (or temporarily discontinue atorvastatin) with concomitant itraconazole

Lipitor® (Pfizer) PoM

Tablets, all f/c, atorvastatin (as calcium trihydrate) 10 mg, net price 28-tab pack = £13.00; 20 mg, 28-tab pack = £24.64; 40 mg 28-tab pack = £24.64; 80 mg, 28-tab pack = £28.21. Counselling, muscle effects, see notes above

FLUVASTATIN

Note The *Scottish Medicines Consortium* (p. 4) has advised (February 2004) that fluvastatin is accepted for restricted use for the secondary prevention of coronary events after percutaneous coronary angioplasty; if the patient has previously been receiving another statin, then there is no need to change the statin

Indications adjunct to diet in primary hypercholesterolaemia or combined (mixed) hyperlipidaemia (types IIa and IIb); adjunct to diet to slow progression of coronary atherosclerosis in primary hypercholesterolaemia and concomitant coronary heart disease; prevention of coronary events after percutaneous coronary intervention

Cautions see notes above

Hepatic impairment see notes above

Renal impairment manufacturer advises doses above 40 mg daily should be initiated with caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *very rarely* vasculitis

Dose

- Hypercholesterolaemia or combined hyperlipidaemia, initially 20–40 mg daily in the evening, adjusted at intervals of at least 4 weeks; up to 80 mg daily may be required; CHILD under 18 years, see *BNF for Children*
- Prevention of progression of coronary atherosclerosis, 40 mg daily in the evening
- Following percutaneous coronary intervention, 80 mg daily

Fluvastatin (Non-proprietary) PoM

Capsules, fluvastatin (as sodium salt) 20 mg, net price 28-cap pack = £5.03; 40 mg, 28-cap pack = £5.36. Counselling, muscle effects, see notes above

Lescol® (Novartis) PoM

Capsules, fluvastatin (as sodium salt) 20 mg (brown/yellow), net price 28-cap pack = £15.26; 40 mg (brown/orange), 28-cap pack = £15.26, 56-cap pack = £30.53. Counselling, muscle effects, see notes above

Modified release

Lescol® XL (Novartis) PoM

Tablets, m/r, yellow, fluvastatin (as sodium salt) 80 mg, net price 28-tab pack = £19.20. Label: 25, counselling, muscle effects, see notes above

Dose 80 mg once daily (dose form not appropriate for initial dose titration in hypercholesterolaemia or combined hyperlipidaemia)

PRAVASTATIN SODIUM

Indications adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control; adjunct to diet to prevent cardiovascular events in patients with hypercholesterolaemia; prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina; reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation

Cautions see notes above

Hepatic impairment see notes above

Renal impairment manufacturer advises initial dose of 10 mg once daily in moderate to severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; *less commonly* abnormal urination (including dysuria, nocturia and frequency); *very rarely* fulminant hepatic necrosis

Dose

- Hypercholesterolaemia or combined hyperlipidaemias, 10–40 mg once daily at night, adjusted at intervals of at least 4 weeks
- Familial hypercholesterolaemia, CHILD 8–14 years 10–20 mg once daily at night, 14–18 years 10–40 mg once daily at night
- Prevention of cardiovascular events, 40 mg once daily at night
- Post-transplantation hyperlipidaemia, initially 20 mg once daily at night, increased if necessary (under close medical supervision) to max. 40 mg once daily at night

Pravastatin (Non-proprietary) PoM

Tablets, pravastatin sodium 10 mg, net price 28-tab pack = £1.72; 20 mg, 28-tab pack = £2.02; 40 mg, 28-tab pack = £2.78. Counselling, muscle effects, see notes above

Lipostat® (Squibb) PoM

Tablets, all yellow, pravastatin sodium 10 mg, net price 28-tab pack = £14.18; 20 mg, 28-tab pack = £26.01; 40 mg, 28-tab pack = £26.01. Counselling, muscle effects, see notes above

ROSUVASTATIN

Indications primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of cardiovascular events in patients at high risk of a first cardiovascular event

Cautions see notes above; patients of Asian origin (see under Dose); max. dose 20 mg in patients with risk factors for myopathy or rhabdomyolysis (including personal or family history of muscular disorders or toxicity)

Hepatic impairment see notes above

Renal impairment initially 5 mg once daily (do not exceed 20 mg daily) if eGFR 30–60 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also diabetes mellitus; proteinuria; *very rarely* haematuria

Dose

- Hypercholesterolaemia, initially 5–10 mg once daily increased if necessary at intervals of at least 4 weeks to 20 mg once daily, increased after further 4 weeks to 40 mg daily only in severe hypercholesterolaemia with high cardiovascular risk and under specialist supervision; ELDERLY initially 5 mg once daily; patient of ASIAN origin, initially 5 mg once daily increased if necessary to max. 20 mg daily
  Note Initially 5 mg once daily with concomitant fibrate increased if necessary to max. 20 mg daily
- Prevention of cardiovascular events, 20 mg once daily

Crestor® (AstraZeneca) ▼ PoM

Tablets, f/c, rosuvastatin (as calcium salt) 5 mg (yellow), net price 28-tab pack = £18.03; 10 mg (pink), 28-tab pack = £18.03; 20 mg (pink), 28-tab pack = £26.02; 40 mg (pink), 28-tab pack = £29.69. Counselling, muscle effects, see notes above

SIMVASTATIN

Indications primary hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus

Cautions see notes above; also 80-mg dose only for those with severe hypercholesterolaemia and at high risk of cardiovascular complications

Hepatic impairment see notes above

Renal impairment doses above 10 mg daily should be used with caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also *rarely* anaemia

Dose

- Primary hypercholesterolaemia, combined hyperlipidaemia, 10–20 mg daily at night, adjusted at intervals of at least 4 weeks; usual range 10–80 mg once daily at night
- Homozygous familial hypercholesterolaemia, 40 mg daily at night *or* 80 mg daily in 3 divided doses (with largest dose at night)
- Prevention of cardiovascular events, initially 20–40 mg once daily at night, adjusted at intervals of at least 4 weeks; max. 80 mg once daily at night

Note Max. 10 mg daily with concomitant ciclosporin, danazol, or fibrate (except fenofibrate). Max. 20 mg daily with concomitant amiodarone or verapamil. Max. 40 mg daily with diltiazem or amlodipine

[1] **Simvastatin** (Non-proprietary) ▼ PoM

Tablets, simvastatin 10 mg, net price 28-tab pack = 90p, 20 mg, 28-tab pack = £1.01; 40 mg, 28-tab pack = £1.32; 80 mg, 28-tab pack = £2.29. Counselling, muscle effects, see notes above
Brands include *Simvador®*

Oral suspension, simvastatin 20 mg/5 mL, net price 150 mL = £99.50, 40 mg/5 mL, 150 mL = £152.00. Counselling, muscle effects, see notes above
Excipients may include propylene glycol

[1] **Zocor®** (MSD) ▼ PoM

Tablets, all f/c, simvastatin 10 mg (peach), net price 28-tab pack = £18.03; 20 mg (tan), 28-tab pack = £29.69; 40 mg (red), 28-tab pack = £29.69; 80 mg (red), 28-tab pack = £29.69. Counselling, muscle effects, see notes above

With ezetimibe

Note For homozygous familial hypercholesterolaemia, primary hypercholesterolaemia, and mixed hyperlipidaemia in patients stabilised on the individual components in the same proportions, or for patients not adequately controlled by statin alone. For prescribing information on ezetimibe, see Ezetimibe

Inegy® (MSD, Schering-Plough) PoM

Tablets, simvastatin 20 mg, ezetimibe 10 mg, net price 28-tab pack = £33.42; simvastatin 40 mg, ezetimibe 10 mg, 28-tab pack = £38.98; simvastatin 80 mg, ezetimibe 10 mg, 28-tab pack = £41.21. Counselling, muscle effects, see notes above

Bile acid sequestrants

Colesevelam, **colestipol**, and **colestyramine** are bile acid sequestrants used in the management of hypercholesterolaemia. They act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma. Bile

1. Simvastatin 10 mg tablets can be sold to the public to reduce risk of first coronary event in individuals at moderate risk of coronary heart disease (approx. 10–15% risk of major event in 10 years), max. daily dose 10 mg and pack size of 28 tablets; treatment should form part of a programme to reduce risk of coronary heart disease

acid sequestrants effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia.

Cautions Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged. **Interactions:** Appendix 1 (bile acid sequestrants)

Pregnancy and breast-feeding Bile acid sequestrants should be used with caution as although the drugs are not absorbed, they may cause fat-soluble vitamin deficiency on prolonged use.

Side-effects As bile acid sequestrants are not absorbed, gastro-intestinal side-effects predominate. Constipation is common, but diarrhoea has occurred, as have nausea, vomiting, and gastro-intestinal discomfort. Hypertriglyceridaemia may be aggravated. An increased bleeding tendency has been reported due to hypoprothrombinaemia associated with vitamin K deficiency.

Counselling Other drugs should be taken at least 1 hour before (4 hours before colesevelam), or 4–6 hours after bile acid sequestrants to reduce possible interference with absorption. Colesevelam can be taken at the same time as a statin or ezetimibe.

COLESEVELAM HYDROCHLORIDE

Indications primary hypercholesterolaemia as an adjunct to dietary measures, either alone or with a statin; primary and familial hypercholesterolaemia, in combination with ezetimibe, either with or without a statin

Cautions see notes above; also gastro-intestinal motility disorders, major gastro-intestinal surgery, inflammatory bowel disease; patients receiving ciclosporin should have their blood-ciclosporin concentration monitored before, during, and after treatment with colesevelam; **interactions:** Appendix 1 (colesevelam)

Contra-indications bowel or biliary obstruction

Hepatic impairment manufacturer advises caution

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also headache; myalgia

Dose

- Monotherapy, 3.75 g daily in 1–2 divided doses; max. 4.375 g daily
- Combination therapy with a statin, or ezetimibe, or both, 2.5–3.75 g daily in 1–2 divided doses

Cholestagel® (Genzyme) ▼ PoM
Tablets, f/c, colesevelam hydrochloride 625 mg, net price 180-cap pack = £87.36. Label: 21, counselling, avoid other drugs at same time (see notes above)

COLESTYRAMINE
(Cholestyramine)

Indications hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures; primary prevention of coronary heart disease in men aged 35–59 years with primary hypercholesterolaemia who have not responded to diet and other appropriate measures; pruritus associated with partial biliary obstruction and primary biliary cirrhosis (section 1.9.2); diarrhoeal disorders (section 1.9.2)

Cautions see notes above; **interactions**: Appendix 1 (colestyramine)

Contra-indications complete biliary obstruction (not likely to be effective)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; intestinal obstruction reported rarely and hyperchloraemic acidosis reported on prolonged use

Dose

- Lipid reduction, initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in 1–4 divided doses, then adjusted as required; max. 36 g daily
- Pruritus, see section 1.9.2
- Diarrhoeal disorders, see section 1.9.2
- CHILD 6–12 years, see *BNF for Children*

Note The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content

Colestyramine (Non-proprietary) PoM
Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £18.34. Label: 13, counselling, avoid other drugs at same time (see notes above)
Excipients may include aspartame (see section 9.4.1)

Questran® (Bristol-Myers Squibb) PoM
Powder, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £10.76. Label: 13, counselling, avoid other drugs at same time (see notes above)
Excipients include sucrose 3.79 g/sachet

Questran Light® (Bristol-Myers Squibb) PoM
Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £16.15. Label: 13, counselling, avoid other drugs at same time (see notes above)
Excipients include aspartame (see section 9.4.1)

COLESTIPOL HYDROCHLORIDE

Indications hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures

Cautions see notes above; **interactions:** Appendix 1 (colestipol)

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- Initially 5 g 1–2 times daily in liquid increased if necessary in 5-g increments at intervals of 1 month to max. 30 g daily (in 1–2 divided doses)

Note The contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, yoghurt, and pulpy fruits with a high moisture content

Colestid® (Pharmacia) PoM
Granules, yellow, colestipol hydrochloride 5 g/sachet, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)
Colestid Orange, granules, yellow/orange, colestipol hydrochloride 5 g/sachet, with aspartame, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol. It is licensed as an adjunct to dietary manipulation in patients with primary hypercholesterolaemia in combination with a statin or alone (if a statin is inappropriate), in patients with homozygous familial hypercholesterolaemia in combination with a statin, and in patients with homozygous familial sitosterolaemia (phytosterolaemia). If ezetimibe is used in combination with a statin, there is an increased risk of rhabdomyolysis (see also Muscle Effects, p. 162)

NICE guidance
Ezetimibe for the treatment of primary hypercholesterolaemia (November 2007)
Ezetimibe, used in accordance with the licensed indications for *Ezetrol®*, is an option for the treatment of adults with primary hypercholesterolaemia.

EZETIMIBE

Indications adjunct to dietary measures and statin treatment in primary hypercholesterolaemia and homozygous familial hypercholesterolaemia (ezetimibe alone in primary hypercholesterolaemia if statin inappropriate or not tolerated); adjunct to dietary measures in homozygous sitosterolaemia

Cautions **interactions:** Appendix 1 (ezetimibe)

Hepatic impairment avoid in moderate and severe impairment—may accumulate

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances; headache, fatigue; myalgia; *rarely* arthralgia, hypersensitivity reactions (including rash, angioedema, and anaphylaxis), hepatitis; *very rarely* pancreatitis, cholelithiasis, cholecystitis, thrombocytopenia, raised creatine kinase, myopathy, and rhabdomyolysis

Dose

- ADULT and CHILD over 10 years, 10 mg once daily

Ezetrol® (MSD, Schering-Plough) PoM
Tablets, ezetimibe 10 mg, net price 28-tab pack = £26.31

With simvastatin

See under Simvastatin

Fibrates

Bezafibrate, **ciprofibrate**, **fenofibrate**, and **gemfibrozil** act mainly by decreasing serum triglycerides; they have variable effects on LDL-cholesterol. Although a fibrate can reduce the risk of coronary heart disease events in those with low HDL-cholesterol or with raised triglycerides, a statin should be used first. Fibrates are first-line therapy only in those whose serum-triglyceride concentration is greater than 10 mmol/litre or in those who cannot tolerate a statin. In type 2 diabetes a fibrate can be added to a statin for those with a serum-triglyceride concentration exceeding 2.3 mmol/litre, despite 6 months of treatment with a statin and optimal glycaemic control.

Fibrates can cause a myositis-like syndrome, especially if renal function is impaired. Also, combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution (see Muscle Effects, p. 162) and monitoring of liver function and creatine kinase should be considered; gemfibrozil and statins should **not** be used concomitantly.

BEZAFIBRATE

Indications hyperlipidaemias of types IIa, IIb, III, IV, and V in patients who have not responded adequately to diet and other appropriate measures; also see notes above

Cautions correct hypothyroidism before initiating treatment (see p. 161); **interactions:** Appendix 1 (fibrates)

Contra-indications hypoalbuminaemia, primary biliary cirrhosis, gall bladder disease, nephrotic syndrome

Hepatic impairment avoid in severe liver disease

Renal impairment reduce dose to 400 mg daily if eGFR 40–60 mL/minute/1.73 m^2; reduce dose to 200 mg every 1–2 days if eGFR 15–40 mL/minute/1.73 m^2; avoid if eGFR less than 15 mL/minute/1.73 m^2; avoid modified-release preparations if eGFR less than 60 mL/minute/1.73 m^2

Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly

Pregnancy manufacturers advise avoid—embryotoxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances, anorexia; *less commonly* cholestasis, weight gain, dizziness, headache, fatigue, drowsiness, renal impairment, raised serum creatinine (unrelated to renal impairment), erectile dysfunction, myotoxicity (with myasthenia or myalgia)—special risk in renal impairment (see Cautions), urticaria, pruritus, photosensitivity reactions; *very rarely* gallstones, hypoglycaemia, anaemia, leucopenia, thrombocytopenia, increased platelet count, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

- See preparations below

Bezafibrate (Non-proprietary) PoM
Tablets, bezafibrate 200 mg, net price 100-tab pack = £6.86 Label: 21
Dose 200 mg 3 times daily; CHILD over 10 years, see *BNF for Children*

Bezalip® (Actavis) PoM
Tablets, f/c, bezafibrate 200 mg, net price 100-tab pack = £8.63. Label: 21
Dose 200 mg 3 times daily; CHILD over 10 years, see *BNF for Children*

Modified release

Bezafibrate (Non-proprietary) PoM
Tablets, m/r, bezafibrate 400 mg, net price 28-tab pack = £3.25. Label: 21, 25
Dose 400 mg once daily (dose form not appropriate in patients with renal impairment)
Brands include *Fibrazate® XL*, *Zimbacol® XL*

Bezalip® Mono (Actavis) PoM

Tablets, m/r, f/c, bezafibrate 400 mg, net price 30-tab pack = £7.63. Label: 21, 25

Dose 400 mg once daily (dose form not appropriate in patients with renal impairment)

CIPROFIBRATE

Indications hyperlipidaemias of types IIa, IIb, III, and IV in patients who have not responded adequately to diet; also see notes above

Cautions see under Bezafibrate

Contra-indications see under Bezafibrate

Hepatic impairment avoid in severe liver disease

Renal impairment manufacturer advises reduce dose to 100 mg on alternate days in moderate impairment; avoid in severe impairment; see also Myotoxicity under Bezafibrate

Pregnancy manufacturers advise avoid—embryotoxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects see under Bezafibrate

Dose

- 100 mg daily

Ciprofibrate (Non-proprietary) PoM

Tablets, ciprofibrate 100 mg, net price 28-tab pack = £28.00

FENOFIBRATE

Indications hyperlipidaemias of types IIa, IIb, III, IV, and V in patients who have not responded adequately to diet and other appropriate measures; also see notes above

Cautions see under Bezafibrate; liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised)

Contra-indications gall bladder disease; pancreatitis (unless due to severe hypertriglyceridemia); photosensitivity to ketoprofen

Hepatic impairment avoid in severe liver disease

Renal impairment reduce dose to 134 mg daily if eGFR less than 60 mL/minute/1.73 m^2; reduce dose to 67 mg daily if eGFR less than 20 mL/minute/1.73 m^2; avoid if eGFR less than 15 mL/minute/1.73 m^2; see also Myotoxicity under Bezafibrate

Pregnancy manufacturers advise avoid—embryotoxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Bezafibrate; also *very rarely* hepatitis, pancreatitis, and interstitial pneumopathies

Dose

- See preparations below

Fenofibrate (Non-proprietary) PoM

Capsules, fenofibrate (micronised) 200 mg, net price 28-cap pack = £3.53. Label: 21

Dose 1 capsule daily (dose form not appropriate for children or in renal impairment)

Capsules, fenofibrate (micronised) 267 mg, net price 28-cap pack = £11.69. Label: 21

Dose severe hyperlipidaemia, 1 capsule daily (dose form not appropriate for children or in renal impairment)

Lipantil® (Solvay) PoM

Lipantil® Micro 67 capsules, yellow, fenofibrate (micronised) 67 mg, net price 90-cap pack = £23.30. Label: 21

Dose initially 3 capsules daily in divided doses; usual range 2–4 capsules daily; CHILD 4–15 years 1 capsule/20 kg daily

Lipantil® Micro 200 capsules, orange, fenofibrate (micronised) 200 mg, net price 28-cap pack = £17.95. Label: 21

Dose initially 1 capsule daily (dose form not appropriate for children or in renal impairment)

Lipantil® Micro 267 capsules, orange/cream, fenofibrate (micronised) 267 mg, net price 28-cap pack = £21.75. Label: 21

Dose severe hyperlipidaemia, 1 capsule daily (dose form not appropriate for children or in renal impairment)

Supralip® 160 (Abbott) PoM

Tablets, f/c, fenofibrate (micronised) 160 mg, net price 28-tab pack = £6.69. Label: 21

Dose 160 mg daily (dose form not appropriate for children or in renal impairment)

GEMFIBROZIL

Indications hyperlipidaemias of types IIa, IIb, III, IV and V in patients who have not responded adequately to diet and other appropriate measures; primary prevention of cardiovascular disease in men with hyperlipidaemias that have not responded to diet and other appropriate measures; also see notes above

Cautions lipid profile, blood counts, and liver-function tests before initiating long-term treatment; preferably avoid use with statins (high risk of rhabdomyolysis); correct hypothyroidism before initiating treatment (see p. 161); elderly; **interactions:** Appendix 1 (fibrates)

Contra-indications alcoholism, biliary-tract disease including gallstones; photosensitivity to fibrates

Hepatic impairment avoid in liver disease

Renal impairment initially 900 mg daily if eGFR 30–80 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2; see also Myotoxicity under Bezafibrate

Pregnancy manufacturers advise avoid—embryotoxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances; headache, fatigue, vertigo; eczema, rash; *less commonly* atrial fibrillation; *rarely* pancreatitis, appendicitis, disturbances in liver function including hepatitis and cholestatic jaundice, dizziness, paraesthesia, sexual dysfunction, thrombocytopenia, anaemia, leucopenia, eosinophilia, bone-marrow suppression, myalgia, myopathy, myasthenia, myositis accompanied by increase in creatine kinase (discontinue if raised significantly), blurred vision, exfoliative dermatitis, alopecia, and photosensitivity)

Dose

- 1.2 g daily, usually in 2 divided doses; range 0.9–1.2 g daily; CHILD not recommended

Gemfibrozil (Non-proprietary) PoM

Capsules, gemfibrozil 300 mg, net price 112-cap pack = £35.57. Label: 22

Tablets, gemfibrozil 600 mg, net price 30-tab pack = £13.88, 56-tab pack = £31.43. Label: 22

Lopid® (Pfizer) PoM

'300' capsules, white/maroon, gemfibrozil 300 mg, net price 112-cap pack = £35.57. Label: 22

'600' tablets, f/c, gemfibrozil 600 mg, net price 56-tab pack = £35.57. Label: 22

Nicotinic acid group

The value of **nicotinic acid** is limited by its side-effects, especially vasodilatation. In doses of 1.5 to 3 g daily it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis; it also increases HDL-cholesterol. Nicotinic acid is licensed for use with a statin if the statin alone cannot adequately control dyslipidaemia (raised LDL-cholesterol, triglyceridaemia, and low HDL-cholesterol); it can be used alone if the patient is intolerant of statins (for advice on treatment of dyslipidaemia, including use of combination treatment, see p. 161).

A preparation combining laropiprant with nicotinic acid (*Tredaptive®*) is available; laropiprant has no lipid-regulating effect, but reduces the symptoms of flushing associated with nicotinic acid.

Acipimox seems to have fewer side-effects than nicotinic acid but may be less effective in its lipid-regulating capabilities.

ACIPIMOX

Indications hyperlipidaemias of types IIb and IV in patients who have not responded adequately to diet and other appropriate measures

Contra-indications peptic ulcer

Renal impairment reduce dose if eGFR 30–60 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid

Breast-feeding manufacturer advises avoid

Side-effects vasodilatation, flushing, itching, rashes, urticaria, erythema; heartburn, epigastric pain, nausea, diarrhoea, headache, malaise, dry eyes; rarely angioedema, bronchospasm, anaphylaxis

Dose

- Usually 500–750 mg daily in divided doses

Olbetam® (Pharmacia) PoM

Capsules, brown/pink, acipimox 250 mg, net price 90-cap pack = £46.33. Label: 21

NICOTINIC ACID

Indications adjunct to statin in dyslipidaemia or used alone if statin not tolerated (see also p. 161)

Cautions unstable angina, acute myocardial infarction, diabetes mellitus, gout, history of peptic ulceration; **interactions:** Appendix 1 (nicotinic acid)

Contra-indications arterial bleeding; active peptic ulcer disease

Hepatic impairment manufacturer advises monitor liver function in mild to moderate impairment and avoid in severe impairment; discontinue if severe abnormalities in liver function tests

Renal impairment manufacturer advises use with caution—no information available

Pregnancy no information available—manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding present in milk—avoid

Side-effects diarrhoea, nausea, vomiting, abdominal pain, dyspepsia; flushing; pruritus, rash; *less commonly* tachycardia, palpitation, shortness of breath, peripheral oedema, headache, dizziness, increase in uric acid, hypophosphataemia, prolonged prothrombin time, and reduced platelet count; *rarely* hypotension, syncope, rhinitis, insomnia, reduced glucose tolerance, myalgia, myopathy, myasthenia; *very rarely* anorexia, rhabdomyolysis, visual disturbance, and jaundice also reported

Note Prostaglandin-mediated symptoms (such as flushing) can be reduced by low initial doses taken with meals or, if patient taking aspirin, aspirin dose should be taken 30 minutes before nicotinic acid

Dose

- See under preparation

Modified release

Niaspan® (Abbott) PoM

Tablets, m/r, nicotinic acid 500 mg, net price 56-tab pack = £18.98; 750 mg, 56-tab pack = £28.88; 1 g, 56-tab pack = £38.23; 21-day starter pack of 7 × 375-mg tab with 7 × 500-mg tab and 7 × 750-mg tab = £15.40. Label: 21, 25

Dose 375 mg once daily at night (after a low-fat snack) for 1 week, then 500 mg once daily at night for 1 week, then 750 mg once daily at night for 1 week, then 1 g once daily at night for 4 weeks, increased if necessary in steps of 500 mg at intervals of at least 4 weeks to max. 2 g daily; usual maintenance dose 1–2 g once daily at night

With laropiprant

Tredaptive® (MSD) ▼ PoM

Tablets, m/r, nicotinic acid 1 g, laropiprant 20 mg, net price 28-tab pack = £16.73; 56-tab pack = £33.46. Label: 21, 25

Dose 1 tablet once daily at night, increased after 4 weeks to 2 tablets once daily at night

Omega-3 fatty acid compounds

The omega-3 fatty acid compounds comprise omega-3-acid ethyl esters (*Omacor®*) and omega-3-marine triglycerides (*Maxepa®*). Omega-3 fatty acid compounds may be used to reduce triglycerides, as an alternative to a fibrate and in addition to a statin, in patients with combined (mixed) hyperlipidaemia not adequately controlled with a statin alone. A triglyceride concentration exceeding 10 mmol/litre is associated with acute pancreatitis and lowering the concentration reduces this risk. The fat content of omega-3 fatty acid compounds (including excipients in the preparations) should be taken into consideration when treating hypertriglyceridaemia. There is little clinical trial evidence that the triglyceride lowering effect decreases the risk of cardiovascular disease.

The *Scottish Medicines Consortium* (p. 4) has advised (November 2002) that omega-3-acid ethyl esters (*Omacor®*) is **not** recommended for use within NHS Scotland for the treatment of hypertriglyceridaemia.

OMEGA-3-ACID ETHYL ESTERS

Indications adjunct to diet and statin in type IIb or III hypertriglyceridaemia; adjunct to diet in type IV hypertriglyceridaemia; adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months

Cautions haemorrhagic disorders, anticoagulant treatment (bleeding time increased)

Hepatic impairment monitor liver function

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances; *less commonly* taste disturbances, dizziness, and hypersensitivity reactions; *rarely* hepatic disorders, headache, hyperglycaemia, acne, and rash; *very rarely* hypotension, nasal dryness, urticaria, and increased white cell count

Dose

- See under preparation below

Omacor® (Abbott Healthcare)

Capsules, 1 g of omega-3-acid ethyl esters 90 containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg, net price 28-cap pack = £14.24, 100-cap pack = £50.84. Label: 21

Dose hypertriglyceridaemia, initially 2 capsules daily with food, increased if necessary to 4 capsules daily

Secondary prevention after myocardial infarction, 1 capsule daily with food

OMEGA-3-MARINE TRIGLYCERIDES

Indications adjunct in the reduction of plasma triglycerides in severe hypertriglyceridaemia

Cautions haemorrhagic disorders, anticoagulant treatment; aspirin-sensitive asthma; type 2 diabetes

Side-effects occasional nausea and belching

Dose

- See under preparations below

Maxepa® (Seven Seas)

Capsules, 1 g (approx. 1.1 mL) concentrated fish oils containing eicosapentaenoic acid 170 mg, docosahexaenoic acid 115 mg. Vitamin A content less than 100 units/g, vitamin D content less than 10 units/g, net price 200-cap pack = £29.28. Label: 21

Dose 5 capsules twice daily with food

Liquid, golden-coloured, concentrated fish oils containing eicosapentaenoic acid 170 mg, docosahexaenoic acid 115 mg/g (1.1 mL). Vitamin A content less than 100 units/g, vitamin D content less than 10 units/g, net price 150 mL = £21.59. Label: 21

Dose 5 mL twice daily with food

2.13 Local sclerosants

Ethanolamine oleate and sodium tetradecyl sulphate are used in sclerotherapy of varicose veins, and phenol is used in haemorrhoids (section 1.7.3).

ETHANOLAMINE OLEATE
(Monoethanolamine Oleate)

Indications sclerotherapy of varicose veins

Cautions extravasation may cause necrosis of tissues

Contra-indications inability to walk, acute phlebitis, oral contraceptive use, obese legs

Side-effects allergic reactions (including anaphylaxis)

Ethanolamine Oleate (UCB Pharma) PoM

Injection, ethanolamine oleate 5%, net price 2-mL amp = £3.19, 5-mL amp = £5.98

Dose by slow injection into empty isolated segment of vein, 2–5 mL divided between 3–4 sites; repeated at weekly intervals

SODIUM TETRADECYL SULPHATE

Indications sclerotherapy of varicose veins

Cautions see under Ethanolamine Oleate

Contra-indications see under Ethanolamine Oleate

Side-effects see under Ethanolamine Oleate

Fibro-Vein® (STD Pharmaceutical) PoM

Injection, sodium tetradecyl sulphate 0.2%, net price 5-mL amp = £5.51; 0.5%, 2-mL amp = £2.87; 1%, 2-mL amp = £3.31; 3%, 2-mL amp = £4.07, 5-mL vial = £10.25

Dose by slow injection into empty isolated segment of vein, 0.1–1 mL according to site and condition being treated (consult product literature)

3 Respiratory system

3.1 Bronchodilators 170
3.1.1 Adrenoceptor agonists 175
3.1.1.1 Selective beta$_2$ agonists 175
3.1.1.2 Other adrenoceptor agonists 179
3.1.2 Antimuscarinic bronchodilators 179
3.1.3 Theophylline 181
3.1.4 Compound bronchodilator preparations 182
3.1.5 Peak flow meters, inhaler devices and nebulisers 182
3.2 Corticosteroids 184
3.3 Cromoglicate and related therapy, leukotriene receptor antagonists, and phosphodiesterase type-4 inhibitors 189
3.3.1 Cromoglicate and related therapy 189
3.3.2 Leukotriene receptor antagonists 190
3.3.3 Phosphodiesterase type-4 inhibitors 191
3.4 Antihistamines, hyposensitisation, and allergic emergencies 191
3.4.1 Antihistamines 191
3.4.2 Allergen Immunotherapy 195
3.4.3 Allergic emergencies 197
3.5 Respiratory stimulants and pulmonary surfactants 199
3.5.1 Respiratory stimulants 199
3.5.2 Pulmonary surfactants 200
3.6 Oxygen 201
3.7 Mucolytics 202
3.8 Aromatic inhalations 203
3.9 Cough preparations 204
3.9.1 Cough suppressants 204
3.9.2 Demulcent and expectorant cough preparations 205
3.10 Systemic nasal decongestants 205

This chapter also includes advice on the drug management of the following:

- severe acute asthma, p. 171
- anaphylaxis, p. 197
- angioedema, p. 199
- chronic asthma, p. 172
- chronic obstructive pulmonary disease, p. 171
- croup, p. 174

3.1 Bronchodilators

3.1.1 Adrenoceptor agonists
3.1.2 Antimuscarinic bronchodilators
3.1.3 Theophylline
3.1.4 Compound bronchodilator preparations
3.1.5 Peak flow meters, inhaler devices and nebulisers

Asthma

Drugs used in the management of asthma include beta$_2$ agonists (section 3.1.1), antimuscarinic bronchodilators (section 3.1.2), theophylline (section 3.1.3), corticosteroids (section 3.2), cromoglicate and nedocromil (section 3.3.1), leukotriene receptor antagonists (section 3.3.2), and, in specialist centres, omalizumab (section 3.4.2).

For tables outlining the management of chronic and acute asthma, see p. 172 and p. 173. For advice on the management of medical emergencies in dental practice, see p. 27.

Administration of drugs for asthma

Inhalation This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced. See also Inhaler devices, section 3.1.5.

Solutions for nebulisation are available for use in severe acute asthma. They are administered over 5–10 minutes from a nebuliser, usually driven by oxygen in hospital. See also Nebulisers, section 3.1.5.

Oral The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta$_2$ agonists, corticosteroids, theophylline, and leukotriene receptor antagonists.

Parenteral Drugs such as beta$_2$ agonists, corticosteroids, and aminophylline can be given by injection in acute severe asthma when administration by nebulisation is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

Pregnancy and breast-feeding

It is particularly important that asthma should be well controlled during pregnancy; when this is achieved asthma has no important effects on pregnancy, labour, or on the fetus. Drugs for asthma should preferably be administered by inhalation to minimise exposure of the fetus. Inhaled drugs, theophylline, and prednisolone (see section 6.3.2) can be taken as normal during pregnancy and breast-feeding. Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

Severe acute exacerbations of asthma can have an adverse effect on pregnancy and should be treated

promptly in hospital with conventional therapy, including nebulisation of a beta$_2$ agonist and oral or parenteral administration of a corticosteroid; prednisolone is the preferred corticosteroid for oral administration since very little of the drug reaches the fetus. Oxygen should be given immediately to maintain arterial oxygen saturation of 94–98% and prevent maternal and fetal hypoxia. An intravenous beta$_2$ agonist, aminophylline, or magnesium sulphate can be used during pregnancy if necessary; parenteral beta$_2$ agonists can affect the myometrium (see section 7.1.3).

Management of severe acute asthma

> **Important**
> Regard each emergency consultation as being for severe acute asthma until shown otherwise.
> Failure to respond adequately at any time requires immediate transfer to hospital.

Severe acute asthma can be fatal and **must** be treated promptly and energetically. All patients with severe acute asthma should be given high-flow **oxygen** (if available) and an inhaled **short-acting beta$_2$ agonist** via a large-volume spacer or nebuliser; give 2–10 puffs of **salbutamol** 100 micrograms/metered inhalation, each puff inhaled separately via a large-volume spacer, and repeat at 10–20 minute intervals or as necessary. If there are life-threatening features, give salbutamol or **terbutaline** via an oxygen-driven nebuliser every 20–30 minutes or as necessary, see p. 177 and p. 179. In all cases, a systemic **corticosteroid** (section 6.3.2) should be given. For adults, give prednisolone 40–50 mg by mouth for at least 5 days, or intravenous hydrocortisone (preferably as sodium succinate) 100 mg every 6 hours until conversion to oral prednisolone is possible. For children, give prednisolone 1–2 mg/kg by mouth (max. 40 mg) for up to 3 days, *or* longer if necessary, *or* intravenous hydrocortisone (preferably as sodium succinate) 4 mg/kg (CHILD under 2 years max. 25 mg, 2–5 years max. 50 mg, 6–12 years max. 100 mg) every 6 hours until conversion to oral prednisolone is possible. If the child has been taking an oral corticosteroid for more than a few days, then give prednisolone 2 mg/kg (max. 60 mg). In severe or life-threatening asthma, also consider initial treatment with **ipratropium** by nebuliser, 500 micrograms every 4–6 hours (CHILD under 12 years 250 micrograms repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary).

Most patients do not require and do not benefit from the addition of **intravenous aminophylline** or of **intravenous beta$_2$ agonist**; both cause more adverse effects than nebulised beta$_2$ agonists. Nevertheless, an occasional patient who has not been taking theophylline may benefit from aminophylline infusion (see p. 181). **Magnesium sulphate** [unlicensed indication] 1.2–2 g by intravenous infusion over 20 minutes can be used for patients with severe acute asthma, but evidence of benefit is limited.

Treatment of severe acute asthma is safer in hospital where resuscitation facilities are immediately available. Treatment should **never** be delayed for investigations, patients should **never** be sedated, and the possibility of a pneumothorax should be considered.

If the patient's condition deteriorates despite pharmacological treatment, intermittent positive pressure ventilation may be needed.

For a table outlining the management of acute asthma, see p. 173.

Follow up in all cases Episodes of acute asthma should be regarded as a failure of preventative therapy. A careful history should be taken to establish the reason for the exacerbation. Inhaler technique should be checked and regular treatment should be reviewed in accordance with the Management of Chronic Asthma table, p. 172. Patients should be given a written asthma action plan aimed at preventing relapse, optimising treatment, and preventing delay in seeking assistance in future exacerbations. Follow-up within 48 hours should be arranged with the general practitioner or appropriate primary care health professional. Patients should also be reviewed by a respiratory specialist within one month of the exacerbation.

Chronic obstructive pulmonary disease

Smoking cessation (section 4.10.2) reduces the progressive decline in lung function in chronic obstructive pulmonary disease (COPD, chronic bronchitis, or emphysema). Infection can complicate chronic obstructive pulmonary disease and may be prevented by vaccination (pneumococcal vaccine and influenza vaccine, section 14.4).

A trial of a high-dose inhaled corticosteroid *or* an oral corticosteroid is recommended for patients with moderate or severe airflow obstruction if the diagnosis is in doubt.

Symptoms of chronic obstructive pulmonary disease may be alleviated by an inhaled **short-acting beta$_2$ agonist** (section 3.1.1.1) or a **short-acting antimuscarinic bronchodilator** (section 3.1.2) used as required.

When the airways obstruction is more severe, regular inhaled therapy should be used, see also Use of Inhaled Therapies in Chronic Obstructive Pulmonary Disease, p. 174.

If the Forced Expiratory Volume in 1 second (FEV_1), is 50% of predicted or more, *either* a long-acting antimuscarinic bronchodilator (section 3.1.2) *or* a long-acting beta$_2$ agonist (section 3.1.1.1) should be used. Short-acting antimuscarinic bronchodilators should be discontinued when a long-acting antimuscarinic bronchodilator is started. A long-acting beta$_2$ agonist with a corticosteroid (section 3.2) in a combination inhaler can be used for patients who remain symptomatic despite regular treatment with a long-acting beta$_2$ agonist.

If FEV_1 is less than 50% of predicted, *either* a long-acting antimuscarinic bronchodilator *or* a long-acting beta$_2$ agonist with a corticosteroid in a combination inhaler should be used.

In any patient who remains breathless or continues to have exacerbations, triple therapy with a long-acting beta$_2$ agonist and a corticosteroid in a combination inhaler *plus* a long-acting antimuscarinic bronchodilator should be used.

If an inhaled corticosteroid is not appropriate, a long-acting antimuscarinic bronchodilator can be used with a long-acting beta$_2$ agonist.

If symptoms persist or if the patient is unable to use an inhaler, oral modified-release **aminophylline** or **theophylline** (section 3.1.3) can be used.

Management of chronic asthma

Important Start at **step most appropriate** to initial severity; before initiating a new drug consider whether diagnosis is correct, check compliance and inhaler technique, and eliminate trigger factors for acute exacerbations

Adult and Child over 5 years

Step 1: occasional relief bronchodilator

Inhaled short-acting beta$_2$ agonist as required (up to once daily)

Note Move to step 2 if needed more than twice a week, or if night-time symptoms more than once a week, or if exacerbation in the last 2 years

Step 2: regular inhaled preventer therapy

Inhaled short-acting beta$_2$ agonist as required

plus

Regular standard-dose[1] inhaled corticosteroid (alternatives[2] are considerably less effective)

Step 3: inhaled corticosteroid + long-acting inhaled beta$_2$ agonist

Inhaled short-acting beta$_2$ agonist as required

plus

Regular standard-dose[1] inhaled corticosteroid

plus

Regular inhaled long-acting beta$_2$ agonist (salmeterol *or* formoterol)

If asthma not controlled

Increase dose of inhaled corticosteroid to upper end of standard dose range[1]

and

Either stop long-acting beta$_2$ agonist if of no benefit
Or continue long-acting beta$_2$ agonist if of some benefit

If asthma still not controlled and long-acting beta$_2$ agonist stopped, add one of

- Leukotriene receptor antagonist
- Modified-release oral theophylline
- Modified-release oral beta$_2$ agonist; CHILD under 12 years not recommended

Step 4: high-dose inhaled corticosteroid + regular bronchodilators

Inhaled short-acting beta$_2$ agonist as required

with

Regular high-dose[3] inhaled corticosteroid

plus

Inhaled long-acting beta$_2$ agonist

plus

In adults 6-week sequential therapeutic trial of one or more of

- Leukotriene receptor antagonist
- Modified-release oral theophylline
- Modified-release oral beta$_2$ agonist

Step 5: regular corticosteroid tablets

Refer to a respiratory specialist

Inhaled short-acting beta$_2$ agonist as required

with

Regular high-dose[3] inhaled corticosteroid

and

One or more long-acting bronchodilators (see step 4)

plus

Regular prednisolone tablets (as single daily dose)

Note In addition to regular prednisolone, continue high-dose inhaled corticosteroid (in exceptional cases may exceed licensed doses); these patients should normally be referred to an asthma clinic

Stepping down

Review treatment every 3 months; if control achieved, stepwise reduction may be possible; reduce dose of *inhaled* corticosteroid slowly (consider reduction every 3 months, decreasing dose by up to 50% each time)

Child under 5 years[4]

Step 1: occasional relief bronchodilator

Short-acting beta$_2$ agonist as required (not more than once daily)

Note Preferably by inhalation (less effective and more side-effects when given by mouth)

Move to step 2 if needed more than twice a week, or if night-time symptoms more than once a week, or if exacerbation in the last 2 years

Step 2: regular preventer therapy

Inhaled short-acting beta$_2$ agonist as required

plus

Either regular standard-dose[1] inhaled corticosteroid
Or (if inhaled corticosteroid cannot be used) leukotriene receptor antagonist

Step 3: add-on therapy

Child under 2 years:

Refer to respiratory paediatrician

Child 2–5 years:

Inhaled short-acting beta$_2$ agonist as required

plus

Regular inhaled corticosteroid in standard dose[1]

plus

Leukotriene receptor antagonist

Step 4: persistent poor control

Refer to respiratory paediatrician

Stepping down

Regularly review need for treatment

1. Standard-dose inhaled corticosteroids

   Beclometasone dipropionate or **budesonide** 100–400 micrograms twice daily; CHILD under 12 years 100–200 micrograms twice daily

   Fluticasone propionate 50–200 micrograms twice daily; CHILD 4–12 years 50–100 micrograms twice daily

   Mometasone furoate 200 micrograms twice daily

   Note. Dose adjustments may be required for some inhaler devices, see under individual preparations, section 3.2

2. Alternatives to inhaled corticosteroid are leukotriene receptor antagonists, theophylline, inhaled cromoglicate, or inhaled nedocromil

3. High-dose inhaled corticosteroids

   Beclometasone dipropionate or budesonide 0.4–1 mg twice daily; CHILD 5–12 years 200–400 micrograms twice daily

   Fluticasone propionate 200–500 micrograms twice daily; CHILD 5–12 years 100–200 micrograms twice daily

   Mometasone furoate 200–400 micrograms twice daily

   Note. Dose adjustments may be required for some inhaler devices, see under individual preparations, section 3.2. Failure to achieve control with these doses is unusual, see also Side-effects of Inhaled Corticosteroids, section 3.2

4. Lung-function measurements cannot be used to guide management in those under 5 years

Advice on the management of chronic asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated June 2009); updates available at www.brit-thoracic.org.uk

Management of acute asthma

Important Patients with severe or life-threatening acute asthma may not be distressed and may not have all of these abnormalities; the presence of any should alert the doctor. Regard each emergency consultation as being for **severe acute asthma** until shown otherwise

Moderate acute asthma

- Able to talk
- Respiration (breaths/minute) < 25; CHILD 2–5 years ≤ 40, 5–12 years ≤ 30
- Pulse (beats/minute) < 110; CHILD 2–5 years ≤ 140, 5–12 years ≤ 125
- Arterial oxygen saturation ≥ 92%
- Peak flow > 50% of predicted or best; CHILD 5–12 years ≥ 50%

Treat at home or in surgery and assess response to treatment

Treatment

- Inhaled **short-acting beta$_2$ agonist** via a large-volume spacer or oxygen-driven nebuliser (if available); give 2–10 puffs of **salbutamol** 100 micrograms/metered inhalation each inhaled separately, and repeat at 10–20 minute intervals if necessary *or* give nebulised **salbutamol** 5 mg (CHILD under 5 years 2.5 mg, 5–12 years 2.5–5 mg) or **terbutaline** 10 mg (CHILD under 5 years 5 mg, 5–12 years 5–10 mg), and repeat at 20–30 minute intervals if necessary
- **Prednisolone** 40–50 mg by mouth for at least 5 days; CHILD 1–2 mg/kg (max. 40 mg) for up to 3 days, or longer if necessary; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg)

Monitor response for 15–30 minutes

If response is poor or a relapse occurs in 3–4 hours, send immediately to hospital for assessment and further treatment

Severe acute asthma

- Cannot complete sentences in one breath; CHILD too breathless to talk or feed
- Respiration (breaths/minute) ≥ 25; CHILD 2–5 years > 40; 5–12 years > 30
- Pulse (beats/minute) ≥ 110; CHILD 2–5 years > 140; 5–12 years > 125
- Arterial oxygen saturation ≥ 92%; CHILD under 12 years < 92%
- Peak flow 33–50% of predicted or best; CHILD 5–12 years 33–50%

Start treatment below and send immediately to hospital

Treatment

- High-flow **oxygen** (if available)
- Inhaled **short-acting beta$_2$ agonist** via a large-volume spacer or oxygen-driven nebuliser (if available) as for moderate acute asthma
- **Prednisolone** by mouth as for moderate acute asthma *or* intravenous **hydrocortisone** (preferably as sodium succinate) 100 mg every 6 hours until conversion to oral prednisolone is possible; CHILD 4 mg/kg (CHILD under 2 years max. 25 mg, 2–5 years max. 50 mg, 6–12 years max. 100 mg)

Monitor response for 15–30 minutes

If response is poor:

- Inhaled **ipratropium bromide** via oxygen-driven nebuliser (if available) 500 micrograms every 4–6 hours (CHILD under 12 years 250 micrograms repeated every 20–30 minutes for the first 2 hours, then every 4–6 hours as necessary)

Refer those who fail to respond and require ventilatory support to an intensive care or high-dependency unit

- Consider intravenous **beta$_2$ agonists**, **aminophylline** (p. 181) or **magnesium sulphate** [unlicensed indication] (p. 171) only after consultation with senior medical staff

Life-threatening acute asthma

- Silent chest, feeble respiratory effort, cyanosis
- Hypotension, bradycardia, arrhythmia, exhaustion, agitation (in children), or reduced level of consciousness
- Arterial oxygen saturation < 92%
- Peak flow < 33% of predicted or best; CHILD 5–12 years < 33%

Start treatment below and send immediately to hospital; consult with senior medical staff and refer to intensive care

Treatment

- High-flow **oxygen** (if available)
- **Short-acting beta$_2$ agonist** via oxygen-driven nebuliser (if available); give **salbutamol** 5 mg (CHILD under 5 years 2.5 mg, 5–12 years 2.5–5 mg) or **terbutaline** 10 mg (CHILD under 5 years 5 mg, 5–12 years 5–10 mg), and repeat at 20–30 minute intervals or as necessary; reserve intravenous beta$_2$ agonists for those in whom inhaled therapy cannot be used reliably
- **Prednisolone** by mouth as for moderate acute asthma *or* intravenous **hydrocortisone** as for severe acute asthma
- Inhaled **ipratropium bromide** via oxygen-driven nebuliser (if available) as for severe acute asthma

Monitor response for 15–30 minutes

If response is poor:

- Consider intravenous **aminophylline** (p. 181) or **magnesium sulphate** [unlicensed indication] (p. 171) only after consultation with senior medical staff

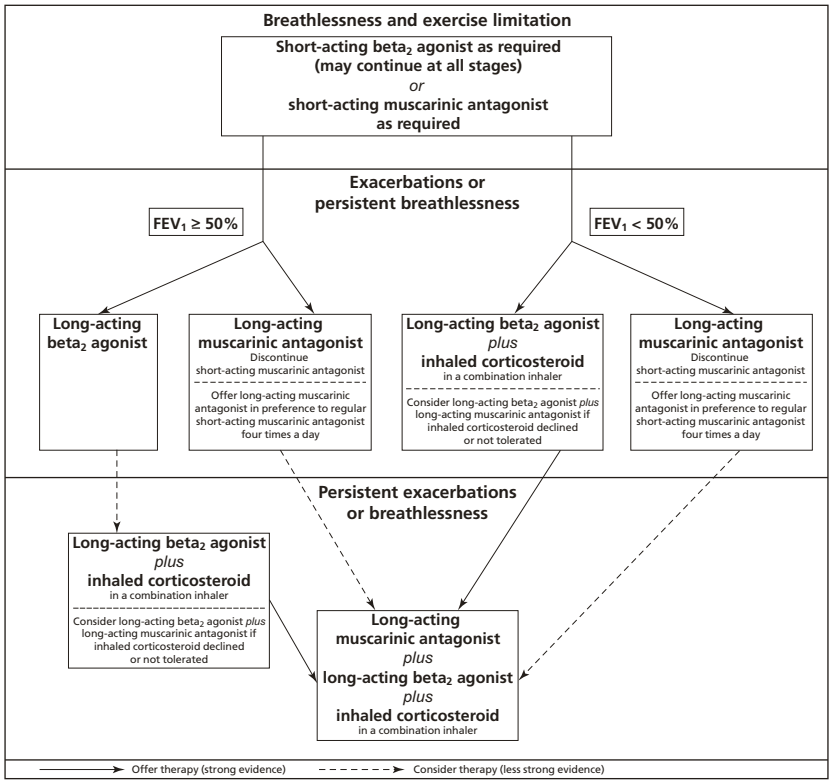
Follow up in all cases

Monitor symptoms and peak flow. Set up asthma action plan and check inhaler technique

Review by general practitioner or appropriate primary care health professional within 48 hours, see also p. 171

Advice on the management of acute asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated June 2009); updates available at www.brit-thoracic.org.uk

Use of inhaled therapies in chronic obstructive pulmonary disease



Advice on the use of inhaled therapies in chronic obstructive pulmonary disease is based on the recommendations of the National Institute for Health and Clinical Excellence (2010). Management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: NICE. Available from www.nice.org.uk/CG101 Reproduced with permission

Indacaterol (section 3.1.1.1) is a long-acting beta$_2$ agonist licensed for the maintenance treatment of chronic obstructive pulmonary disease.

In patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations, **roflumilast** (section 3.3.3) is licensed as an adjunct to existing bronchodilator treatment.

A **mucolytic** drug (section 3.7) may be considered for a patient with a chronic productive cough.

Long-term **oxygen** therapy (section 3.6) prolongs survival in patients with severe chronic obstructive pulmonary disease and hypoxaemia.

During an exacerbation of chronic obstructive pulmonary disease, bronchodilator therapy can be administered through a nebuliser if necessary and oxygen given if appropriate. **Aminophylline** can be given intravenously if response to nebulised bronchodilators is poor. A short course of **oral corticosteroid** (section 6.3.2), such as prednisolone 30 mg daily for 7–14 days, should be given if increased breathlessness interferes with daily activities. **Antibacterial** treatment (Table 1, section 5.1) is required when sputum becomes purulent or if there are other signs of infection.

Patients who have had an episode of hypercapnic respiratory failure should be given a 24% or 28% Venturi mask and an *oxygen alert card* (see below) endorsed with the oxygen saturations required during previous exacerbations. Patients and their carers should be instructed to show the card to emergency healthcare providers in the event of an exacerbation, see also section 3.6.

Oxygen alert card

Name: _____

I am at risk of type II respiratory failure with a raised CO_2 level.

Please use my ____% Venturi mask to achieve an oxygen saturation of _____% to _____% during exacerbations.

Use compressed air to drive nebulisers (with nasal oxygen at 2 litres/minute). If compressed air not available, limit oxygen-driven nebulisers to 6 minutes.

Oxygen alert card based on British Thoracic Society guideline for emergency oxygen use in adult patients (October 2008); available at www.brit-thoracic.org.uk

Croup

Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg) by mouth may be of benefit.

More severe croup (or mild croup that might cause complications) calls for hospital admission; a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg or prednisolone 1–2 mg/kg by mouth, section 6.3.2) should be administered before transfer to hospital. In hospital, dexamethasone 150 micrograms/kg (by mouth or by injection) or budesonide 2 mg (by nebulisation, section 3.2) will often reduce symptoms; the dose may need to be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline solution 1 in 1000 (1 mg/mL) should be given with close clinical monitoring in a dose of 400 micrograms/kg (max. 5 mg) repeated after 30 minutes if necessary; the effects of nebulised adrenaline last 2–3 hours and the child needs to be monitored carefully for recurrence of the obstruction.

3.1.1 Adrenoceptor agonists (Sympathomimetics)

3.1.1.1 Selective beta$_2$ agonists
3.1.1.2 Other adrenoceptor agonists

The selective beta$_2$ agonists (selective beta$_2$-adrenoceptor agonists, selective beta$_2$ stimulants) (section 3.1.1.1) such as salbutamol or terbutaline are the safest and most effective short-acting beta$_2$ agonists for asthma. Less selective beta$_2$ agonists such as ephedrine (section 3.1.1.2) should be avoided whenever possible.

Adrenaline (epinephrine) (which has both alpha- and beta-adrenoceptor agonist properties) is used in the emergency management of allergic and anaphylactic reactions (section 3.4.3) and in the management of croup (see above).

3.1.1.1 Selective beta$_2$ agonists

Selective beta$_2$ agonists produce bronchodilation. A short-acting beta$_2$ agonist is used for immediate relief of asthma symptoms while some long-acting beta$_2$ agonists are added to an inhaled corticosteroid in patients requiring prophylactic treatment.

Management of Chronic Asthma table, see p. 172
Management of Acute Asthma table, see p. 173

Short-acting beta$_2$ agonists Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta$_2$ agonist such as **salbutamol** or **terbutaline**. If beta$_2$ agonist inhalation is needed more often than once daily, prophylactic treatment should be considered, using a stepped approach as outlined in the Management of Chronic Asthma table, p. 172. Regular treatment with an inhaled short-acting beta$_2$ agonist is less effective than 'as required' inhalation and is not appropriate prophylactic treatment.

A short-acting beta$_2$ agonist inhaled immediately before exertion reduces *exercise-induced asthma*; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.

Long-acting beta$_2$ agonists **Formoterol** (eformoterol) and **salmeterol** are longer-acting beta$_2$ agonists which are administered by inhalation. They should be used for asthma only in patients who regularly use an inhaled corticosteroid (see CHM advice below). They have a role in the long-term control of chronic asthma (see Management of Chronic Asthma table, p. 172) and they can be useful in nocturnal asthma. Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline. Formoterol is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm; its speed of onset of action is similar to that of salbutamol.

Combination inhalers that contain a long-acting beta$_2$ agonist and a corticosteroid (section 3.2) ensure that long-acting beta$_2$ agonists are not used without concomitant corticosteroids, but reduce the flexibility to adjust the dose of each component.

CHM advice

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta$_2$ agonists (formoterol and salmeterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients with rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- not be used for the relief of exercise-induced asthma symptoms unless regular inhaled corticosteroids are also used;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

A daily dose of 24 micrograms of formoterol should be sufficient for the majority of children, particularly for younger age-groups; higher doses should be used rarely, and only when control is not maintained on the lower dose.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta$_2$ agonist, see Management of Chronic Asthma table, p. 172.

Indacaterol is a long-acting beta$_2$ agonist recently licensed for chronic obstructive pulmonary disease; it is not indicated for the relief of acute bronchospasm.

Inhalation *Pressurised-metered dose inhalers* are an effective and convenient method of drug administration in mild to moderate asthma. A spacer device (section 3.1.5) may improve drug delivery. At recommended inhaled doses the duration of action of salbutamol, terbutaline and fenoterol is about 3 to 5 hours and for salmeterol and formoterol 12 hours. The **dose**, the frequency, and the maximum number of inhalations in 24 hours of the beta$_2$ agonist should be **stated explicitly** to the patient. The patient should be advised to seek medical advice when the prescribed dose of beta$_2$ agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the patient may require a prophylactic drug such as an inhaled corticosteroid (see Management of Chronic Asthma table, p. 172).

Nebuliser (or respirator) solutions of salbutamol and terbutaline are used for the treatment of severe acute asthma in hospital or in general practice. Patients with a severe attack of asthma should preferably have oxygen during nebulisation since $beta_2$ agonists can increase arterial hypoxaemia. For the use of nebulisers in chronic obstructive pulmonary disease, see section 3.1.5. The dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution, see also section 3.1.5.

Oral Oral preparations of $beta_2$ agonists may be used by patients who cannot manage the inhaled route. They are sometimes used for children and the elderly, but inhaled $beta_2$ agonists are more effective and have fewer side-effects. The longer-acting oral preparations, including bambuterol, may be of value in nocturnal asthma but they have a limited role and inhaled long-acting $beta_2$ agonists are usually preferred.

Parenteral Salbutamol or terbutaline can be given intravenously for severe or life-threatening acute asthma; patients should be carefully monitored and the dose adjusted according to response and heart rate. The regular use of $beta_2$ agonists by the subcutaneous route is not recommended since the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started. $Beta_2$ agonists may also be given by intramuscular injection.

Children Selective $beta_2$ agonists are useful even in children under the age of 18 months. They are most effective by the inhaled route; a pressurised metered-dose inhaler should be used with a spacer device in children under 5 years (see NICE guidance, section 3.1.5). A $beta_2$ agonist may also be given by mouth but administration by inhalation is preferred; a long-acting inhaled $beta_2$ agonist may be used where appropriate (see Management of Chronic Asthma table, p. 172). In severe attacks nebulisation using a selective $beta_2$ agonist or ipratropium is advisable (see also Management of Chronic Asthma table and Management of Acute Asthma table, p. 172 and p. 173).

Cautions $Beta_2$ agonists should be used with caution in hyperthyroidism, cardiovascular disease, arrhythmias, susceptibility to QT-interval prolongation, and hypertension. $Beta_2$ agonists should be used with caution in diabetes—monitor blood glucose (risk of ketoacidosis, especially when $beta_2$ agonist given intravenously). **Interactions:** Appendix 1 (sympathomimetics, $beta_2$).

Hypokalaemia Potentially serious hypokalaemia may result from $beta_2$ agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

Side-effects Side-effects of the $beta_2$ agonists include fine tremor (particularly in the hands), nervous tension, headache, muscle cramps, and palpitation. Other side-effects include tachycardia, arrhythmias, peripheral vasodilation, myocardial ischaemia, and disturbances of sleep and behaviour. Paradoxical bronchospasm (occasionally severe), urticaria, angioedema, hypotension, and collapse have also been reported. High doses of $beta_2$ agonists are associated with hypokalaemia (see Hypokalaemia above).

BAMBUTEROL HYDROCHLORIDE

Note Bambuterol is a pro-drug of terbutaline

Indications asthma and other conditions associated with reversible airways obstruction

Cautions see notes above

Hepatic impairment avoid in severe impairment

Renal impairment reduce initial dose by half if eGFR less than 50 mL/minute/1.73m^2

Pregnancy manufacturer advises avoid—no information available; see also p. 170

Breast-feeding see p. 170

Side-effects see notes above

Dose

- 20 mg once daily at bedtime if patient has previously tolerated $beta_2$ agonists; other patients, initially 10 mg once daily at bedtime, increased if necessary after 1–2 weeks to 20 mg once daily; CHILD not recommended

Bambec® (AstraZeneca) PoM

Tablets, both scored, bambuterol hydrochloride 10 mg, net price 28-tab pack = £12.05; 20 mg, 28-tab pack = £13.14

FENOTEROL HYDROBROMIDE

Indications reversible airways obstruction

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above

Compound preparations

For **compound preparation** containing fenoterol, see section 3.1.4

FORMOTEROL FUMARATE

(Eformoterol fumarate)

Indications reversible airways obstruction (including nocturnal asthma and prophylaxis of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy, see also Management of Chronic Asthma table, p. 172; chronic obstructive pulmonary disease

Note For use in asthma only in patients who regularly use an inhaled corticosteroid, see notes above

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; *very rarely* QT- interval prolongation; taste disturbances, nausea, dizziness, rash, and pruritus also reported

Dose

- See under preparations below

Counselling Advise patients not to exceed prescribed dose, and to follow manufacturer's directions; if a previously effective dose of inhaled formoterol fails to provide adequate relief, a doctor's advice should be obtained as soon as possible

Formoterol (Non-proprietary) PoM

Dry powder for inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 120-dose unit = £23.75. Counselling, administration

Brands include *Easyhaler® Formoterol*

Dose by inhalation of powder, asthma, ADULT and CHILD over 6 years, 12 micrograms twice daily, increased to 24 micr-

ograms twice daily in more severe airways obstruction (see also CHM advice above)

Chronic obstructive pulmonary disease, 12 micrograms twice daily

Atimos Modulite® (Chiesi) ▼ PoM

Aerosol inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 100-dose unit = £30.06. Counselling, administration

Dose by aerosol inhalation, asthma, ADULT and CHILD over 12 years, 12 micrograms twice daily, increased to max. 24 micrograms twice daily in more severe airways obstruction

Chronic obstructive pulmonary disease, ADULT over 18 years, 12 micrograms twice daily; for symptom relief additional doses may be taken to total max. 48 micrograms daily (max. single dose 24 micrograms)

Foradil® (Novartis) PoM

Dry powder for inhalation, formoterol fumarate 12 micrograms/capsule, net price 60-cap pack (with inhaler device) = £23.38. Counselling, administration

Dose by inhalation of powder, asthma, ADULT and CHILD over 12 years, 12 micrograms twice daily, increased to max. 24 micrograms twice daily in more severe airways obstruction; CHILD 5–12 years 12 micrograms twice daily

Chronic obstructive pulmonary disease, 12 micrograms twice daily

Oxis® (AstraZeneca) PoM

Turbohaler® (= dry powder inhaler), formoterol fumarate 6 micrograms/metered inhalation, net price 60-dose unit = £24.80; 12 micrograms/metered inhalation, 60-dose unit = £24.80. Counselling, administration

Dose by inhalation of powder, chronic asthma, 6–12 micrograms 1–2 times daily, increased up to 24 micrograms twice daily if necessary; occasionally up to 72 micrograms daily may be needed (max. single dose 36 micrograms); reassess treatment if additional doses required on more than 2 days a week; CHILD 6–18 years, 6–12 micrograms 1–2 times daily; occasionally up to 48 micrograms daily may be needed (max. single dose 12 micrograms) (see also CHM advice above)

Relief of bronchospasm, ADULT and CHILD over 6 years, 6–12 micrograms

Prophylaxis of exercise-induced bronchospasm, 12 micrograms before exercise; CHILD 6–18 years, 6–12 micrograms before exercise

Chronic obstructive pulmonary disease, 12 micrograms 1–2 times daily; for symptom relief additional doses can be taken to total max. 48 micrograms daily (max. single dose 24 micrograms)

Compound preparations

For **compound preparations** containing formoterol, see section 3.2

INDACATEROL

Indications maintenance treatment of chronic obstructive pulmonary disease

Cautions see notes above; convulsive disorders

Hepatic impairment use with caution in severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—present in milk in *animal* studies

Side-effects see notes above; also peripheral oedema, cough, pharyngolaryngeal pain, nasopharyngitis, sinusitis, rhinorrhoea; *less commonly* atrial fibrillation, non-cardiac chest pain, paraesthesia

Dose

- By inhalation of powder, ADULT over 18 years, 150 micrograms once daily, increased to max. 300 micrograms once daily

Onbrez Breezhaler® (Novartis) ▼ PoM

Inhalation powder, hard capsule (for use with *Onbrez Breezhaler®* device), indacaterol (as maleate) 150 micrograms, net price 30-cap pack with *Onbrez Breezhaler®* device = £29.26; 300 micrograms, net price 30-cap pack with *Onbrez Breezhaler®* device = £29.26. Counselling, administration

SALBUTAMOL

(Albuterol)

Indications asthma and other conditions associated with reversible airways obstruction; premature labour (section 7.1.3)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also lactic acidosis with high doses

Dose

- By mouth (but use by inhalation preferred), 4 mg (elderly and sensitive patients initially 2 mg) 3–4 times daily; max. single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated); CHILD under 2 years see *BNF for Children*; 2–6 years 1–2 mg 3–4 times daily, 6–12 years 2 mg 3–4 times daily
- By subcutaneous *or* intramuscular injection, 500 micrograms, repeated every 4 hours if necessary
- By slow intravenous injection (but see also Management of Acute Asthma table, p. 173), (dilute to a concentration of 50 micrograms/mL), 250 micrograms, repeated if necessary; CHILD under 18 years see *BNF for Children*
- By intravenous infusion (but see also Management of Acute Asthma table, p. 173), initially 5 micrograms/minute, adjusted according to response and heart-rate usually in range 3–20 micrograms/minute, or more if necessary; CHILD under 18 years see *BNF for Children*
- By aerosol inhalation (but see also Management of Acute Asthma table, p. 173, *or* Management of Chronic Asthma table, p. 172), 100–200 micrograms (1–2 puffs); for persistent symptoms up to 4 times daily; CHILD 100 micrograms (1 puff), increased to 200 micrograms (2 puffs) if necessary; for persistent symptoms up to 4 times daily

  Prophylaxis of allergen- or exercise-induced bronchospasm, 200 micrograms (2 puffs); CHILD 100 micrograms (1 puff), increased to 200 micrograms (2 puffs) if necessary
- By inhalation of powder (but see also Management of Chronic Asthma table, p. 172), 200–400 micrograms; for persistent symptoms up to 4 times daily; CHILD over 5 years 200 micrograms; for persistent symptoms up to 4 times daily (for *Asmasal Clickhaler®*, *Salbulin Novolizer®*, and *Ventolin Accuhaler®* doses, see under preparations)

  Prophylaxis of allergen- or exercise-induced bronchospasm, 400 micrograms; CHILD 200 micrograms
- By inhalation of nebulised solution, ADULT and CHILD over 5 years 2.5–5 mg, repeated up to 4 times daily or more frequently in severe cases; CHILD under 5 years 2.5 mg, repeated up to 4 times daily or more frequently in severe cases; see also Management of Acute Asthma table, p. 173 and Management of Chronic Asthma table, p. 172

Oral

Salbutamol (Non-proprietary) PoM

Tablets, salbutamol (as sulphate) 2 mg, net price 28-tab pack = £17.74; 4 mg, 28-tab pack = £16.40

Oral solution, salbutamol (as sulphate) 2 mg/5 mL, net price 150 mL = £1.55

Brands include *Salapin®* (sugar-free)

Ventmax® SR (Chiesi) PoM

Capsules, m/r, salbutamol (as sulphate) 4 mg (green/grey), net price 56-cap pack = £8.08; 8 mg (white), 56-cap pack = £9.69. Label: 25

Dose 8 mg twice daily; CHILD 3–12 years 4 mg twice daily

Ventolin® (A&H) PoM

Syrup, sugar-free, salbutamol (as sulphate) 2 mg/5 mL, net price 150 mL = 60p

Parenteral

Ventolin® (A&H) PoM

Injection, salbutamol (as sulphate) 500 micrograms/mL, net price 1-mL amp = 38p

Solution for intravenous infusion, salbutamol (as sulphate) 1 mg/mL. Dilute before use. Net price 5-mL amp = £2.48

Inhalation

Counselling Advise patients not to exceed prescribed dose and to follow manufacturer's directions; if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor's advice should be obtained as soon as possible.

Salbutamol (Non-proprietary) PoM

Aerosol inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £3.19. Counselling, administration

Brands include *Salamol®*, *Salbumalin®*

Dry powder for inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose unit = £3.31; 200 micrograms/metered inhalation, 100-dose unit = £4.85, 200-dose unit = £6.63. Counselling, administration

Brands include *Easyhaler® Salbutamol*, *Pulvinal® Salbutamol*

Inhalation powder, *hard capsule* (for use with *Cyclohaler®* device), salbutamol 200 micrograms, net price 120-cap pack = £8.99; 400 micrograms, 120-cap pack = £12.99. Counselling, administration

Brands include *Salbutamol Cyclocaps®*

Nebuliser solution, salbutamol (as sulphate) 1 mg/mL, net price 20 × 2.5 mL (2.5 mg) = £1.91; 2 mg/mL, 20 × 2.5 mL (5 mg) = £3.82. May be diluted with sterile sodium chloride 0.9%

Brands include *Salamol Steri-Neb®*

Airomir® (IVAX) PoM

Aerosol inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.97. Counselling, administration

Autohaler (breath-actuated aerosol inhalation), salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £6.02. Counselling, administration

Asmasal Clickhaler® (UCB Pharma) PoM

Dry powder for inhalation, salbutamol (as sulphate) 95 micrograms/metered inhalation, net price 200-dose unit = £5.65. Counselling, administration

Dose acute bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 1–2 puffs; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma table, p. 172)

Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 1–2 puffs

Salamol Easi-Breathe® (IVAX) PoM

Aerosol inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose breath-actuated unit = £6.30. Counselling, administration

Salbulin Novolizer® (Meda) PoM

Dry powder for inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price refillable 200-dose unit = £4.95; 200-dose refill = £2.75. Counselling, administration

Dose acute bronchospasm, by inhalation of powder, ADULT 100–200 micrograms; for persistent symptoms up to 800 micrograms daily (but see also Management of Chronic Asthma table, p. 172); CHILD 6–12 years 100–200 micrograms; for persistent symptoms up to 400 micrograms daily (but see also Management of Chronic Asthma table, p. 172)

Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT 200 micrograms; CHILD 6–12 years 100–200 micrograms

Ventolin® (A&H) PoM

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salbutamol (as sulphate) 200 micrograms/blister with *Accuhaler®* device, net price = £4.92. Counselling, administration

Dose acute bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 200 micrograms; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma table, p. 172)

Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 200 micrograms

Evohaler® (aerosol inhalation), salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.50. Counselling, administration

Nebules® (for use with nebuliser), salbutamol (as sulphate) 1 mg/mL, net price 20 × 2.5 mL (2.5 mg) = £1.65; 2 mg/mL, 20 × 2.5 mL (5 mg) = £2.78. May be diluted with sterile sodium chloride 0.9% if administration time in excess of 10 minutes is required

Respirator solution (for use with a nebuliser or ventilator), salbutamol (as sulphate) 5 mg/mL, net price 20 mL = £2.18 (hosp. only). May be diluted with sterile sodium chloride 0.9%

Compound preparations

For **compound preparations** containing salbutamol, see section 3.1.4

Management of Chronic Asthma table, see p. 172
Management of Acute Asthma table, see p. 173

SALMETEROL

Indications reversible airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy, see also Management of Chronic Asthma table, p. 172; chronic obstructive pulmonary disease

Note Not for immediate relief of acute asthma attacks; for use in asthma only in patients who regularly use an inhaled corticosteroid, see notes above

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; nausea, dizziness, arthralgia, and rash also reported

Dose

- By inhalation, asthma, 50 micrograms (2 puffs or 1 blister) twice daily; up to 100 micrograms (4 puffs or 2 blisters) twice daily in more severe airways obstruc-

tion; CHILD 5–12 years, 50 micrograms (2 puffs or 1 blister) twice daily

Chronic obstructive pulmonary disease 50 micrograms (2 puffs or 1 blister) twice daily

Counselling Advise patients that salmeterol should **not** be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer's directions; if a previously effective dose of inhaled salmeterol fails to provide adequate relief, a doctor's advice should be obtained as soon as possible

Serevent® (A&H) PoM

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £29.26. Counselling, administration

Evohaler® aerosol inhalation ▼, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £29.26. Counselling, administration

Diskhaler® (dry powder for inhalation), disks containing 4 blisters of salmeterol (as xinafoate) 50 micrograms/blister, net price 15 disks with *Diskhaler®* device = £35.79, 15-disk refill = £35.15. Counselling, administration

Compound preparations

For **compound preparations** containing salmeterol, see section 3.2

TERBUTALINE SULPHATE

Indications asthma and other conditions associated with reversible airways obstruction; premature labour (section 7.1.3)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above

Dose

- By mouth (but use by inhalation preferred), initially 2.5 mg 3 times daily for 1–2 weeks, then up to 5 mg 3 times daily; CHILD 1 month–7 years 75 micrograms/kg 3 times daily; 7–15 years 2.5 mg 2–3 times daily
- By subcutaneous *or* slow intravenous injection, 250–500 micrograms up to 4 times daily; CHILD 2–15 years 10 micrograms/kg to a max. of 300 micrograms
- By continuous intravenous infusion as a solution containing 3–5 micrograms/mL, 90–300 micrograms/hour for 8–10 hours; CHILD 1 month–18 years, initially 2–4 micrograms/kg as a loading dose, then 1–10 micrograms/kg/hour according to response and heart rate (max. 300 micrograms/hour); high doses with close monitoring
- By inhalation of powder (*Turbohaler®*), ADULT and CHILD over 5 years, 500 micrograms (1 inhalation); for persistent symptoms up to 4 times daily (but see Management of Chronic Asthma table, p. 172)
- By inhalation of nebulised solution (but see also Management of Acute Asthma table, p. 173), 5–10 mg 2–4 times daily; additional doses may be necessary in severe acute asthma; CHILD under 5 years 5 mg 2–4 times daily, 5–12 years 5–10 mg 2–4 times daily [unlicensed dose]

Oral and parenteral

Bricanyl® (AstraZeneca) PoM

Tablets, scored, terbutaline sulphate 5 mg, net price 100- tab pack= £4.09

Syrup, sugar-free, terbutaline sulphate 1.5 mg/5 mL, net price 100 mL = £2.00

Injection, terbutaline sulphate 500 micrograms/mL, net price 1-mL amp = 30p; 5-mL amp = £1.40

Inhalation

Counselling Advise patients not to exceed prescribed dose and to follow manufacturer's directions; if a previously effective dose of inhaled terbutaline fails to provide at least 3 hours relief, a doctor's advice should be obtained as soon as possible

Bricanyl® (AstraZeneca) PoM

Turbohaler® (= dry powder inhaler), terbutaline sulphate 500 micrograms/metered inhalation, net price 100-dose unit = £6.92. Counselling, administration

Respules® (= single-dose units for nebulisation), terbutaline sulphate 2.5 mg/mL, net price 20 × 2-mL units (5-mg) = £4.04

3.1.1.2 Other adrenoceptor agonists

Ephedrine is less suitable and less safe for use as a bronchodilator than the selective beta$_2$ agonists, because it is more likely to cause arrhythmias and other side-effects; it should be avoided whenever possible.

Adrenaline (epinephrine) injection (1 in 1000) is used in the emergency treatment of acute allergic and anaphylactic reactions (section 3.4.3), in angioedema (section 3.4.3), and in cardiopulmonary resuscitation (section 2.7.3). Adrenaline solution (1 in 1000) is used by nebulisation in the management of severe croup (section 3.1).

EPHEDRINE HYDROCHLORIDE

Indications reversible airways obstruction, but see notes above

Cautions hyperthyroidism; diabetes mellitus; ischaemic heart disease; hypertension; elderly; prostatic hypertrophy (risk of acute retention); **interactions:** Appendix 1 (sympathomimetics)

Renal impairment use with caution

Pregnancy manufacturer advises avoid

Breast-feeding present in milk; manufacturer advises avoid—irritability and disturbed sleep reported

Side-effects tachycardia; anxiety, restlessness, insomnia; tremor, arrhythmias, dry mouth, and cold extremities also reported

Dose

- 15–60 mg 3 times daily; CHILD up to 1 year 7.5 mg 3 times daily, 1–5 years 15 mg 3 times daily, 6–12 years 30 mg 3 times daily

[1] **Ephedrine Hydrochloride** (Non-proprietary) PoM

Tablets, ephedrine hydrochloride 15 mg, net price 28 = £6.62; 30 mg, 28 = £10.01

1. For exemptions see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

3.1.2 Antimuscarinic bronchodilators

Ipratropium can provide short-term relief in chronic asthma, but short-acting beta$_2$ agonists act more quickly and are preferred. Ipratropium by nebulisation can be added to other standard treatment in life-threatening asthma or if acute asthma fails to improve with standard

therapy (see Management of Acute Asthma table, p. 173).

The aerosol inhalation of ipratropium can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Its maximal effect occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Tiotropium, a long-acting antimuscarinic bronchodilator, is effective for the management of chronic obstructive pulmonary disease; it is not suitable for the relief of acute bronchospasm.

Cautions Antimuscarinic bronchodilators should be used with caution in patients with prostatic hyperplasia, bladder outflow obstruction, and those susceptible to angle-closure glaucoma (see below); **interactions:** Appendix 1 (antimuscarinics).

Glaucoma *Acute angle-closure glaucoma* reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other $beta_2$ agonists); care needed to protect patient's eyes from nebulised drug or from drug powder.

Side-effects Dry mouth is the most common side-effect of antimuscarinic bronchodilators; also constipation, cough, paradoxical bronchospasm, headache, dizziness; less commonly nausea, tachycardia, palpitation, atrial fibrillation, urinary retention, angle-closure glaucoma, and blurred vision occur. Raised intra-ocular pressure has occurred rarely.

IPRATROPIUM BROMIDE

Indications reversible airways obstruction, particularly in chronic obstructive pulmonary disease; rhinitis (section 12.2.2)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also vomiting, diarrhoea, local irritation; *rarely* laryngospasm, eye pain, mydriasis

Dose

- By aerosol inhalation, 20–40 micrograms, 3–4 times daily; CHILD up to 6 years 20 micrograms 3 times daily, 6–12 years 20–40 micrograms 3 times daily
- By inhalation of powder, ADULT and CHILD over 12 years, 40 micrograms 3–4 times daily (may be doubled in less responsive patients)
- By inhalation of nebulised solution, reversible airways obstruction in chronic obstructive pulmonary disease, 250–500 micrograms 3–4 times daily
  Acute bronchospasm (but see also Management of Acute Asthma table, p. 173), 500 micrograms repeated as necessary; CHILD under 5 years 125–250 micrograms, max. 1 mg daily; 6–12 years 250 micrograms, max. 1 mg daily
  Counselling Advise patient not to exceed prescribed dose and to follow manufacturer's directions

Ipratropium Bromide (Non-proprietary) PoM

Nebuliser solution, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £6.75, 60 × 1-mL = £21.78; 20 × 2-mL (500-microgram) = £7.43, 60 × 2-mL = £26.97. If dilution is necessary use only sterile sodium chloride 0.9%

Atrovent® (Boehringer Ingelheim) PoM

Aerocaps® (dry powder for inhalation; for use with *Atrovent Aerohaler®*), green, ipratropium bromide 40 micrograms, net price pack of 100 caps with *Aerohaler®* = £14.53; 100 caps = £10.53. Counselling, administration

Note One *Atrovent Aerocap®* is equivalent to 2 puffs of *Atrovent®* metered aerosol inhalation

Aerosol inhalation ▼, ipratropium bromide 20 micrograms/metered inhalation, net price 200-dose unit = £5.05. Counselling, administration

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL unit-dose vials = £4.14, 60 × 1-mL vials = £12.44; 20 × 2-mL vials = £4.87, 60 × 2-mL vials = £14.59. If dilution is necessary use only sterile sodium chloride 0.9%

Ipratropium Steri-Neb® (IVAX) PoM

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £8.72; 20 × 2-mL (500-microgram) = £9.94. If dilution is necessary use only sterile sodium chloride 0.9%

Respontin® (A&H) PoM

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £4.78; 20 × 2-mL (500-microgram) = £5.60. If dilution is necessary use only sterile sodium chloride 0.9%

Compound ipratropium preparations

Section 3.1.4

TIOTROPIUM

Indications maintenance treatment of chronic obstructive pulmonary disease

Cautions see notes above; also cardiac rhythm disorders (with *Spiriva Respimat*)

Renal impairment plasma-tiotropium concentration raised; use with caution if eGFR less than 50 mL/minute/1.73 m^2

Side-effects see notes above; *less commonly* taste disturbance, stomatitis, gastro-oesophageal reflux disease, pharyngitis, dysphonia, dysphagia, dysuria, epistaxis, oropharyngeal candidiasis; *rarely* intestinal obstruction (including paralytic ileus), laryngitis, insomnia, urinary-tract infection, skin infection, sinusitis, dental caries, gingivitis, glossitis, skin ulcer; *also reported* dehydration, joint swelling, dry skin

Dose

- See under preparations below

Spiriva® (Boehringer Ingelheim) PoM

Inhalation powder, hard capsule (for use with *HandiHaler®* device), green, tiotropium (as tiotropium bromide monohydrate) 18 micrograms, net price 30-cap pack with *HandiHaler®* device = £34.87, 30-cap refill = £31.89. Counselling, administration

Dose by inhalation of powder, ADULT over 18 years, 18 micrograms once daily

Respimat® (solution for inhalation) ▼, tiotropium (as tiotropium bromide monohydrate) 2.5 micrograms/metered inhalation, net price 60-dose unit = £36.27. Counselling, administration

Dose by inhalation, ADULT over 18 years, 5 micrograms (2 puffs) once daily

Note The *Scottish Medicines Consortium* has advised (November 2007) that *Spiriva Respimat®* is restricted for use in chronic obstructive pulmonary disease in patients who have poor manual dexterity and difficulty using the *Handihaler®* device

3.1.3 Theophylline

Theophylline is a xanthine used as a bronchodilator in *asthma* (see Management of Chronic Asthma table, p. 172) and stable *chronic obstructive pulmonary disease*, (see p. 171); it is not generally effective in exacerbations of chronic obstructive pulmonary disease. Theophylline may have an additive effect when used in conjunction with small doses of beta$_2$ agonists; the combination may increase the risk of side-effects, including hypokalaemia (see p. 176).

Theophylline is metabolised in the liver. The plasma-theophylline concentration is *increased* in heart failure, hepatic impairment, viral infections, in the elderly, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is *decreased* in smokers, by alcohol consumption, and by drugs that induce its metabolism. For **interactions:** see Appendix 1 (theophylline).

Differences in the half-life of theophylline are important because the toxic dose is close to the therapeutic dose. In most individuals, satisfactory bronchodilation is associated with a plasma-theophylline concentration of 10–20 mg/litre (see Note below), although a lower plasma-theophylline concentration may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

Theophylline is given by injection as **aminophylline**, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe acute asthma, see Management of Acute Asthma table, p. 173. It must be given by **very slow** intravenous injection (over at least 20 minutes); it is too irritant for intramuscular use. Measurement of plasma-theophylline concentration may be helpful, and is **essential** if aminophylline is to be given to patients who are already taking theophylline, because serious side-effects such as convulsions and arrhythmias can occasionally precede other symptoms of toxicity.

Caffeine is a xanthine derivative used as a respiratory stimulant in *neonatal apnoea*, see *BNF for Children* section 3.5.1.

THEOPHYLLINE

Indications reversible airways obstruction, severe acute asthma; see also Management of Chronic Asthma table p. 172 and Management of Acute Asthma table p. 173

Cautions see notes above, also cardiac disease; hypertension; hyperthyroidism; peptic ulcer; epilepsy; elderly; fever; hypokalaemia risk, see p. 176; avoid in acute porphyria (section 9.8.2); monitor plasma-theophylline concentration (see notes above); dose adjustment may be necessary if smoking started or stopped during treatment

Hepatic impairment reduce dose

Pregnancy neonatal irritability and apnoea have been reported; see also p. 170

Breast-feeding present in milk—irritability in infant reported; modified release preparations preferable; see also p. 170

Side-effects nausea, vomiting, gastric irritation, diarrhoea; palpitation, tachycardia, arrhythmias, hypotension; anxiety, dizziness, tremor, headache, CNS stimulation, insomnia, and convulsions; **overdosage:** see Emergency Treatment of Poisoning, p. 39

Dose

- See under preparations below

  Note Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); 4–6 hours after a dose and at least 5 days after starting treatment; narrow margin between therapeutic and toxic dose, see also notes above

Modified release

Note The rate of absorption from modified-release preparations can vary between brands. If a prescription for a modified-release oral theophylline preparation does not specify a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

Nuelin SA® (Meda)

SA tablets, m/r, theophylline 175 mg, net price 60-tab pack = £3.19. Label: 21, 25

Dose 175–350 mg every 12 hours; CHILD 6–12 years 175 mg every 12 hours

SA 250 tablets, m/r, scored, theophylline 250 mg, net price 60-tab pack = £4.46. Label: 21, 25

Dose 250–500 mg every 12 hours; CHILD 6–12 years 125–250 mg every 12 hours

Slo-Phyllin® (Merck Serono)

Capsules, m/r, theophylline 60 mg (white/clear, enclosing white pellets), net price 56-cap pack = £2.76; 125 mg (brown/clear, enclosing white pellets), 56-cap pack = £3.48; 250 mg (blue/clear, enclosing white pellets), 56-cap pack = £4.34. Label: 25, or counselling, see below

Dose 250–500 mg every 12 hours; CHILD 2–6 years 60–120 mg every 12 hours, 6–12 years 125–250 mg every 12 hours

Counselling Swallow whole with fluid *or* swallow enclosed granules with soft food (e.g. yoghurt)

Uniphyllin Continus® (Napp)

Tablets, m/r, scored, theophylline 200 mg, net price 56-tab pack = £2.94; 300 mg, 56-tab pack = £4.77; 400 mg, 56-tab pack = £5.32. Label: 25

Dose 200 mg every 12 hours, increased according to response to 400 mg every 12 hours; CHILD 2–12 years, 9 mg/kg (up to 200 mg) every 12 hours; some children with chronic asthma may require 10–16 mg/kg (max. 400 mg) every 12 hours

Note May be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

AMINOPHYLLINE

Note Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water

Indications reversible airways obstruction, severe acute asthma

Cautions see under Theophylline

Hepatic impairment see under Theophylline

Pregnancy see under Theophylline

Breast-feeding see under Theophylline

Side-effects see under Theophylline; also allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis; hypotension, arrhythmias, and convulsions especially if given rapidly by intravenous injection

Dose

- See under preparations, below

  Note Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); measure plasma-theophylline concentration 4–6 hours after dose by

mouth and at least 5 days after starting oral treatment; measure plasma-theophylline concentration 4–6 hours after the start of intravenous infusion; narrow margin between therapeutic and toxic dose, see also notes above

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal weight for height

Aminophylline (Non-proprietary) PoM

Injection, aminophylline 25 mg/mL, net price 10-mL amp = 84p

Dose severe acute asthma or acute exacerbation of chronic obstructive pulmonary disease in patients **not** previously treated with theophylline, by slow intravenous injection over at least 20 minutes (with close monitoring), 250–500 mg (5 mg/kg), then see below; CHILD under 12 years 5 mg/kg, then see below

Severe acute asthma or acute exacerbation of chronic obstructive pulmonary disease by intravenous infusion (with close monitoring), 500–700 micrograms/kg/hour, adjusted according to plasma-theophylline concentration; ELDERLY 300 micrograms/kg/hour; CHILD under 12 years 1 mg/kg/hour, adjusted according to plasma-theophylline concentration

Note Patients taking oral theophylline or aminophylline should not normally receive a loading dose of intravenous aminophylline; plasma-theophylline concentration should be measured in all patients receiving intravenous aminophylline (see note above)

Modified release

Note Advice about modified-release theophylline preparations (see p. 181) also applies to modified-release aminophylline preparations

Phyllocontin Continus® (Napp)

Tablets, m/r, yellow, f/c, aminophylline hydrate 225 mg, net price 56-tab pack = £2.39. Label: 25

Dose ADULT and CHILD body-weight over 40 kg initially 1 tablet twice daily, increased after 1 week to 2 tablets twice daily according to plasma-theophylline concentration

Forte tablets, m/r, yellow, f/c, aminophylline hydrate 350 mg, net price 56-tab pack = £4.22. Label: 25

Dose initially 1 tablet twice daily, increased after 1 week to 2 tablets twice daily if necessary

Note *Phyllocontin Continus® Forte* tablets are for smokers and other patients with shorter theophylline half-life (see notes above)

3.1.4 Compound bronchodilator preparations

In general, patients are best treated with single-ingredient preparations, such as a selective beta$_2$ agonist (section 3.1.1.1) or ipratropium bromide (section 3.1.2), so that the dose of each drug can be adjusted. This flexibility is lost with compound bronchodilator preparations. However, a combination product may be appropriate for patients stabilised on individual components in the same proportion.

For prescribing information, see under individual drugs.

Ipratropium bromide with salbutamol (Non-proprietary) PoM

Nebuliser solution, ipratropium bromide 500 micrograms, salbutamol (as sulphate) 2.5 mg/2.5-mL vial, net price 60 unit-dose vials = £23.75

Brands include *Salipraneb, Ipramol*

Dose bronchospasm in chronic obstructive pulmonary disease, by inhalation of nebulised solution, ADULT and CHILD over 12 years, 1 vial (2.5 mL) 3–4 times daily

Glaucoma In addition to other potential side-effects acute angle-closure glaucoma has been reported with nebulised ipratropium—for details, see p. 180

Combivent® (Boehringer Ingelheim) PoM

Nebuliser solution, isotonic, ipratropium bromide 500 micrograms, salbutamol (as sulphate) 2.5 mg/2.5-mL vial, net price 60 unit-dose vials = £24.10

Dose bronchospasm in chronic obstructive pulmonary disease, by inhalation of nebulised solution, ADULT and CHILD over 12 years, 1 vial (2.5 mL) 3–4 times daily

Glaucoma In addition to other potential side-effects acute angle-closure glaucoma has been reported with nebulised ipratropium—for details, see p. 180

Duovent® (Boehringer Ingelheim) PoM

Nebuliser solution, isotonic, fenoterol hydrobromide 1.25 mg, ipratropium bromide 500 micrograms/4-mL vial, net price 20 unit-dose vials = £8.00

Dose acute severe asthma or acute exacerbation of chronic asthma, by inhalation of nebulised solution, ADULT and CHILD over 14 years, 1 vial (4 mL); may be repeated up to max. 4 vials in 24 hours

Glaucoma In addition to other potential side-effects acute angle-closure glaucoma has been reported with nebulised ipratropium—for details, see p. 180

3.1.5 Peak flow meters, inhaler devices and nebulisers

Peak flow meters

Measurement of peak flow is particularly helpful for patients who are 'poor perceivers' and hence slow to detect deterioration in their asthma, and for those with moderate or severe asthma.

Standard-range peak flow meters are suitable for both adults and children; low-range peak flow meters are appropriate for severely restricted airflow in adults and children. Patients must be given clear guidelines as to the action they should take if their peak flow falls below a certain level. Patients can be encouraged to adjust some of their own treatment (within specified limits) according to changes in peak flow rate.

Standard Range Peak Flow Meter

Conforms to standard EN ISO 23747:2007

AirZone®, range 60–720 litres/minute, net price = £4.50, replacement mouthpiece = 38p (Clement Clarke)

Medi®, range 60–800 litres/minute, net price = £4.50 (Medicare)

MicroPeak®, range 60–800 litres/minute, net price = £6.50, replacement mouthpiece = 38p (Micro Medical)

Mini-Wright®, range 60–800 litres/minute, net price = £6.86, replacement mouthpiece = 38p (Clement Clarke)

Personal Best®, range 60–800 litres/minute, net price = £6.86, replacement mouthpiece = 25p (Respironics)

Piko-1®, range 15–999 litres/minute, net price = £9.50, replacement mouthpiece = 38p (nSPIRE Health)

Pinnacle®, range 60–900 litres/minute, net price = £6.50 (Fyne Dynamics)

Pocketpeak®, range 60–800 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)

Vitalograph®, range 50–800 litres/minute, net price = £4.75 (children's coloured version also available), replacement mouthpiece = 40p (Vitalograph)

Note Readings from new peak flow meters are often lower than those obtained from old Wright-scale peak flow meters and the correct recording chart should be used

Low Range Peak Flow Meter

Compliant to standard EN 23747:2007 except for scale range

Medi®, range 40–420 litres/minute, net price = £6.50 (Medicare)

Mini-Wright®, range 30–400 litres/minute, net price = £6.90, replacement mouthpiece = 38p (Clement Clarke)

Pocketpeak®, range 50–400 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)

Note Readings from new peak flow meters are often lower than those obtained from old Wright-scale peak flow meters and the correct recording chart should be used

Drug delivery devices

Inhaler devices These include *pressurised metered-dose inhalers*, *breath-actuated inhalers*, and *dry powder inhalers*. Many patients can be taught to use a pressurised metered-dose inhaler effectively but some patients, particularly the elderly and children, find them difficult to use. *Spacer devices* (see below) can help such patients because they remove the need to coordinate actuation with inhalation. Dry powder inhalers may be useful in adults and children over 5 years who are unwilling or unable to use a pressurised metered-dose inhaler. Alternatively, breath-actuated inhalers are suitable for adults and older children provided they can use the device effectively.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation. Coughing may also occur.

The patient should be instructed carefully on the use of the inhaler and it is important to check that the inhaler continues to be used correctly because inadequate inhalation technique may be mistaken for a lack of response to the drug.

NICE guidance

Inhaler devices for children with chronic asthma (children under 5 years, August 2000; children 5–15 years, March 2002)

A child's needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

For children aged under 5 years:

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child's condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered [but see notes above].

For children aged 5–15 years:

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

Spacer devices Spacer devices remove the need for coordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring high doses of inhaled corticosteroids (see Management of Chronic Asthma table, p. 172), for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (*Volumatic®*) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.

Use and care of spacer devices Patients should inhale from the spacer device as soon as possible after actuation because the drug aerosol is very short-lived; single-dose actuation is recommended. Tidal breathing is as effective as single breaths. The device should be cleaned once a month by washing in mild detergent and then allowed to dry in air without rinsing; the mouthpiece should be wiped clean of detergent before use. Some manufacturers recommend more frequent cleaning, but this should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

Able Spacer® (Clement Clarke)

Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price standard device = £4.20; with infant, child or adult mask = £6.86

AeroChamber® Plus (GSK)

Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price standard device (blue) = £4.53, with mask (blue) = £7.56; infant device (orange) with mask = £7.56; child device (yellow) with mask = £7.56

Babyhaler® (A&H) NHS

Spacer device, for paediatric use with *Flixotide®*, and *Ventolin®* inhalers, net price = £11.34

Haleraid® (A&H) NHS

Inhalation aid, device to place over pressurised (aerosol) inhalers to aid when strength in hands is impaired (e.g. in arthritis). For use with *Flixotide®*, *Seretide®*, *Serevent®*, and *Ventolin®* inhalers. Available as *Haleraid®-120* for 120-dose inhalers and *Haleraid®-200* for 200-dose inhalers, net price = 80p

Nebuchamber® (AstraZeneca)

Spacer device, for use with *Pulmicort®* aerosol inhalers, net price = £8.56

Optichamber® (Respironics)

Spacer device, for use with all pressurised (aerosol) inhalers, net price = £4.28; with small, medium or large mask = £7.00

PARI Vortex Spacer® (Pari)

Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price with mouthpiece = £6.07 NHS; with mask for infant or child = £7.91; with adult mask = £9.97 NHS

Pocket Chamber® (nSPIRE Health)

Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price = £4.18; with infant, small, medium, or large mask = £9.75

Volumatic® (A&H)

Spacer inhaler, large-volume device. For use with *Clenil Modulite®*, *Flixotide®*, *Seretide®*, *Serevent®*, and *Ventolin®* inhalers, net price = £2.81; with paediatric mask = £2.81

Nebulisers

In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff).

A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are to deliver:

- a beta$_2$ agonist or ipratropium to a patient with an *acute exacerbation* of asthma or of chronic obstructive pulmonary disease;
- a beta$_2$ agonist, corticosteroid, or ipratropium on a *regular basis* to a patient with severe asthma or reversible airways obstruction when the patient is unable to use other inhalational devices;
- an antibiotic (such as colistin) or a mucolytic to a patient with cystic fibrosis;
- budesonide or adrenaline to a child with severe croup;
- pentamidine for the prophylaxis and treatment of pneumocystis pneumonia.

The use of nebulisers in chronic persistent asthma and chronic obstructive pulmonary disease should be considered only:

- after a review of the diagnosis;
- after review of therapy (see Management of Chronic Asthma, p. 172 and Chronic Obstructive Pulmonary Disease, p. 171) and the patient's ability to use hand-held devices;
- after increased doses of inhaled therapy from hand-held inhalers (with a spacer if necessary) have been tried for 2 weeks;
- if the patient remains breathless, despite correctly using optimal therapy

Before prescribing a nebuliser, a home trial should preferably be undertaken to monitor response for up to 2 weeks on standard treatment and up to 2 weeks on nebulised treatment. If prescribed, patients must:

- have clear instructions from a doctor, specialist nurse or pharmacist on the use of the nebuliser (including maintenance and cleaning) and on peak-flow monitoring;
- be instructed not to treat acute attacks at home without also seeking help;
- have regular follow up by a doctor, specialist nurse or physiotherapist after about 1 month and annually thereafter

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30%, it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on the droplet size, pattern of breath inhalation, and condition of the lung. Droplets with a mass median diameter of 1–5 microns are deposited in the airways and are therefore appropriate for asthma, whereas a particle size of 1–2 microns is needed for alveolar deposition of pentamidine to combat pneumocystis infection. The type of nebuliser is therefore chosen according to the deposition required and according to the viscosity of the solution (antibiotic solutions usually being more viscous).

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum gas flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

For patients at risk of hypercapnia, such as those with chronic obstructive pulmonary disease, oxygen can be dangerous and the nebuliser should be driven by air (see section 3.1). If oxygen is required, it should be given simultaneously by nasal cannula.

Tubing
The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

Ultrasonic nebulisers produce an aerosol by ultrasonic vibration of the drug solution and therefore do not require a gas flow; they are not suitable for the nebulisation of some drugs, such as dornase alfa and nebulised suspensions.

Nebuliser diluent

Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline).

Sodium Chloride (Non-proprietary) PoM
Nebuliser solution, sodium chloride 0.9%, net price 20 × 2.5 mL = £11.50
Brands include *Saline Steripoule®*, *Saline Steri-Neb®*

3.2 Corticosteroids

Corticosteroids are used for the management of reversible and irreversible airways disease. An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; clear improvement over 3–4 weeks suggests asthma.

Asthma Corticosteroids are effective in *asthma*; they reduce airway inflammation (and hence reduce oedema and secretion of mucus into the airway).

An inhaled corticosteroid is used regularly for prophylaxis of asthma when patients require a beta$_2$ agonist more than twice a week, or if symptoms disturb sleep more than once a week, or if the patient has suffered exacerbations in the last 2 years requiring a systemic corticosteroid or a nebulised bronchodilator (see Management of Chronic Asthma table, p. 172). *Regular use* of inhaled corticosteroids reduces the risk of exacerbation of asthma.

Current and previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary.

Corticosteroid inhalers must be used regularly for maximum benefit; alleviation of symptoms usually occurs 3

to 7 days after initiation. **Beclometasone dipropionate**, **budesonide**, **fluticasone propionate**, and **mometasone furoate** appear to be equally effective. Preparations that combine a corticosteroid with a long-acting $beta_2$ agonist may be helpful for patients stabilised on the individual components in the same proportion.

In adults using an inhaled corticosteroid and a long-acting $beta_2$ agonist for the prophylaxis of asthma, but who are poorly controlled, (see step 3 of the Management of Chronic Asthma table, p. 172) *Symbicort®* (budesonide with formoterol) can be used as a reliever (instead of a short-acting $beta_2$ agonist), in addition to its regular use for the prophylaxis of asthma. *Symbicort®* can also be used in this way in adults using an inhaled corticosteroid with a dose greater than beclometasone dipropionate 400 micrograms daily[1], but who are poorly controlled (see step 2 of the Management of Chronic Asthma table, p. 172). When starting this treatment, the total regular daily dose of inhaled corticosteroid should not be reduced. Patients must be carefully instructed on the appropriate dose and management of exacerbations before initiating this therapy, see *Symbicort®* p. 188. Patients using budesonide with formoterol as a reliever once a day or more should have their treatment reviewed regularly. This management approach is also used by some specialists in children 12–18 years [unlicensed]. It has not been investigated with combination inhalers containing other corticosteroids and long-acting $beta_2$ agonists.

High doses of inhaled corticosteroid can be prescribed for patients who respond only partially to standard doses with a long-acting $beta_2$ agonist or another long-acting bronchodilator (see Management of Chronic Asthma table, p. 172). High doses should be continued only if there is clear benefit over the lower dose. The recommended maximum dose of an inhaled corticosteroid should not generally be exceeded. However, if a higher dose is required, then it should be initiated and supervised by a specialist. The use of high doses of inhaled corticosteroid can minimise the requirement for an oral corticosteroid.

Systemic corticosteroid therapy may be necessary during episodes of stress, such as severe infection, or if the asthma is worsening, when higher doses are needed and access of inhaled drug to small airways may be reduced; patients may need a reserve supply of corticosteroid tablets.

Chronic obstructive pulmonary disease In *chronic obstructive pulmonary disease* inhaled corticosteroid therapy may reduce exacerbations when given in combination with an inhaled long-acting $beta_2$ agonist, see section 3.1, p. 171.

Cautions of inhaled corticosteroids

Paradoxical bronchospasm The potential for paradoxical bronchospasm (calling for discontinuation and alternative therapy) should be borne in mind—mild bronchospasm may be prevented by inhalation of a short-acting $beta_2$ agonist beforehand (or by transfer from an aerosol inhalation to a dry powder inhalation).

CFC-free inhalers Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers have been replaced by hydrofluoroalkane (HFA) propellants.

1. For standard doses of other inhaled corticosteroids, see Management of Chronic Asthma table, p. 172.

Doses for corticosteroid CFC-free pressurised metered-dose inhalers may be different from traditional CFC-containing inhalers and may differ between brands, see MHRA/CHM advice below.

For **interactions:** see Appendix 1 (corticosteroids)

MHRA/CHM advice (July 2008)

- Beclometasone dipropionate CFC-free pressurised metered-dose inhalers (*Qvar®* and *Clenil Modulite®*) are **not** interchangeable and should be prescribed by brand name; *Qvar®* has extra-fine particles, is more potent than traditional beclometasone dipropionate CFC-containing inhalers, and is approximately twice as potent as *Clenil Modulite®*;
- *Fostair®* is a combination beclometasone dipropionate and formoterol fumarate CFC-free pressurised metered-dose inhaler; *Fostair®* has extra-fine particles and is more potent than traditional beclometasone dipropionate CFC-free inhalers.

Side-effects of inhaled corticosteroids Inhaled corticosteroids have considerably fewer systemic effects than oral corticosteroids (section 6.3.2), but adverse effects have been reported.

High doses of inhaled corticosteroids (see Management of Chronic Asthma table, p. 172) used for prolonged periods can induce adrenal suppression. Inhaled corticosteroids have been associated with adrenal crisis and coma in children; excessive doses should be **avoided**. Patients using high doses of inhaled corticosteroids should be given a 'steroid card' (section 6.3.2) and specific written advice to consider corticosteroid replacement during an episode of stress, such as severe intercurrent illness or an operation.

High doses of inhaled corticosteroid have been associated with lower respiratory tract infections, including pneumonia, in older patients with chronic obstructive pulmonary disease.

Bone mineral density may be reduced following long-term inhalation of higher doses of corticosteroids, predisposing patients to osteoporosis (section 6.6). It is therefore sensible to ensure that the dose of an inhaled corticosteroid is no higher than necessary to keep a patient's asthma under good control.

In children, growth restriction associated with systemic corticosteroid therapy does not seem to occur with recommended doses of inhaled therapy; although initial growth velocity may be reduced, there appears to be no effect on achieving normal adult height. However, the height of children receiving prolonged treatment of inhaled corticosteroid should be monitored; if growth is slowed, referral to a paediatrician should be considered. Large-volume spacer devices should be used for administering inhaled corticosteroids in children under 5 years (see NICE guidance, section 3.1.5); they are also useful in older children and adults, particularly if high doses are required. Spacer devices increase airway deposition and reduce oropharyngeal deposition.

A small risk of glaucoma with prolonged high doses of inhaled corticosteroids has been reported; cataracts have also been reported with inhaled corticosteroids. Hoarseness and candidiasis of the mouth or throat have been reported, usually only with large doses (see also below). Hypersensitivity reactions (including rash and

angioedema) have been reported rarely. Other side-effects that have been reported very rarely include paradoxical bronchospasm, anxiety, depression, sleep disturbances, and behavioural changes including hyperactivity, irritability, and aggression (particularly in children); skin thinning and bruising have also been reported.

Candidiasis The risk of oral candidiasis can be reduced by using a spacer device with the corticosteroid inhaler; rinsing the mouth with water (or cleaning a child's teeth) after inhalation of a dose may also be helpful. Antifungal oral suspension or lozenges (section 12.3.2) can be used to treat oral candidiasis without discontinuing therapy.

Oral An acute attack of asthma should be treated with a short course of an oral corticosteroid starting with a high dose, see Management of Acute Asthma table, p. 173. Patients whose asthma has deteriorated rapidly usually respond quickly to corticosteroids. The dose can usually be stopped abruptly; tapering is not needed provided that the patient receives an inhaled corticosteroid in an adequate dose (apart from those on maintenance oral corticosteroid treatment or where oral corticosteroids are required for 3 or more weeks); see also Withdrawal of Corticosteroids, section 6.3.2. In patients who have needed several courses of oral corticosteroids and in whom the possibility of a period on maintenance corticosteroids is being considered, it may be useful to taper the corticosteroid dose gradually to identify a threshold dose for asthma control. This should only be done after other standard options for controlling asthma have been tried (see the Management of Chronic Asthma table, p. 172).

In chronic asthma, when the response to other drugs has been inadequate, longer term administration of an oral corticosteroid may be necessary; in such cases high doses of an inhaled corticosteroid should be continued to minimise oral corticosteroid requirements, see Management of Chronic Asthma table, p. 172. Patients taking long-term oral corticosteroids for asthma can often be transferred to an inhaled corticosteroid but the transfer must be slow, with gradual reduction in the dose of the oral corticosteroid, and at a time when the asthma is well controlled.

During an acute exacerbation of chronic obstructive pulmonary disease, prednisolone 30 mg daily should be given for 7–14 days; treatment can be stopped abruptly. Prolonged treatment with oral prednisolone is of no benefit and maintenance treatment is not normally recommended.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Regular peak-flow measurements help to optimise the dose.

Parenteral For the use of hydrocortisone injection in the emergency treatment of acute severe asthma, see Management of Acute Asthma table, p. 173.

BECLOMETASONE DIPROPIONATE
(Beclomethasone Dipropionate)

Indications prophylaxis of asthma (see also Management of Chronic Asthma, p. 172)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above

Dose

- By aerosol inhalation, see Management of Chronic Asthma, p. 172 (**important:** for *Clenil Modulite®* and *Qvar®*, see under preparations)
- By inhalation of dry powder (**important:** for *Asmabec®* and *Becodisks®*, see under preparations), 200–400 micrograms twice daily; adjusted as necessary up to 800 micrograms twice daily; CHILD over 5 years 100–200 micrograms twice daily, adjusted as necessary

Beclometasone (Non-proprietary) PoM

Dry powder for inhalation, beclometasone dipropionate 100 micrograms/metered inhalation, net price 100-dose unit = £5.36; 200 micrograms/metered inhalation, 100-dose unit = £9.89, 200-dose unit = £14.93; 400 micrograms/metered inhalation, 100-dose unit = £19.61. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Pulvinal® Beclometasone Dipropionate, Easyhaler® Beclometasone Dipropionate*

Inhalation powder, hard capsule (for use with *Cyclohaler®* device), beclometasone dipropionate 100 micrograms, net price 120-cap pack = £15.99; 200 micrograms, 120-cap pack = £25.00; 400 micrograms, 120-cap pack = £32.25. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Beclometasone Cyclocaps®*

Asmabec Clickhaler® (UCB Pharma) PoM

Dry powder for inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £6.42; 100 micrograms/metered inhalation, 200-dose unit = £9.43; 250 micrograms/metered inhalation, 100-dose unit = £11.83. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, prophylaxis of asthma, 100–400 micrograms twice daily, adjusted as necessary; max. 1 mg twice daily; CHILD 6–12 years 50–200 micrograms twice daily, adjusted as necessary

Becodisks® (A&H) PoM

Dry powder for inhalation, disks containing 8 blisters of beclometasone dipropionate 100 micrograms/blister, net price 15 disks with *Diskhaler®* device = £11.30, 15-disk refill = £10.76; 200 micrograms/blister, 15 disks with *Diskhaler®* device = £21.54, 15-disk refill = £20.99; 400 micrograms/blister, 15 disks with *Diskhaler®* device = £42.52, 15-disk refill = £41.98. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, prophylaxis of asthma, 400 micrograms twice daily, adjusted as necessary to 800 micrograms twice daily; CHILD 5–12 years 100–200 micrograms twice daily, adjusted as necessary

Clenil Modulite® (Chiesi) PoM

Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.70; 100 micrograms/metered inhalation = £7.42; 200 micrograms/metered inhalation = £16.17; 250 micrograms/metered inhalation = £16.29.

Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by aerosol inhalation, 200–400 micrograms twice daily, adjusted as necessary up to 1 mg twice daily; CHILD under 12 years 100–200 micrograms twice daily

Note *Clenil Modulite®* is not interchangeable with other CFC-free beclometasone dipropionate inhalers; the MHRA has advised (July 2008) that CFC-free beclometasone dipropionate inhalers should be prescribed by brand name, see p. 185

Dental prescribing on NHS *Clenil Modulite®* 50 micrograms/metered inhalation may be prescribed

Qvar® (TEVA UK) PoM

Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, administration; also 10 and steroid card with high doses

Autohaler® (breath-actuated aerosol inhalation), beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, administration; also 10 and steroid card with high doses

Easi-Breathe® (breath-actuated aerosol inhalation), beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose = £7.74; 100 micrograms/metered inhalation, 200-dose = £16.95. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 12 years, 50–200 micrograms twice daily, increased if necessary to max. 400 micrograms twice daily

Important When switching a patient with well-controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of *Qvar®* should be prescribed for:

- 200–250 micrograms of beclometasone dipropionate or budesonide
- 100 micrograms of fluticasone propionate

When switching a patient with poorly controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of *Qvar®* should be prescribed for 100 micrograms of beclometasone dipropionate, budesonide, or fluticasone propionate; the dose of *Qvar®* should be adjusted according to response

Note *Qvar®* is not interchangeable with other CFC-free beclometasone dipropionate inhalers; the MHRA has advised (July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name, p. 185.

Compound preparations

For prescribing information on formoterol fumarate, see section 3.1.1.1

Fostair® (Chiesi) ▼ PoM

Aerosol inhalation, beclometasone dipropionate 100 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £29.32. Label: 8, counselling, administration, 10, steroid card with high doses

Dose by aerosol inhalation, asthma, ADULT over 18 years, 1–2 puffs twice daily; max. 4 puffs daily

When switching patients from other beclometasone dipropionate and formoterol fumarate inhalers, *Fostair® 100/6* can be prescribed for patients already using beclometasone dipropionate 250 micrograms in another CFC-free inhaler; the dose of *Fostair®* should be adjusted according to response

Note The MHRA has advised (July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name, see p. 185

BUDESONIDE

Indications prophylaxis of asthma (see also Management of Chronic Asthma, p. 172); croup

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above

Dose

- See preparations below

Budesonide (Non-proprietary) PoM

Dry powder for inhalation, budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £8.86; 200 micrograms/metered inhalation, 200-dose unit = £17.71; 400 micrograms/metered inhalation, 100-dose unit = £17.71. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Easyhaler® Budesonide*

Inhalation powder, hard capsule (for use with *Cyclohaler®* device), budesonide 200 micrograms, net price 100-cap pack = £15.48; 400 micrograms, 50-cap pack = £15.48. Label: 8, counselling, administration; also 10 and steroid card with high doses

Brands include *Budesonide Cyclocaps®*

Dose by inhalation of powder, ADULT and CHILD over 12 years, 100–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 6–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening

Budelin Novolizer® (Meda) PoM

Dry powder for inhalation, budesonide 200 micrograms, net price refillable inhaler device and 100-dose cartridge = £14.86; 100-dose refill cartridge = £9.59. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, ADULT and CHILD over 12 years, 200–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 6–12 years 200–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening

Pulmicort® (AstraZeneca) PoM

Aerosol inhalation ▼, budesonide 100 micrograms/metered inhalation, net price 120-dose unit = £9.60; 200 micrograms/metered inhalation, 120-dose unit = £13.20. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by aerosol inhalation, ADULT and CHILD over 12 years, 100–400 micrograms twice daily, adjusted as necessary; max. 800 micrograms twice daily; CHILD 2–12 years, 100–400 micrograms twice daily adjusted as necessary

Turbohaler® (= dry powder inhaler), budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £11.84; 200 micrograms/metered inhalation, 100-dose unit = £11.84; 400 micrograms/metered inhalation, 50-dose unit = £13.86. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, ADULT and CHILD over 12 years, 100–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 5–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening

Respules® (= single-dose units for nebulisation), budesonide 250 micrograms/mL, net price 20 × 2-mL

(500-microgram) unit = £20.02; 500 micrograms/mL, 20 × 2-mL (1-mg) unit = £30.30. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, administration, 10, steroid card

Dose prophylaxis of asthma, by inhalation of nebulised suspension, ADULT and CHILD over 12 years, 1–2 mg twice daily, reduced to 0.5–1 mg twice daily; CHILD 3 months–12 years, 0.5–1 mg twice daily, reduced to 250–500 micrograms twice daily

Croup, by inhalation of nebulised suspension, 2 mg as a single dose (*or* as two 1-mg doses separated by 30 minutes)

Note Not suitable for use in ultrasonic nebulisers

Compound preparations

For prescribing information on formoterol fumarate, see section 3.1.1.1

Symbicort® (AstraZeneca) PoM

Symbicort 100/6 Turbohaler® (= dry powder inhaler), budesonide 100 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £33.00. Label: 8, counselling, administration

Dose by inhalation of powder, asthma maintenance therapy, 1–2 puffs twice daily increased if necessary to max. 4 puffs twice daily, reduced to 1 puff once daily if control maintained; CHILD 6–12 years, 1–2 puffs twice daily reduced to 1 puff once daily if control maintained; 12–17 years, 1–2 puffs twice daily reduced to 1 puff once daily if control maintained

Asthma, maintenance and reliever therapy, (but see p. 185) 2 puffs daily in 1–2 divided doses; for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily; up to 12 puffs daily can be used for a limited time but medical assessment should be considered; CHILD 12–18 years, see *BNF for Children*

Symbicort 200/6 Turbohaler® (= dry powder inhaler), budesonide 200 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £38.00. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, asthma maintenance therapy, 1–2 puffs twice daily increased if necessary to max. 4 puffs twice daily, reduced to 1 puff once daily if control maintained; CHILD 12–17 years 1–2 puffs twice daily reduced to 1 puff once daily if control maintained

Asthma, maintenance and reliever therapy, (but see p. 185) 2 puffs daily in 1–2 divided doses, increased if necessary to 2 puffs twice daily; for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily; up to 12 puffs daily can be used for a limited time but medical assessment should be considered; CHILD 12–18 years, see *BNF for Children*

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second <50% of predicted, 2 puffs twice daily

Symbicort 400/12 Turbohaler® (= dry powder inhaler), budesonide 400 micrograms, formoterol fumarate 12 micrograms/metered inhalation, net price 60-dose unit = £38.00. Label: 8, counselling, administration; also 10 and steroid card with high doses

Dose by inhalation of powder, asthma maintenance therapy, 1 puff twice daily increased if necessary to max. 2 puffs twice daily, reduced to 1 puff once daily if control maintained; CHILD 12–17 years 1 puff twice daily reduced to 1 puff once daily if control maintained

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second <50% of predicted, 1 puff twice daily

CICLESONIDE

Indications prophylaxis of asthma

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above

Dose

- By aerosol inhalation, 160 micrograms daily as a single dose reduced to 80 micrograms daily if control maintained; dose may be increased to max. 320 micrograms twice daily if necessary in severe asthma [unlicensed]; CHILD 12–18 years, 160 micrograms daily as a single dose reduced to 80 micrograms daily if control maintained

Alvesco® (Nycomed) PoM

Aerosol inhalation, ciclesonide 80 micrograms/metered inhalation, net price 120-dose unit = £32.83; 160 micrograms/metered inhalation, 60-dose unit = £19.31, 120-dose unit = £38.62. Label: 8, counselling, administration

FLUTICASONE PROPIONATE

Indications prophylaxis of asthma (see also Management of Chronic Asthma table, p. 172)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also *very rarely* dyspepsia, hyperglycaemia, and arthralgia

Dose

- See preparations below

Flixotide® (A&H) PoM

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 50 micrograms/blister with *Accuhaler®* device, net price = £6.38; 100 micrograms/blister with *Accuhaler®* device = £8.93; 250 micrograms/blister with *Accuhaler®* device = £21.26; 500 micrograms/blister with *Accuhaler®* device = £36.14. Label: 8, counselling, administration; also label 10 and steroid card with high doses

Note *Flixotide Accuhaler®* 250 micrograms and 500 micrograms are not indicated for children

Dose by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 16 years, 100–500 micrograms twice daily, increased according to severity of asthma; max. 1 mg twice daily (doses above 500 micrograms twice daily initiated by a specialist); CHILD 5–16 years, 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Evohaler® *aerosol inhalation*, fluticasone propionate 50 micrograms/metered inhalation, net price 120-dose unit = £5.44; 125 micrograms/metered inhalation, 120-dose unit = £21.26; 250 micrograms/metered inhalation, 120-dose unit = £36.14. Label: 8, counselling, administration; also label 10 and steroid card with high doses

Note *Flixotide Evohaler®* 125 micrograms and 250 micrograms not indicated for children

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 16 years, 100–500 micrograms twice daily, increased according to severity of asthma; max. 1 mg twice daily; (doses above 500 micrograms twice daily initiated by a specialist); CHILD 4–16 years, 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Nebules® (= single-dose units for nebulisation), fluticasone propionate 250 micrograms/mL, net price 10 × 2-mL (500-microgram) unit = £9.34; 1 mg/mL, 10 × 2-mL (2-mg) unit = £37.35. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, administration, 10, steroid card

Dose by inhalation of nebulised suspension, prophylaxis of asthma, ADULT and CHILD over 16 years, 0.5–2 mg twice daily; CHILD 4–16 years, 1 mg twice daily

Note Not suitable for use in ultrasonic nebulisers

Compound preparations

For prescribing information on salmeterol, see section 3.1.1.1

Seretide® (A&H) PoM

Seretide 100 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 100 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £31.19. Label: 8, counselling, administration

Dose by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 5 years, 1 blister twice daily, reduced to 1 blister once daily if control maintained

Seretide 250 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 250 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £35.00. Label: 8, counselling, administration, 10, steroid card

Dose by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 12 years, 1 blister twice daily

Seretide 500 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 500 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with *Accuhaler®* device, net price = £40.92. Label: 8, counselling, administration, 10, steroid card

Dose by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 12 years, 1 blister twice daily

Chronic obstructive pulmonary disease with forced expiratory volume in 1 second <60% of predicted (but see notes, p. 171), ADULT 1 blister twice daily

Note The *Scottish Medicines Consortium* has advised (December 2008) that *Seretide 500 Accuhaler®* is **not** recommended for use within NHS Scotland for chronic obstructive pulmonary disease in patients with a forced expiratory volume in 1 second (FEV_1) less than 60% and greater than 50% of the predicted normal value, with significant symptoms despite regular bronchodilator therapy, and a history of repeated exacerbations

Seretide 50 Evohaler® (aerosol inhalation), fluticasone propionate 50 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £18.00. Label: 8, counselling, administration

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 5 years, 2 puffs twice daily, reduced to 2 puffs once daily if control maintained

Seretide 125 Evohaler® (aerosol inhalation), fluticasone propionate 125 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £35.00. Label: 8, counselling, administration, 10, steroid card

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 12 years, 2 puffs twice daily

Seretide 250 Evohaler® (aerosol inhalation), fluticasone propionate 250 micrograms, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £59.48. Label: 8, counselling, administration, 10, steroid card

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 12 years, 2 puffs twice daily

MOMETASONE FUROATE

Indications prophylaxis of asthma (see also Management of Chronic Asthma, p. 172)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also pharyngitis, headache; *less commonly* palpitation

Dose

- By inhalation of powder, 200–400 micrograms as a single dose in the evening or in 2 divided doses; dose increased to 400 micrograms twice daily if necessary; CHILD not recommended

Asmanex® (Schering-Plough) ▼ PoM

Twisthaler (= dry powder inhaler), mometasone furoate 200 micrograms/metered inhalation, net price 30-dose unit = £15.70, 60-dose unit = £23.54; 400 micrograms/metered inhalation, 30-dose unit = £21.78, 60-dose unit = £36.05. Label: 8, counselling, administration, 10, steroid card

Note The *Scottish Medicines Consortium* has advised (November 2003) that *Asmanex®* is restricted for use following failure of first-line inhaled corticosteroids

3.3 Cromoglicate and related therapy, leukotriene receptor antagonists, and phosphodiesterase type-4 inhibitors

3.3.1 Cromoglicate and related therapy
3.3.2 Leukotriene receptor antagonists
3.3.3 Phosphodiesterase type-4 inhibitors

3.3.1 Cromoglicate and related therapy

The mode of action of **sodium cromoglicate** and **nedocromil** is not completely understood. They may be of value in asthma with an allergic basis, but, in practice, it is difficult to predict who will benefit; they could probably be given for 4 to 6 weeks to assess response. Dose frequency is adjusted according to response but is usually 3 to 4 times a day initially; this may subsequently be reduced. Withdrawal of sodium cromoglicate or nedocromil should be done gradually over a period of one week—symptoms of asthma may recur.

In general, *prophylaxis* with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalations (see Management of Chronic Asthma table, p. 172). There is evidence of efficacy of nedocromil in children aged 5–12 years. Sodium cromoglicate and nedocromil are of no value in the treatment of acute attacks of asthma.

Sodium cromoglicate can prevent exercise-induced asthma. However, exercise-induced asthma may reflect poor overall control and the patient should be reassessed.

Paradoxical bronchospasm If paradoxical bronchospasm occurs, a short-acting $beta_2$ agonist such as salbutamol or terbutaline (section 3.1.1.1) should be used to control symptoms; treatment with sodium cromoglicate or nedocromil should be discontinued.

Side-effects Side-effects associated with inhalation of sodium cromoglicate and nedocromil include throat irritation, cough, bronchospasm (including paradoxical bronchospasm—see above), and headache.

SODIUM CROMOGLICATE
(Sodium Cromoglycate)

Indications prophylaxis of asthma (see also Management of Chronic Asthma table, p. 172); food allergy (section 1.5.4); allergic conjunctivitis (section 11.4.2); allergic rhinitis (section 12.2.1)

Cautions see notes above; also discontinue if eosinophilic pneumonia occurs

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also rhinitis; *very rarely* eosinophilic pneumonia

Dose

- By aerosol inhalation, ADULT and CHILD over 5 years, 10 mg (2 puffs) 4 times daily, increased if necessary to 6–8 times daily; or additional dose may also be taken before exercise; maintenance, 5 mg (1 puff) 4 times daily

Intal® CFC-Free Inhaler (Sanofi-Aventis) PoM
Aerosol inhalation, sodium cromoglicate 5 mg/metered inhalation, net price 112-dose unit = £14.84. Label: 8, counselling, administration

NEDOCROMIL SODIUM

Indications prophylaxis of asthma (see also Management of Chronic Asthma table, p. 172)

Cautions see notes above

Pregnancy see p. 170

Breast-feeding see p. 170

Side-effects see notes above; also nausea, vomiting, dyspepsia, abdominal pain, pharyngitis; *rarely* taste disturbances

Dose

- By aerosol inhalation, ADULT and CHILD over 6 years 4 mg (2 puffs) 4 times daily, when control achieved may be possible to reduce to twice daily
  Counselling Regular use is necessary

Tilade® CFC-free Inhaler (Sanofi-Aventis) ▼ PoM
Aerosol inhalation, mint-flavoured, nedocromil sodium 2 mg/metered inhalation, net price 112-dose unit = £39.94. Label: 8, counselling, administration

3.3.2 Leukotriene receptor antagonists

The leukotriene receptor antagonists, **montelukast** and **zafirlukast**, block the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with an inhaled corticosteroid (see Management of Chronic Asthma table p. 172).

Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid, but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis, but they are less effective in those with severe asthma who are also receiving high doses of other drugs.

Churg-Strauss syndrome has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. Prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

Pregnancy There is limited evidence for the safe use of leukotriene receptor antagonists during pregnancy; however, they can be taken as normal in women who have shown a significant improvement in asthma not achievable with other drugs before becoming pregnant, see also p. 170.

MONTELUKAST

Indications prophylaxis of asthma, see notes above and Management of Chronic Asthma table, p. 172; symptomatic relief of seasonal allergic rhinitis in patients with asthma

Cautions **interactions:** Appendix 1 (leukotriene receptor antagonists)

Pregnancy manufacturer advises avoid unless essential, see also notes above

Breast-feeding manufacturer advises avoid unless essential

Side-effects abdominal pain, thirst; hyperkinesia (in young children), headache; *very rarely* Churg-Strauss syndrome (see notes above); dry mouth, diarrhoea, dyspepsia, nausea, vomiting, hepatic disorders, palpitation, oedema, increased bleeding, epistaxis, hypersensitivity reactions (including anaphylaxis, angioedema, and skin reactions), respiratory infections, depression, suicidal thoughts and behaviour, tremor, asthenia, dizziness, hallucinations, paraesthesia, hypoaesthesia, sleep disturbances, sleepwalking, abnormal dreams, agitation, anxiety, aggression, seizures, pyrexia, arthralgia, and myalgia, also reported

Dose

- Prophylaxis of asthma, ADULT and CHILD over 15 years, 10 mg once daily in the evening; CHILD 6 months–6 years 4 mg once daily in the evening, 6–15 years 5 mg once daily in the evening
- Seasonal allergic rhinitis, ADULT and CHILD over 15 years, 10 mg once daily in the evening

Singulair® (MSD) PoM

Chewable tablets, pink, cherry-flavoured, montelukast (as sodium salt) 4 mg, net price 28-tab pack = £25.69; 5 mg, 28-tab pack = £25.69. Label: 23, 24
Excipients include aspartame equivalent to phenylalanine 674 micrograms/4-mg tablet and 842 micrograms/5-mg tablet (section 9.4.1)

Granules, montelukast (as sodium salt) 4 mg, net price 28-sachet pack = £25.69. Counselling, administration
Counselling Granules may be swallowed or mixed with cold food (but not fluid) and taken immediately

Tablets, beige, f/c, montelukast (as sodium salt) 10 mg, net price 28-tab pack = £26.97

Note The *Scottish Medicines Consortium* has advised (June 2007) that *Singulair®* chewable tablets and granules are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2–14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; *Singulair®* chewable tablets and granules should be initiated by a specialist in paediatric asthma

ZAFIRLUKAST

Indications prophylaxis of asthma, see notes above and Management of Chronic Asthma table, p. 172

Cautions elderly; **interactions:** Appendix 1 (leukotriene receptor antagonists)

Hepatic disorders Patients or their carers should be told how to recognise development of liver disorder and advised to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise, or jaundice develop

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises caution in moderate to severe impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk; see also notes above

Breast-feeding present in milk—manufacturer advises avoid

Side-effects gastro-intestinal disturbances, respiratory infections, headache, insomnia, malaise; *rarely* bleeding disorders, hypersensitivity reactions including angioedema and skin reactions, arthralgia, myalgia, hepatitis, hyperbilirubinaemia, thrombocytopenia; *very rarely* Churg-Strauss syndrome (see notes above), agranulocytosis

Dose

- ADULT and CHILD over 12 years, 20 mg twice daily

Accolate® (AstraZeneca) PoM

Tablets, f/c, zafirlukast 20 mg, net price 56-tab pack = £17.75. Label: 23

3.3.3 Phosphodiesterase type-4 inhibitors

Roflumilast is a phosphodiesterase type-4 inhibitor with anti-inflammatory properties; it is licensed as an adjunct to bronchodilators for the maintenance treatment of patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of frequent exacerbations.

ROFLUMILAST

Indications see notes above

Cautions monitor body-weight; latent infection (such as tuberculosis, viral hepatitis, herpes infection); moderate to severe cardiac failure; history of psychiatric illness, or concomitant use of drugs likely to cause psychiatric events; **interactions:** Appendix 1 (roflumilast)

Contra-indications severe immunological disease; severe acute infectious disease; cancer (except basal cell carcinoma); concomitant treatment with immunosuppressive drugs (except short-term systemic corticosteroids)

Hepatic impairment caution in mild impairment; avoid in moderate to severe impairment

Pregnancy manufacturer advises avoid—toxicity in *animal* studies; women of child-bearing age should use effective contraception

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects diarrhoea, nausea, abdominal pain, weight loss, decreased appetite, headache, insomnia; *less commonly* gastritis, vomiting, gastro-oesophageal reflux, dyspepsia, palpitation, anxiety, tremor, vertigo, dizziness, malaise, muscle spasm, myalgia, back pain, rash; *rarely* taste disturbances, haematochezia, constipation, respiratory tract infections, depression, nervousness, suicidal ideation, gynaecomastia, raised creatine kinase, urticaria

Dose

- ADULT over 18 years, 500 micrograms once daily

Daxas® (MSD) ▼ PoM

Tablets, yellow, f/c, roflumilast 500 micrograms, net price 30-tab pack = £37.71, 90-tab pack = £113.14. Counselling, patient card

Counselling Patients should be given a patient card before starting treatment and advised to record body-weight at regular intervals

3.4 Antihistamines, hyposensitisation, and allergic emergencies

3.4.1 Antihistamines
3.4.2 Allergen Immunotherapy
3.4.3 Allergic emergencies

3.4.1 Antihistamines

All antihistamines are of potential value in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever), and they may be of some value in vasomotor rhinitis. They reduce rhinorrhoea and sneezing but are usually less effective for nasal congestion. Antihistamines are used topically in the eye (section 11.4.2), in the nose (section 12.2.1), and on the skin (section 13.3).

Oral antihistamines are also of some value in preventing urticaria and are used to treat urticarial rashes, pruritus, and insect bites and stings; they are also used in drug allergies. Injections of chlorphenamine or promethazine are used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and angioedema (section 3.4.3). For the use of antihistamines (including cinnarizine, cyclizine, and promethazine teoclate) in nausea and vomiting, see section 4.6. Buclizine is included as an anti-emetic in a preparation for migraine (section 4.7.4.1). For reference to the use of antihistamines for occasional insomnia, see section 4.1.1.

All older antihistamines cause sedation but **alimemazine** and **promethazine** may be more sedating whereas **chlorphenamine** and **cyclizine** (section 4.6) may be less so. This sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older, 'sedating' antihistamines is superior to another and patients vary widely in their response.

Non-sedating antihistamines such as **acrivastine**, **cetirizine**, **desloratadine** (an active metabolite of loratadine), **fexofenadine** (an active metabolite of terfenadine), **levocetirizine** (an isomer of cetirizine), **loratadine**, **mizolastine**, and **rupatadine** cause less sedation and psychomotor impairment than the older

antihistamines because they penetrate the blood brain barrier only to a slight extent.

Cautions and contra-indications Sedating antihistamines have significant antimuscarinic activity and they should therefore be used with caution in prostatic hypertrophy, urinary retention, susceptibility to angle-closure glaucoma, and pyloroduodenal obstruction. Caution may be required in epilepsy. Children and the elderly are more susceptible to side-effects. Many antihistamines should be avoided in acute porphyria but some are thought to be safe, see section 9.8.2. **Interactions:** Appendix 1 (antihistamines).

Hepatic impairment Sedating antihistamines should be avoided in severe liver disease—increased risk of coma.

Pregnancy Most manufacturers of antihistamines advise avoiding their use during pregnancy; however, there is no evidence of teratogenicity except for hydroxyzine where toxicity has been reported with high doses in *animal* studies. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

Breast-feeding Most antihistamines are present in breast milk in varying amounts; although not known to be harmful, most manufacturers advise avoiding their use in mothers who are breast-feeding.

Side-effects Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely, especially with high doses or in children and the elderly. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines (see also notes above). Side-effects that are more common with the older antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances.

Other rare side-effects of antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis, rashes, and photosensitivity reactions), blood disorders, liver dysfunction, and angle-closure glaucoma.

Non-sedating antihistamines

Driving Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. driving); excess alcohol should be avoided.

ACRIVASTINE

Indications symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

Cautions see notes above

Contra-indications see notes above; also hypersensitivity to triprolidine; elderly

Renal impairment avoid in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- ADULT and CHILD over 12 years, 8 mg 3 times daily

Acrivastine (Non-proprietary)

Capsules, acrivastine 8 mg, net price 12-cap pack = £2.59, 24-cap pack = £4.49. Counselling, driving

Brands include *Benadryl® Allergy Relief*

CETIRIZINE HYDROCHLORIDE

Indications symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

Cautions see notes above

Contra-indications see notes above

Renal impairment use half normal dose if eGFR 30–50 mL/minute/1.73 m^2; use half normal dose and reduce dose frequency to alternate days if eGFR 10–30 mL/minute/1.73 m^2; avoid if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- ADULT and CHILD over 12 years, 10 mg once daily; CHILD 1–2 years see *BNF for Children*, 2–6 years 2.5 mg twice daily, 6–12 years 5 mg twice daily

Cetirizine (Non-proprietary)

Tablets, cetirizine hydrochloride 10 mg, net price 30-tab pack = 95p. Counselling, driving

Dental prescribing on NHS Cetirizine 10 mg tablets may be prescribed

Oral solution, cetirizine hydrochloride 5 mg/5 mL, net price 200 mL = £2.03. Counselling, driving

Note Sugar-free versions are available and can be ordered by specifying sugar-free on the prescription

Excipients may include propylene glycol (see Excipients, p. 2)

DESLORATADINE

Note Desloratadine is a metabolite of loratadine

Indications symptomatic relief of allergic rhinitis and urticaria

Cautions see notes above

Contra-indications see notes above; also hypersensitivity to loratadine

Renal impairment use with caution in severe impairment

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; *rarely* myalgia; *very rarely* hallucinations

Dose

- 5 mg once daily; CHILD 1–6 years 1.25 mg once daily, 6–12 years 2.5 mg once daily

Neoclarityn® (Schering-Plough) PoM

Tablets, blue, f/c, desloratadine 5 mg, net price 30-tab pack = £6.77. Counselling, driving

Oral solution, desloratadine 2.5 mg/5 mL, net price 100 mL (bubblegum-flavour) = £6.77, 150 mL = £10.15. Counselling, driving

Excipients include propylene glycol (see Excipients, p. 2)

FEXOFENADINE HYDROCHLORIDE

Note Fexofenadine is a metabolite of terfenadine

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- Seasonal allergic rhinitis, 120 mg once daily; CHILD 6–12 years, 30 mg twice daily
- Chronic idiopathic urticaria, ADULT and CHILD over 12 years, 180 mg once daily

Fexofenadine (Non-proprietary) PoM
Tablets, f/c, fexofenadine hydrochloride 120 mg, net price 30-tab pack = £2.95; 180 mg, 30-tab pack = £3.68. Label: 5, counselling, driving

Telfast® (Sanofi-Aventis) PoM
Tablets, f/c, peach, fexofenadine hydrochloride 30 mg, net price 60-tab pack = £5.46; 120 mg, 30-tab pack = £5.99; 180 mg, 30-tab pack = £7.58. Label: 5, counselling, driving

LEVOCETIRIZINE HYDROCHLORIDE

Note Levocetirizine is an isomer of cetirizine

Indications symptomatic relief of allergy such as hay fever, urticaria
Cautions see notes above
Contra-indications see notes above
Renal impairment 5 mg on alternate days if eGFR 30–50 mL/minute/1.73 m^2; 5 mg every 3 days if eGFR 10–30 mL/minute/1.73 m^2; avoid if eGFR less than 10 mL/minute/1.73 m^2
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; *very rarely* weight gain
Dose
- ADULT and CHILD over 6 years, 5 mg once daily; CHILD 2–6 years 1.25 mg twice daily

Xyzal® (UCB Pharma) PoM
Tablets, f/c, levocetirizine hydrochloride 5 mg, net price 30-tab pack = £4.39. Counselling, driving
Oral solution, sugar-free, levocetirizine hydrochloride 2.5 mg/5 mL, net price 200 mL = £6.00. Counselling, driving

LORATADINE

Indications symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria
Cautions see notes above
Contra-indications see notes above
Hepatic impairment reduce dose frequency to alternate days in severe impairment
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- ADULT and CHILD over 12 years 10 mg once daily; CHILD 2–12 years, body-weight under 30 kg, 5 mg once daily; body-weight over 30 kg, 10 mg once daily

Loratadine (Non-proprietary)
Tablets, loratadine 10 mg, net price 30-tab pack = £1.20. Counselling, driving
Dental prescribing on NHS Loratadine 10 mg may be prescribed
Syrup, loratadine 5 mg/5 mL, net price 100 mL = £2.65. Counselling, driving
Excipients may include propylene glycol (see Excipients, p. 2)

MIZOLASTINE

Indications symptomatic relief of allergy such as hay fever, urticaria
Cautions see notes above
Contra-indications see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia)
Hepatic impairment manufacturer advises avoid in significant impairment
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; weight gain; anxiety, asthenia; *less commonly* arthralgia and myalgia
Dose
- ADULT and CHILD over 12 years, 10 mg once daily

Mizollen® (Sanofi-Aventis) PoM
Tablets, m/r, f/c, scored, mizolastine 10 mg, net price 30-tab pack = £5.77. Label: 25, counselling, driving

RUPATADINE

Indications symptomatic relief of allergic rhinitis, chronic idiopathic urticaria
Cautions see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia); elderly
Hepatic impairment manufacturer advises avoid—no information available
Renal impairment manufacturer advises avoid—no information available
Pregnancy manufacturer advises caution—limited information available; see also notes above
Breast-feeding manufacturer advises caution; see also notes above
Side-effects see notes above; also asthenia; *less commonly* pyrexia, irritability, increased appetite, arthralgia, and myalgia
Dose
- ADULT and CHILD over 12 years, 10 mg once daily

Rupafin® (GSK) ▼ PoM
Tablets, pink, rupatadine (as fumarate) 10 mg, net price 30-tab pack = £5.00. Counselling, driving

Sedating antihistamines

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

ALIMEMAZINE TARTRATE

(Trimeprazine tartrate)

Indications urticaria and pruritus, premedication
Cautions see notes above; see also section 4.2.1
Contra-indications see notes above; see also section 4.2.1
Hepatic impairment see notes above
Renal impairment avoid
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; see also section 4.2.1
Dose
- Urticaria and pruritus, 10 mg 2–3 times daily, in severe cases up to max. 100 mg daily has been used; ELDERLY 10 mg 1–2 times daily; CHILD under 2 years, see

BNF for Children, 2–5 years 2.5 mg 3–4 times daily, 5–12 years 5 mg 3–4 times daily

- Premedication, CHILD 2–7 years up to 2 mg/kg 1–2 hours before operation

Alimemazine (Non-proprietary) PoM

Tablets, alimemazine tartrate 10 mg, net price 28-tab pack = £4.28. Label: 2

Syrup, alimemazine tartrate 7.5 mg /5 mL, net price 100 mL = £6.83; 30 mg/5 mL, 100 mL = £7.55. Label: 2

CHLORPHENAMINE MALEATE

(Chlorpheniramine maleate)

Indications symptomatic relief of allergy such as hay fever, urticaria; emergency treatment of anaphylactic reactions (section 3.4.3)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also exfoliative dermatitis and tinnitus reported; injections may cause transient hypotension or CNS stimulation and may be irritant

Dose

- By mouth, 4 mg every 4–6 hours, max. 24 mg daily (ELDERLY max. 12 mg daily); CHILD under 1 year see *BNF for Children*, 1–2 years 1 mg twice daily; 2–6 years 1 mg every 4–6 hours, max. 6 mg daily; 6–12 years 2 mg every 4–6 hours, max. 12 mg daily
- By intramuscular injection *or* by intravenous injection over 1 minute, 10 mg, repeated if required up to max. 4 doses in 24 hours; CHILD under 6 months 250 micrograms/kg (max. 2.5 mg); 6 months–6 years 2.5 mg; 6–12 years 5 mg; these doses may be repeated if required up to max. 4 doses in 24 hours

Chlorphenamine (Non-proprietary)

Tablets, chlorphenamine maleate 4 mg, net price 28 = £1.01. Label: 2

Dental prescribing on NHS Chlorphenamine tablets may be prescribed

Oral solution, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.51. Label: 2

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Chlorphenamine oral solution may be prescribed

Injection PoM[1], chlorphenamine maleate 10 mg/mL, net price 1-mL amp = £1.79

1. PoM restriction does not apply where administration is for saving life in emergency

Piriton® (GSK Consumer Healthcare)

Tablets, yellow, scored, chlorphenamine maleate 4 mg, net price 28 = £1.62. Label: 2

Syrup, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.39. Label: 2

CLEMASTINE

Indications symptomatic relief of allergy such as hay fever, urticaria

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- 1 mg twice daily, increased up to 6 mg daily if required; INFANT under 1 year not recommended, CHILD 1–3 years 250–500 micrograms twice daily; 3–6 years 500 micrograms twice daily; 6–12 years 0.5–1 mg twice daily

Tavegil® (Novartis Consumer Health)

Tablets, scored, clemastine (as hydrogen fumarate) 1 mg. Net price 60-tab pack = £2.35. Label: 2

CYPROHEPTADINE HYDROCHLORIDE

Indications symptomatic relief of allergy such as hay fever, urticaria

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- Allergy, usual dose 4 mg 3–4 times daily; usual range 4–20 mg daily, max. 32 mg daily; INFANT under 2 years not recommended, CHILD 2–6 years 2 mg 2–3 times daily, max. 12 mg daily; 7–14 years 4 mg 2–3 times daily, max. 16 mg daily

Periactin® (MSD)

Tablets, scored, cyproheptadine hydrochloride 4 mg, net price 30-tab pack = 86p. Label: 2

HYDROXYZINE HYDROCHLORIDE

Indications pruritus

Cautions see notes above; also susceptibility to QT-interval prolongation

Contra-indications see notes above

Hepatic impairment reduce daily dose by one-third; see also notes above

Renal impairment reduce daily dose by half

Pregnancy toxicity in *animal* studies with high doses; see also notes above

Breast-feeding manufacturer advises avoid; see also notes above

Side-effects see notes above

Dose

- Pruritus, initially 25 mg at night increased if necessary to 25 mg 3–4 times daily; CHILD 1–6 years initially 5–15 mg at night increased if necessary to 50 mg daily in 3–4 divided doses; 6–12 years initially 15–25 mg at night increased if necessary to 50–100 mg daily in 3–4 divided doses; CHILD under 1 year see *BNF for Children*

Atarax® (Alliance) PoM

Tablets, both f/c, hydroxyzine hydrochloride 10 mg (orange), net price 84-tab pack = £2.18; 25 mg (green), 28-tab pack = £1.17. Label: 2

Ucerax® (UCB Pharma) PoM

Tablets NHS, f/c, scored, hydroxyzine hydrochloride 25 mg, net price 25-tab pack = £1.22. Label: 2

Syrup, hydroxyzine hydrochloride 10 mg/5 mL, net price 200-mL pack = £1.78. Label: 2

KETOTIFEN

Indications allergic rhinitis
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also excitation, irritability, nervousness; *less commonly* cystitis; *rarely* weight gain; *very rarely* Stevens-Johnson syndrome
Dose
- 1 mg twice daily with food increased if necessary to 2 mg twice daily; initial treatment in readily sedated patients 0.5–1 mg at night; CHILD 3 years and over, 1 mg twice daily

Zaditen® (Swedish Orphan) PoM
Tablets, scored, ketotifen (as hydrogen fumarate) 1 mg, net price 60-tab pack = £7.53. Label: 2, 21
Elixir, ketotifen (as hydrogen fumarate), 1 mg/5 mL, net price 300 mL (strawberry-flavoured) = £8.91. Label: 2, 21

PROMETHAZINE HYDROCHLORIDE

Indications symptomatic relief of allergy such as hay fever and urticaria; emergency treatment of anaphylactic reactions; sedation (section 4.1.1); nausea and vomiting (section 4.6)
Cautions see notes above; avoid extravasation with intravenous injection; severe coronary artery disease
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment use with caution
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also restlessness; intramuscular injection may be painful
Dose
- By mouth, 10–20 mg 2–3 times daily; CHILD 2–5 years 5–15 mg daily in 1–2 divided doses, 5–10 years 10–25 mg daily in 1–2 divided doses
- By deep intramuscular injection, 25–50 mg; max. 100 mg; CHILD 5–10 years 6.25–12.5 mg
- By slow intravenous injection in emergencies, 25–50 mg as a solution containing 2.5 mg/mL in water for injections; max. 100 mg

Promethazine (Non-proprietary) PoM
[1]Injection, promethazine hydrochloride 25 mg/mL, net price 1-mL amp = 68p, 2-mL amp = £1.20
1. PoM restriction does not apply where administration is for saving life in emergency

Phenergan® (Sanofi-Aventis)
Tablets, both blue, f/c, promethazine hydrochloride 10 mg, net price 56-tab pack = £2.85; 25 mg, 56-tab pack = £4.34. Label: 2
Dental prescribing on NHS May be prescribed as Promethazine Hydrochloride Tablets 10 mg or 25 mg
Elixir, golden, promethazine hydrochloride 5 mg/5 mL, net price 100 mL = £2.67. Label: 2
Dental prescribing on NHS May be prescribed as Promethazine Hydrochloride Oral Solution 5 mg/5 mL
Injection PoM[1], promethazine hydrochloride 25 mg/mL, net price 1-mL amp = 67p
1. PoM restriction does not apply where administration is for saving life in emergency

3.4.2 Allergen Immunotherapy

Immunotherapy using allergen vaccines containing house dust mite, animal dander (cat or dog), or extracts of grass and tree pollen can reduce symptoms of asthma and allergic rhinoconjunctivitis. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in individuals with hypersensitivity to wasp and bee stings. An oral preparation of grass pollen extract (*Grazax®*) is also licensed for grass pollen-induced rhinitis and conjuctivitis. Those requiring immunotherapy must be referred to a hospital specialist for accurate diagnosis, assessment, and treatment.

In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:
- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venoms.

Desensitising vaccines should generally be avoided or used with particular care in patients with asthma.

Desensitising vaccines should be avoided in pregnant women, in children under five years old, and in those taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction), or ACE inhibitors (risk of severe anaphylactoid reactions).

Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore, cardiopulmonary resuscitation must be immediately available and patients need to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), **even when mild**, the patient should be observed until these have **resolved completely**.

The first dose of oral grass pollen extract (*Grazax®*) should be taken under medical supervision and the patient should be monitored for 20–30 minutes.

For details of the management of anaphylaxis, see section 3.4.3.

Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

BEE AND WASP ALLERGEN EXTRACTS

Indications hypersensitivity to wasp or bee venom (see notes above)
Cautions see notes above and consult product literature
Contra-indications see notes above and consult product literature
Pregnancy avoid
Side-effects consult product literature
Dose
- By subcutaneous injection, consult product literature

Pharmalgen® (ALK-Abelló) PoM
Bee venom extract (*Apis mellifera*) or wasp venom extract (*Vespula* spp.), net price initial treatment set = £54.81 (bee), £67.20 (wasp); maintenance treatment set = £63.76 (bee), £82.03 (wasp)

GRASS AND TREE POLLEN EXTRACTS

Indications treatment of seasonal allergic hay fever due to grass or tree pollen in patients who have failed to respond to anti-allergy drugs (see notes above)

Cautions see notes above and consult product literature

Contra-indications see notes above and consult product literature

Pregnancy avoid

Side-effects see notes above and consult product literature

Dose

- See under preparations below

Pollinex® (Allergy) PoM
Grasses and rye or tree pollen extract, net price initial treatment set (3 vials) and extension course treatment (1 vial) = £450.00
Dose By subcutaneous injection, consult product literature

Grass pollen extract

Grazax® (ALK-Abelló) ▼ PoM
Oral lyophilisates (= freeze-dried tablets), grass pollen extract 75 000 units, net price 30-tab pack = £66.56. Counselling, administration
Dose ADULT and CHILD over 5 years, 1 tablet daily; start treatment at least 4 months before start of pollen season and continue for up to 3 years
Counselling Tablets should be placed under the tongue and allowed to disperse. Advise patient not to swallow for 1 minute, or eat or drink for 5 minutes after taking the tablet

Omalizumab

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). It is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid together with a long-acting $beta_2$ agonist. Omalizumab should be initiated by physicians in specialist centres experienced in the treatment of severe persistent asthma.

Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy. Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

For details on the management of anaphylaxis, see section 3.4.3.

The *Scottish Medicines Consortium* p. 4 has advised (September 2007 and March 2010) that omalizumab is accepted for restricted use within NHS Scotland as add-on therapy to improve asthma control in children (6 to 12 years), adolescents, and adults with severe persistent allergic asthma. Omalizumab is restricted to patients who are prescribed chronic systemic corticosteroids and in whom all other treatments have failed. The response should be assessed at 16 weeks and omalizumab treatment discontinued in patients who have not shown a marked improvement in overall asthma control.

NICE guidance
Omalizumab for severe persistent allergic asthma (November 2007)
Omalizumab is recommended as additional therapy for the prophylaxis of severe persistent allergic asthma in adults and children over 12 years, who cannot be controlled adequately with high-dose inhaled corticosteroids and long-acting $beta_2$ agonists in addition to leukotriene receptor antagonists, theophylline, oral corticosteroids, oral $beta_2$ agonists, and smoking cessation where clinically appropriate. The following conditions apply:

- confirmation of IgE-mediated allergy to a perennial allergen by clinical history and allergy skin testing;
- either 2 or more severe exacerbations of asthma requiring hospital admission within the previous year, or 3 or more severe exacerbations of asthma within the previous year, at least one of which required hospital admission, and a further 2 which required treatment or monitoring in excess of the patient's usual regimen, in an accident and emergency unit.

Omalizumab should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist centre, and discontinued at 16 weeks in patients who have not shown an adequate response to therapy.

NICE guidance
Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years (October 2010)
Omalizumab is **not** recommended for the treatment of severe persistent allergic asthma in children aged 6 to 11 years.

OMALIZUMAB

Indications prophylaxis of allergic asthma (see notes above)

Cautions autoimmune disease; susceptibility to helminth infection—discontinue if infection does not respond to anthelmintic

Hepatic impairment manufacturer advises caution—no information available

Renal impairment manufacturer advises caution—no information available

Pregnancy manufacturer advises avoid unless essential

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects headache; injection-site reactions; *less commonly* nausea, diarrhoea, dyspepsia, flushing, fatigue, dizziness, drowsiness, paraesthesia, influenza-like symptoms, photosensitivity, hypersensitivity reactions (including hypotension, bronchospasm, laryngoedema, rash, pruritus, serum sickness, and anaphylaxis); Churg-Strauss syndrome (see notes above), thrombocytopenia, arthralgia, myalgia, and alopecia also reported

Dose

- By subcutaneous injection, ADULT and CHILD over 6 years, according to immunoglobulin E concentration and body-weight, consult product literature

Xolair® (Novartis) ▼ PoM

Injection, powder for reconstitution, omalizumab, net price 150-mg vial = £256.15 (with solvent)

Excipients include sucrose 108 mg/vial

3.4.3 Allergic emergencies

Adrenaline (**epinephrine**) provides physiological reversal of the immediate symptoms associated with hypersensitivity reactions such as *anaphylaxis* and *angioedema*.

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by the rapid onset of respiratory and/or circulatory problems and is usually associated with skin and mucosal changes; prompt treatment is required. Patients with pre-existing asthma, especially poorly controlled asthma, are at particular risk of life-threatening reactions. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cow's milk protein, peanuts, sesame, shellfish, soy, and tree nuts may also precipitate anaphylaxis. Medicinal products particularly associated with anaphylaxis include blood products, vaccines, hyposensitising (allergen) preparations, antibacterials, aspirin and other NSAIDs, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available for injections associated with special risk. Anaphylactic reactions may also be associated with *additives and excipients* in foods and medicines. Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergenic fats or oils.

First-line treatment of anaphylaxis includes securing the airway, restoration of blood pressure (laying the patient flat and raising the legs, or in the recovery position if unconscious or nauseated and at risk of vomiting) and administration of **adrenaline** (epinephrine) injection. Adrenaline is given **intramuscularly** in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) may be appropriate for *immediate self-administration*. The dose is repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function (**important:** possible need for *intravenous route* using *dilute solution*, see below). Patients receiving beta-blockers require special consideration (see under Adrenaline, p. 198). High-flow **oxygen** administration (section 3.6) and intravenous fluids (section 9.2.2) are also of primary importance. An antihistamine (e.g. **chlorphenamine**, given by slow intravenous injection or intramuscular injection in a dose of 10 mg, see p. 194) is a useful adjunctive treatment, given after adrenaline. An intravenous corticosteroid e.g. **hydrocortisone** (as sodium succinate) in a dose of 200 mg (section 6.3.2) is of secondary value in the initial management of anaphylaxis because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected patients.

Continuing respiratory deterioration requires further treatment with **bronchodilators** including inhaled or intravenous salbutamol (see p. 177), inhaled ipratropium (see p. 180), intravenous aminophylline (see p. 181), or intravenous magnesium sulphate [unlicensed indication] (see Acute Severe Asthma, p. 171); in addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

When a patient is so ill that there is doubt about the adequacy of the circulation, the initial injection of adrenaline may need to be given as a *dilute solution by the intravenous route*; for details of cautions, dose, and strength, see under Intravenous Adrenaline (Epinephrine), p. 198.

Cardiopulmonary arrest may follow an anaphylactic reaction; resuscitation should be started immediately (see p. 139).

For advice on the management of medical emergencies in dental practice, see p. 26.

On discharge, patients should be considered for further treatment with an oral antihistamine (section 3.4.1) and an oral corticosteroid (section 6.3.2) for up to 3 days to reduce the risk of further reaction. Patients should be instructed to return to hospital if symptoms recur and to contact their general practitioner for follow-up.

Patients who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis. Avoidance of the allergen is the principal treatment; if appropriate, an adrenaline auto-injector should be given or a replacement supplied (see Self-administration of Adrenaline).

Intramuscular adrenaline (epinephrine)

The *intramuscular route* is the *first choice route* for the administration of adrenaline (epinephrine) in the management of anaphylaxis. Adrenaline is best given as an intramuscular injection into the anterolateral aspect of the middle third of the thigh; it has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site (the intravenous route should be reserved for extreme emergency when there is doubt about the adequacy of the circulation, see Intravenous Adrenaline (Epinephrine), below).

Patients with severe allergy should be instructed in the self-administration of adrenaline by intramuscular injec-

tion (for details see under Self-administration of Adrenaline (Epinephrine), below).

Prompt injection of adrenaline is of paramount importance. The following adrenaline doses are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

Dose of intramuscular injection of adrenaline (epinephrine) for anaphylaxis

Age	Dose	Volume of adrenaline **1 in 1000** (1 mg/mL)
Child under 6 years	150 micrograms	0.15 mL[1]
Child 6–12 years	300 micrograms	0.3 mL
Adult and child 12–18 years	500 micrograms	0.5 mL[2]

These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function.

1. Use suitable syringe for measuring small volume
2. 300 micrograms (0.3 mL) if child is small or prepubertal

Intravenous adrenaline (epinephrine)

Intravenous adrenaline should be given only by those experienced in its use, in a setting where patients can be carefully monitored. When the patient is severely ill and there is real doubt about the adequacy of the circulation and absorption after intramuscular injection, adrenaline (epinephrine) can be given by **slow** *intravenous injection* in a dose of 50 micrograms (0.5 mL of the dilute 1 in 10 000 adrenaline injection) repeated according to response; if multiple doses are required, adrenaline should be given as a **slow** intravenous infusion *stopping when a response has been obtained*; children may respond to as little as 1 microgram/kg (0.01 mL/kg of the dilute 1 in 10 000 adrenaline injection) by **slow** *intravenous injection*.

Great vigilance is needed to ensure that the *correct strength* of adrenaline injection is used; anaphylactic shock kits need to make a *very clear distinction* between the 1 in 10 000 strength and the 1 in 1000 strength. It is also important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

For reference to the use of the intravenous route for *cardiac resuscitation*, see section 2.7.3.

Self-administration of adrenaline (epinephrine)

Individuals at considerable risk of anaphylaxis need to carry adrenaline (epinephrine) at all times and need to be *instructed in advance* when and how to inject it; injection technique is device specific. In addition, the packs need to be labelled so that in the case of rapid collapse someone else is able to administer the adrenaline. It is important to ensure that an adequate supply is provided to treat symptoms until medical assistance is available.

Adrenaline for administration by intramuscular injection is available in 'auto-injectors' (e.g. *AnaPen*® and *EpiPen*®), pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available).

ADRENALINE/EPINEPHRINE

Indications emergency treatment of acute anaphylaxis; angioedema; cardiopulmonary resuscitation (section 2.7.3); priapism [unlicensed] (section 7.4.5)

Cautions for cautions in non-life-threatening situations, see section 2.7.3

Interactions Severe anaphylaxis in patients taking beta-blockers may not respond to adrenaline, calling for bronchodilator therapy, see intravenous salbutamol (p. 177); adrenaline can cause severe hypertension and bradycardia in those taking non-cardioselective beta-blockers. Other **interactions**, see Appendix 1 (sympathomimetics).

Renal impairment section 2.7.3

Pregnancy section 2.7.3

Breast-feeding section 2.7.3

Side-effects section 2.7.3

Dose

- Acute anaphylaxis, by intramuscular injection (preferably midpoint in anterolateral thigh) of 1 in 1000 (1 mg/mL) solution, see notes and table above
- Acute anaphylaxis when there is doubt as to the adequacy of the circulation, by slow intravenous injection of 1 in 10 000 (100 micrograms/mL) solution (extreme caution—specialist use only), see notes above

Important Intravenous route should be used with **extreme care** by specialists only, see notes above

Intramuscular or subcutaneous

[1] **Adrenaline/Epinephrine 1 in 1000** (Non-proprietary) PoM

Injection, adrenaline (as acid tartrate) 1 mg/mL, net price 0.5-mL amp = 52p; 1-mL amp = 57p

[1] **Minijet® Adrenaline 1 in 1000** (UCB Pharma) PoM

Injection, adrenaline (as hydrochloride) 1 in 1000 (1 mg/mL), net price 1 mL (with 25 gauge × 0.25 inch needle for subcutaneous injection) = £10.79, 1 mL (with 21 gauge × 1.5 inch needle for intramuscular injection) = £6.36 (both disposable syringes)

Excipients include sulphites

Intravenous

Extreme caution, see notes above

Adrenaline/Epinephrine 1 in 10 000, Dilute (Non-proprietary) PoM

Injection, adrenaline (as acid tartrate) 100 micrograms/mL, 10-mL amp, 1-mL and 10-mL prefilled syringe

Minijet® Adrenaline 1 in 10 000 (UCB Pharma) PoM

Injection, adrenaline (as hydrochloride) 1 in 10 000 (100 micrograms/mL), net price 3-mL prefilled syringe = £6.27; 10-mL prefilled syringe = £6.15

Excipients include sulphites

Intramuscular injection for self-administration

Anapen® (Lincoln Medical) PoM

Anapen® 500 (delivering a single dose of adrenaline 500 micrograms), adrenaline 1.7 mg/mL, net price 1.05-mL auto-injector device = £30.67

Excipients include sulphites

Note 0.75 mL of the solution remains in the auto-injector device after use

Dose by intramuscular injection, ADULT and CHILD body-weight over 60 kg or those at risk of severe anaphylaxis, 500 micrograms repeated after 10–15 minutes as necessary

1. PoM restriction does not apply to adrenaline injection 1 mg/mL where administration is for saving life in emergency

[1]Anapen® 300 (delivering a single dose of adrenaline 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 1.05-mL auto-injector device = £30.67
Excipients include sulphites
Note 0.75 mL of the solution remains in the auto-injector device after use
Dose by intramuscular injection, ADULT and CHILD body-weight over 30 kg, 300 micrograms repeated after 10–15 minutes as necessary

Anapen® 150 (delivering a single dose of adrenaline 150 micrograms), adrenaline 500 micrograms/mL (1 in 2000), net price 1.05-mL auto-injector device = £30.67
Excipients include sulphites
Note 0.75 mL of the solution remains in the auto-injector device after use
Dose by intramuscular injection, CHILD body–weight 15–30 kg, 150 micrograms repeated after 10–15 minutes as necessary; CHILD body-weight under 15 kg, [unlicensed] 150 micrograms repeated after 10–15 minutes as necessary

EpiPen® (ALK-Abelló) PoM
[1]EpiPen® Auto-injector 0.3 mg (delivering a single dose of adrenaline 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 2-mL auto-injector device = £28.77
Excipients include sulphites
Note 1.7 mL of the solution remains in the auto-injector device after use
Dose by intramuscular injection, ADULT and CHILD body-weight over 30 kg, 300 micrograms repeated after 5–15 minutes as necessary

Epipen® Jr Auto-injector 0.15 mg (delivering a single dose of adrenaline 150 micrograms), adrenaline 500 micrograms/mL (1 in 2000), net price 2-mL auto-injector device = £28.77
Excipients include sulphites
Note 1.7 mL of the solution remains in the auto-injector device after use
Dose by intramuscular injection, CHILD body-weight 15–30 kg, 150 micrograms (but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children) repeated after 5–15 minutes as necessary; CHILD body-weight under 15 kg, [unlicensed] 150 micrograms repeated after 5–15 minutes as necessary

Angioedema

Angioedema is dangerous if *laryngeal oedema* is present. In this circumstance **adrenaline (epinephrine)** injection and **oxygen** should be given as described under Anaphylaxis (see p. 197); antihistamines and corticosteroids should also be given. Tracheal intubation may be necessary.

Hereditary angioedema The administration of **C1-esterase inhibitor**, an endogenous complement blocker derived from human plasma, (in fresh frozen plasma or in partially purified form) can terminate acute attacks of *hereditary angioedema*, but is not practical for long-term prophylaxis; it can also be used for short-term prophylaxis before surgery or dental procedures [unlicensed indication]. **Icatibant** is licensed for the treatment of acute attacks of hereditary angioedema in adults with C1-esterase inhibitor deficiency.

Tranexamic acid (section 2.11) and **danazol** (section 6.7.2) [unlicensed indication] are used for short-term and long-term prophylaxis of hereditary angioedema. Short-term prophylaxis with tranexamic acid or danazol is started several days before planned procedures (e.g. dental work) and continued for 2–5 days afterwards. Danazol should be avoided in children because of its androgenic effects.

C1-ESTERASE INHIBITOR

Indications acute attacks of hereditary angioedema; prophylaxis prior to surgery or major dental procedures [unlicensed]
Cautions vaccination against hepatitis A, p. 754 and hepatitis B, p. 755 may be required
Pregnancy manufacturer advises avoid unless essential
Breast-feeding manufacturer advises use only if potential benefit outweighs risk—no information available
Side-effects *rarely* injection-site reactions, hypersensitivity reactions (including anaphylaxis)
Dose
- By slow intravenous injection or intravenous infusion, ADULT and CHILD 20 units/kg

Berinert® (CSL Behring) ▼ PoM
Injection, powder for reconstitution C1-esterase inhibitor, net price 500-unit vial = £550.00
Electrolytes Na^+ 2.1 mmol/10 mL vial

ICATIBANT

Indications acute attacks of hereditary angioedema in patients with C1-esterase inhibitor deficiency
Cautions ischaemic heart disease, stroke
Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in *animal* studies
Breast-feeding manufacturer advises avoid for 12 hours after administration
Side-effects dizziness, headache, injection-site reactions, rash, pruritus, erythema
Dose
- By subcutaneous injection, ADULT over 18 years, 30 mg as a single dose, repeated after 6 hours if necessary; a third dose may be given after a further 6 hours (max. 3 doses in 24 hours)

Firazyr® (Shire HGT) ▼ PoM
Injection, icatibant (as acetate) 10 mg/mL, net price 3-mL prefilled syringe = £1395.00

3.5 Respiratory stimulants and pulmonary surfactants

3.5.1 Respiratory stimulants
3.5.2 Pulmonary surfactants

3.5.1 Respiratory stimulants

Respiratory stimulants (analeptic drugs) have a limited place in the treatment of ventilatory failure in patients with chronic obstructive pulmonary disease. They are effective only when given by intravenous injection or infusion and have a short duration of action. Their use has largely been replaced by ventilatory support includ-

1. PoM restriction does not apply to adrenaline injection 1 mg/mL where administration is for saving life in emergency

ing nasal intermittent positive pressure ventilation. However, occasionally when ventilatory support is contra-indicated and in patients with hypercapnic respiratory failure who are becoming drowsy or comatose, respiratory stimulants in the short term may arouse patients sufficiently to co-operate and clear their secretions.

Respiratory stimulants can also be harmful in respiratory failure since they stimulate non-respiratory as well as respiratory muscles. They should only be given under **expert supervision** in hospital and must be combined with active physiotherapy. There is at present no oral respiratory stimulant available for long-term use in chronic respiratory failure.

Doxapram is given by continuous intravenous infusion. Frequent arterial blood gas and pH measurements are necessary during treatment to ensure correct dosage.

For the use of **caffeine** in the management of neonatal apnoea, see *BNF for Children*.

DOXAPRAM HYDROCHLORIDE

Indications see under Dose

Cautions give with oxygen in severe irreversible airways obstruction or severely decreased lung compliance (because of increased work load of breathing); give with beta$_2$ agonist in bronchoconstriction; hypertension (avoid if severe), impaired cardiac reserve; phaeochromocytoma; **interactions:** Appendix 1 (doxapram)

Contra-indications severe hypertension; status asthmaticus; coronary artery disease; hyperthyroidism; epilepsy and other convulsive disorders; physical obstruction of respiratory tract; cerebral oedema, cerebrovascular accident

Hepatic impairment use with caution

Pregnancy no evidence of harm, but manufacturer advises avoid unless benefit outweighs risk

Side-effects nausea, vomiting; hypertension, tachycardia, bradycardia, extrasystoles, arrhythmias, chest pain, flushing; dyspnoea, cough, bronchospasm, laryngospasm; pyrexia, headache, dizziness, hyperactivity, confusion, hallucination, convulsions; urinary retention, incontinence, perineal warmth; muscle spasms

Dose

- Postoperative respiratory depression, by intravenous injection over at least 30 seconds, 1–1.5 mg/kg repeated if necessary after intervals of 1 hour *or* alternatively by intravenous infusion, 2–3 mg/minute adjusted according to response; CHILD not recommended
- Acute respiratory failure, by intravenous infusion, 1.5–4 mg/minute adjusted according to response (given concurrently with oxygen and whenever possible monitor with frequent measurement of blood gas tensions); CHILD not recommended
- Neonatal apnoea, see *BNF for Children*

Dopram® (Goldshield) PoM

Injection, doxapram hydrochloride 20 mg/mL. Net price 5-mL amp = £3.00

Intravenous infusion, doxapram hydrochloride 2 mg/mL in glucose 5%. Net price 500-mL bottle = £21.33

3.5.2 Pulmonary surfactants

Pulmonary surfactants are used in the management of respiratory distress syndrome (hyaline membrane disease) in neonates and preterm neonates. They may also be given prophylactically to those considered at risk of developing the syndrome.

Cautions Continuous monitoring is required to avoid hyperoxaemia caused by rapid improvement in arterial oxygen concentration.

Side-effects Pulmonary haemorrhage and bradycardia have been rarely associated with pulmonary surfactants; obstruction of the endotracheal tube by mucous secretions and intracranial haemorrhage have also been reported.

BERACTANT

Indications treatment of respiratory distress syndrome in preterm neonates over 700 g; prophylaxis of respiratory distress syndrome in preterm neonates less than 32 weeks post-menstrual age

Cautions see notes above and consult product literature

Side-effects see notes above

Dose

- By endotracheal tube, phospholipid 100 mg/kg equivalent to a volume of 4 mL/kg, preferably within 8 hours of birth (preferably within 15 minutes of birth for prophylaxis); dose may be repeated within 48 hours at intervals of at least 6 hours for up to 4 doses

Survanta® (Abbott) PoM

Suspension, beractant (bovine lung extract) providing phospholipid 25 mg/mL, with lipids and proteins, net price 8-mL vial = £306.43

PORACTANT ALFA

Indications treatment of respiratory distress syndrome or hyaline membrane disease in neonates over 700 g; prophylaxis of respiratory distress syndrome in preterm neonates 24–32 weeks post-menstrual age

Cautions see notes above and consult product literature

Side-effects see notes above; also *rarely* hypotension

Dose

- By endotracheal tube, *treatment*, 100–200 mg/kg; further doses of 100 mg/kg may be repeated at intervals of 12 hours; max. total dose 300–400 mg/kg; *prophylaxis*, 100–200 mg/kg soon after birth (preferably within 15 minutes); further doses of 100 mg/kg may be repeated 6–12 hours later and after a further 12 hours if still intubated; max. total dose 300–400 mg/kg

Curosurf® (Chiesi) PoM

Suspension, poractant alfa (porcine lung phospholipid fraction) 80 mg/mL, net price 1.5-mL vial = £281.64; 3-mL vial = £547.40

3.6 Oxygen

Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; the administration of an inappropriate concentration of oxygen can have serious or even fatal consequences.

Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near–normal oxygen saturation; in most acutely ill patients with a normal or low arterial carbon dioxide (P_aCO_2), oxygen saturation should be 94–98% oxygen saturation. However, in some clinical situations such as cardiac arrest and carbon monoxide poisoning (see also Emergency Treatment of Poisoning, p. 40) it is more appropriate to aim for the highest possible oxygen saturation until the patient is stable. A lower target of 88–92% oxygen saturation is indicated for patients at risk of hypercapnic respiratory failure, see below.

High concentration oxygen therapy is safe in uncomplicated cases of conditions such as pneumonia, pulmonary thromboembolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions low arterial oxygen (P_aO_2) is usually associated with low or normal arterial carbon dioxide (P_aCO_2), and therefore there is little risk of hypoventilation and carbon dioxide retention.

In acute severe asthma, the arterial carbon dioxide (P_aCO_2) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide (P_aCO_2) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients at risk of hypercapnic respiratory failure, which is more likely in those with:

- chronic obstructive pulmonary disease;
- advanced cystic fibrosis;
- severe non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target oxygen saturation of 88–92%. The aim is to provide the patient with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis. Patients may carry an *oxygen alert card*, see section 3.1.

Domiciliary oxygen Oxygen should only be prescribed for use in the home after careful evaluation in hospital by respiratory experts.

Patients should be advised of the risks of continuing to smoke when receiving oxygen therapy, including the risk of fire. Smoking cessation therapy (section 4.10.2) should be tried before home oxygen prescription.

Air travel Some patients with arterial hypoxaemia require supplementary oxygen for air travel. The patient's requirement should be discussed with the airline before travel.

Long-term oxygen therapy

Long-term administration of oxygen (usually at least 15 hours daily) prolongs survival in some patients with chronic obstructive pulmonary disease.

Assessment for long-term oxygen therapy requires measurement of arterial blood gas tensions. Measurements should be taken on 2 occasions at least 3 weeks apart to demonstrate clinical stability, and not sooner than 4 weeks after an acute exacerbation of the disease. Long-term oxygen therapy should be considered for patients with:

- chronic obstructive pulmonary disease with $P_aO_2 < 7.3$ kPa when breathing air during a period of clinical stability;
- chronic obstructive pulmonary disease with P_aO_2 7.3–8 kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, peripheral oedema, or evidence of pulmonary hypertension;
- severe chronic asthma with $P_aO_2 < 7.3$ kPa or persistent disabling breathlessness;
- interstitial lung disease with $P_aO_2 < 8$ kPa and in patients with $P_aO_2 > 8$ kPa with disabling dyspnoea;
- cystic fibrosis when $P_aO_2 < 7.3$ kPa *or* if P_aO_2 7.3–8 kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, pulmonary hypertension, or peripheral oedema;
- pulmonary hypertension, without parenchymal lung involvement when $P_aO_2 < 8$ kPa;
- neuromuscular or skeletal disorders, after specialist assessment;
- obstructive sleep apnoea despite continuous positive airways pressure therapy, after specialist assessment;
- pulmonary malignancy or other terminal disease with disabling dyspnoea;
- heart failure with daytime $P_aO_2 < 7.3$ kPa when breathing air or with nocturnal hypoxaemia;
- paediatric respiratory disease, after specialist assessment.

Increased respiratory depression is seldom a problem in patients with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occur.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness not relieved by other treatment in patients with severe chronic obstructive pulmonary disease, interstitial lung disease, heart failure, and in palliative care. It is important, however, that the patient does not rely on oxygen instead of obtaining medical help or taking more specific treatment. Short-burst oxygen therapy can be used

to improve exercise capacity and recovery; it should only be continued if there is proven improvement in breathlessness or exercise tolerance.

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for patients on long-term oxygen therapy who need to be away from home on a regular basis. Patients who are not on long-term oxygen therapy can be considered for ambulatory oxygen therapy if there is evidence of exercise-induced oxygen desaturation and of improvement in blood oxygen saturation and exercise capacity with oxygen. Ambulatory oxygen therapy is not recommended for patients with heart failure or those who smoke.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as **oxygen cylinders**. Oxygen flow can be adjusted as the cylinders are equipped with an oxygen flow meter with 'medium' (2 litres/minute) and 'high' (4 litres/minute) settings.

Oxygen concentrators are more economical for patients who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis (see below). A concentrator is recommended for a patient who requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a 'Y' connection.

A nasal cannula is usually preferred for long-term oxygen therapy from an oxygen concentrator. It can, however, produce dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the patient to talk, eat, and drink, but the concentration of oxygen is not controlled; this may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the patient is underventilating.

Arrangements for supplying oxygen

The following oxygen services may be ordered in England and Wales:

- emergency oxygen;
- short-burst (intermittent) oxygen therapy;
- long-term oxygen therapy;
- ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The supplier will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the patient's consent to pass on the patient's details to the supplier and the fire brigade. The supplier will contact the patient to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the patient to use the equipment.

The clinician should send order forms to the supplier by facsimile (see below); a copy of the HOOF should be sent to the Primary Care Trust or Local Health Board. The supplier will continue to provide the service until a revised order is received, or until notified that the patient no longer requires the home oxygen service.

Eastern England	BOC Medical *to order*: Tel: 0800 136 603 Fax: 0800 169 9989
North East South West	Air Liquide *to order*: Tel: 0808 202 2229 Fax: 0191 497 4340
South London South East Coast South Central	Air Liquide *to order*: Tel: 0500 823 773 Fax: 0800 781 4610
North West Yorkshire and Humberside East Midlands West Midlands North London Wales	Air Products *to order*: Tel: 0800 373 580 Fax: 0800 214 709

In **Scotland** refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. In **Northern Ireland** oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. In **Scotland** and **Northern Ireland** prescriptions for oxygen cylinders and accessories can be dispensed by pharmacists contracted to provide domiciliary oxygen services.

3.7 Mucolytics

Mucolytics are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with chronic obstructive pulmonary disease and a chronic productive cough, mucolytics can reduce exacerbations; mucolytic therapy should be stopped if there is no benefit after a 4-week trial. Steam inhalation with postural drainage is effective in bronchiectasis and in some cases of chronic bronchitis.

Mucolytics should be used with caution in those with a history of peptic ulceration because they may disrupt the gastric mucosal barrier.

For reference to dornase alfa and hypertonic saline, see below.

CARBOCISTEINE

Indications reduction of sputum viscosity, see notes above

Cautions see notes above

Contra-indications active peptic ulceration

Pregnancy manufacturer advises avoid in first trimester

Breast-feeding no information available

Side-effects *rarely* gastro-intestinal bleeding; hypersensitivity reactions (including rash and anaphylaxis) also reported

Dose

- Initially 2.25 g daily in divided doses, then 1.5 g daily in divided doses as condition improves; CHILD 2–5 years 62.5–125 mg 4 times daily, 5–12 years 250 mg 3 times daily

Carbocisteine (Sanofi-Aventis) PoM

Capsules, carbocisteine 375 mg, net price 120-cap pack = £16.03

Brands include *Mucodyne®*

Oral liquid, carbocisteine 125 mg/5 mL, net price 300 mL = £4.39; 250 mg/5 mL, 300 mL = £5.61

Brands include *Mucodyne® Paediatric* 125 mg/5 mL (cherry- and raspberry-flavoured) and *Mucodyne®* 250 mg/5 mL (cinnamon- and rum-flavoured)

ERDOSTEINE

Indications symptomatic treatment of acute exacerbations of chronic bronchitis

Cautions see notes above

Hepatic impairment manufacturer advises max. 300 mg daily in mild to moderate impairment; avoid in severe impairment

Renal impairment avoid if eGFR less than 25 mL/minute/1.73 m^2—no information available

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects *very rarely* nausea, vomiting, diarrhoea, abdominal pain, taste disturbance, headache, rash, and urticaria

Dose

- ADULT over 18 years, 300 mg twice daily for up to 10 days

Erdotin® (Galen) ▼ PoM

Capsules, yellow/green, erdosteine 300 mg, net price 20-cap pack = £5.75

Note The *Scottish Medicines Consortium* (October 2007) has advised that erdosteine (*Erdotin®*) is not recommended for the symptomatic treatment of acute exacerbations of chronic bronchitis

MECYSTEINE HYDROCHLORIDE

(Methyl Cysteine Hydrochloride)

Indications reduction of sputum viscosity

Cautions see notes above

Pregnancy manufacturer advises avoid

Breast-feeding manufacturer advises avoid

Dose

- 200 mg 4 times daily for 2 days, then 200 mg 3 times daily for 6 weeks, then 200 mg twice daily; CHILD 5–12 years 100 mg 3 times daily

Visclair® (Ranbaxy)

Tablets, yellow, s/c, e/c, mecysteine hydrochloride 100 mg, net price 100 = £17.65. Label: 5, 22, 25

Dornase alfa

Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA). It is used in cystic fibrosis and is administered by inhalation using a jet nebuliser (section 3.1.5).

DORNASE ALFA

Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase)

Indications management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function

Pregnancy no evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful—manufacturer advises caution

Side-effects *rarely* dyspepsia, chest pain, dysphonia, dyspnoea, pharyngitis, laryngitis, pyrexia, conjunctivitis, rhinitis, rash, urticaria

Dose

- ADULT and CHILD over 5 years, by inhalation of nebulised solution (by jet nebuliser), 2500 units (2.5 mg) once daily (patients over 21 years may benefit from twice daily dosage)

Pulmozyme® (Roche) PoM

Nebuliser solution, dornase alfa 1000 units (1 mg)/mL. Net price 2.5-mL (2500 units) vial = £16.55

Note For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable

Hypertonic sodium chloride

Nebulised hypertonic sodium chloride solution (3–7%) is used to mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis). Temporary irritation, such as coughing, hoarseness, or reversible bronchoconstriction may occur; an inhaled bronchodilator can be used before treatment with hypertonic sodium chloride to reduce the risk of these adverse effects.

MucoClear® 6% (Pari)

Nebuliser solution, sodium chloride 6%, net price 20 × 4 mL = £12.98; 60 × 4 mL = £27.00

Dose by inhalation of nebulised solution, 4 mL twice daily

Nebusal® 7% (Forest)

Nebuliser solution, sodium chloride 7%, net price 60 × 4 mL = £27.00

Dose by inhalation of nebulised solution, 4 mL up to twice daily

3.8 Aromatic inhalations

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis; boiling water should not be

used owing to the risk of scalding. Inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis. Menthol and eucalyptus inhalation is used to relieve sinusitis affecting the maxillary antrum (section 12.2.2)

Children The use of strong aromatic decongestants (applied as rubs or to pillows) is not advised for infants under the age of 3 months. Carers of young infants in whom nasal obstruction with mucus is a problem can readily be taught appropriate techniques of suction aspiration but sodium chloride 0.9% given as nasal drops is preferred.

Benzoin Tincture, Compound, BP (Friars' Balsam)

Tincture, balsamic acids approx. 4.5%. Label: 15

Dose add one teaspoonful to a pint of hot, **not** boiling, water and inhale the vapour

Menthol and Eucalyptus Inhalation, BP 1980

Inhalation, racementhol or levomenthol 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL

Dose add one teaspoonful to a pint of hot, **not** boiling, water and inhale the vapour

Dental prescribing on the NHS Menthol and Eucalyptus Inhalation BP, 1980 may be prescribed

3.9 Cough preparations

3.9.1 Cough suppressants
3.9.2 Demulcent and expectorant cough preparations

3.9.1 Cough suppressants

Cough may be a symptom of an underlying disorder, such as asthma (section 3.1.1), gastro-oesophageal reflux disease (section 1.1), or rhinitis (section 12.2.1), which should be addressed before prescribing cough suppressants. Cough may be a side-effect of another drug, such as an ACE inhibitor (section 2.5.5.1), or it can be associated with smoking or environmental pollutants. Cough can also have a significant habit component. When there is no identifiable cause, cough suppressants may be useful, for example if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Codeine may be effective but it is constipating and can cause dependence; **dextromethorphan** and **pholcodine** have fewer side-effects.

Sedating antihistamines are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

Children The use of over-the-counter cough suppressants containing codeine should be avoided in children under 18 years. Cough suppressants containing similar opioid analgesics such as dextromethorphan and pholcodine are not generally recommended in children and should be avoided in children under 6 years.

MHRA/CHM advice (March 2008 and February 2009) Over-the-counter cough and cold medicines for children

Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine, or triprolidine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- phenylephrine, pseudoephedrine, ephedrine, oxymetazoline, or xylometazoline (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried, but treatment should be restricted to 5 days or less. Children should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

MHRA/CHM advice (October 2010) Over-the-counter codeine-containing liquid medicines for children

Children under 18 years should not use codeine-containing over-the-counter liquid medicines for cough suppression

CODEINE PHOSPHATE

Indications dry or painful cough; diarrhoea (section 1.4.2); pain (section 4.7.2)

Cautions see notes above and section 4.7.2

Contra-indications section 4.7.2

Hepatic impairment section 4.7.2

Renal impairment section 4.7.2

Pregnancy section 4.7.2

Breast-feeding section 4.7.2

Side-effects section 4.7.2

Dose

- See under preparations below

Codeine Linctus, BP

Linctus (= oral solution), codeine phosphate 15 mg/5 mL. Net price 100 mL = 35p (diabetic, 39p)

Brands include *Galcodine®*

Dose 5–10 mL 3–4 times daily; CHILD (but not generally recommended, see MHRA advice above) 5–12 years, 2.5–5 mL

Note BP directs that when Diabetic Codeine Linctus is prescribed, Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled 'Diabetic Codeine Linctus', shall be dispensed or supplied

Codeine Linctus, Paediatric, BP

Linctus (= oral solution), codeine phosphate 3 mg/5 mL. Net price 100 mL = 18p

Brands include *Galcodine® Paediatric* (sugar-free)

Dose CHILD (but not generally recommended, see MHRA advice above) 2–5 years 5 mL 3–4 times daily

Note BP directs that Paediatric Codeine Linctus may be prepared extemporaneously by diluting Codeine Linctus with a suitable vehicle in accordance with the manufacturer's instructions

Other preparations

Tablets, syrup, and injection section 4.7.2

PHOLCODINE

Indications dry cough
Cautions asthma; chronic, persistent, or productive cough; **interactions**: Appendix 1 (pholcodine)
Contra-indications chronic bronchitis, chronic obstructive pulmonary disease, bronchiectasis, patients at risk of respiratory failure
Hepatic impairment avoid
Renal impairment use with caution; avoid in severe impairment
Pregnancy manufacturer advises avoid unless potential benefit outweighs risk
Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—no information available
Side-effects nausea, vomiting, constipation, sputum retention, drowsiness, dizziness, excitation, confusion, rash
Dose
- See under preparations below

Pholcodine Linctus, BP
Linctus (= oral solution), pholcodine 5 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 1%. Net price 100 mL = 31p
Brands include *Pavacol-D*® (sugar-free), *Galenphol*® (sugar-free)
Dose 5–10 mL 3–4 times daily; CHILD (but not generally recommended, see notes above) 6–12 years 2.5–5 mL

Pholcodine Linctus, Strong, BP
Linctus (= oral solution), pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%. Net price 100 mL = 44p
Dose ADULT and CHILD over 12 years, 5 mL 3–4 times daily
Brands include *Galenphol*®

Galenphol® (Thornton & Ross)
Paediatric linctus (= oral solution), orange, sugar-free, pholcodine 2 mg/5 mL. Net price 90-mL pack = £1.20
Dose CHILD (but not generally recommended, see notes above) 6–12 years 10 mL 3 times daily

Palliative care

Diamorphine and methadone have been used to control distressing cough in terminal lung cancer although morphine is now preferred (see p. 22). In other circumstances they are contra-indicated because they induce sputum retention and ventilatory failure as well as causing opioid dependence. Methadone linctus should be avoided because it has a long duration of action and tends to accumulate.

METHADONE HYDROCHLORIDE

Indications cough in terminal disease
Cautions section 4.7.2
Contra-indications section 4.7.2
Hepatic impairment section 4.7.2
Renal impairment section 4.7.2
Pregnancy section 4.7.2
Breast-feeding section 4.7.2
Side-effects section 4.7.2; longer-acting than morphine therefore effects may be cumulative
Dose
- See below

Methadone Linctus CD
Linctus (= oral solution), methadone hydrochloride 2 mg/5 mL in a suitable vehicle with a tolu flavour. Label: 2
Dose 2.5–5 mL every 4–6 hours, reduced to twice daily on prolonged use

MORPHINE HYDROCHLORIDE

Indications cough in terminal disease (see also Prescribing in Palliative Care p. 22)
Cautions section 4.7.2
Contra-indications section 4.7.2
Hepatic impairment section 4.7.2
Renal impairment section 4.7.2
Pregnancy section 4.7.2
Breast-feeding section 4.7.2
Side-effects section 4.7.2
Dose
- Initially 5 mg every 4 hours

Preparations
Section 4.7.2

3.9.2 Demulcent and expectorant cough preparations

Demulcent cough preparations contain soothing substances such as syrup or glycerol and some patients believe that such preparations relieve a dry irritating cough. Preparations such as **simple linctus** have the advantage of being harmless and inexpensive; **paediatric simple linctus** is particularly useful in children.

Expectorants are claimed to promote expulsion of bronchial secretions, but there is no evidence that any drug can specifically facilitate expectoration.

Compound preparations are on sale to the public for the treatment of cough and colds but should not be used in children under 6 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time, see MHRA/CHM advice, p. 204.

Simple Linctus, BP
Linctus (= oral solution), citric acid monohydrate 2.5% in a suitable vehicle with an anise flavour. Net price 200 mL = 55p
Dose ADULT and CHILD over 12 years 5 mL 3–4 times daily
A sugar-free version is also available

Simple Linctus, Paediatric, BP
Linctus (= oral solution), citric acid monohydrate 0.625% in a suitable vehicle with an anise flavour. Net price 200 mL = 82p
Dose CHILD 1 month–12 years 5–10 mL 3–4 times daily
A sugar-free version is also available

3.10 Systemic nasal decongestants

Nasal decongestants for administration by mouth may not be as effective as preparations for local application (section 12.2.2) but they do not give rise to rebound nasal congestion on withdrawal. **Pseudoephedrine** is

available over the counter; it has few sympathomimetic effects.

Systemic decongestants should be used with **caution** in diabetes, hypertension, hyperthyroidism, susceptibility to angle-closure glaucoma, prostatic hypertrophy, ischaemic heart disease, and should be **avoided** in patients taking monoamine oxidase inhibitors; **interactions:** Appendix 1 (sympathomimetics).

PSEUDOEPHEDRINE HYDROCHLORIDE

Indications see notes above

Cautions see notes above

Hepatic impairment manufacturer advises caution in severe impairment

Renal impairment manufacturer advises caution in moderate to severe impairment

Pregnancy defective closure of the abdominal wall (gastroschisis) reported very rarely in newborns after first trimester exposure

Breast-feeding amount too small to be harmful

Side-effects tachycardia, anxiety, restlessness, insomnia; *rarely* hallucinations, rash; *very rarely* angle-closure glaucoma; urinary retention also reported

Dose

- 60 mg 3–4 times daily; CHILD 6–12 years 30 mg 3–4 times daily

[1] **Galpseud®** (Thornton & Ross)

Tablets, pseudoephedrine hydrochloride 60 mg, net price 24-tab pack = £2.00

Linctus, orange, sugar-free, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = 70p

[1] **Sudafed®** (McNeil)

Tablets, red, f/c, pseudoephedrine hydrochloride 60 mg, net price 24 = £2.12

Elixir, red, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = £1.05

1. Can be sold to the public provided no more than 720 mg of pseudoephedrine salts are supplied, and ephedrine base (or salts) are not supplied at the same time; for details see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

4 Central nervous system

4.1 Hypnotics and anxiolytics 207
4.1.1 Hypnotics 208
4.1.2 Anxiolytics 213
4.1.3 Barbiturates 215
4.2 Drugs used in psychoses and related disorders 215
4.2.1 Antipsychotic drugs 216
4.2.2 Antipsychotic depot injections 227
4.2.3 Antimanic drugs 229
4.3 Antidepressant drugs 232
4.3.1 Tricyclic and related antidepressant drugs 233
4.3.2 Monoamine-oxidase inhibitors 237
4.3.3 Selective serotonin re-uptake inhibitors 239
4.3.4 Other antidepressant drugs 242
4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder 245
4.5 Drugs used in the treatment of obesity 248
4.5.1 Anti-obesity drugs acting on the gastro-intestinal tract 248
4.5.2 Centrally acting appetite suppressants 249
4.6 Drugs used in nausea and vertigo 249
4.7 Analgesics 257
4.7.1 Non-opioid analgesics and compound analgesic preparations 257
4.7.2 Opioid analgesics 262
4.7.3 Neuropathic pain 272
4.7.4 Antimigraine drugs 273
4.7.4.1 Treatment of acute migraine 273
4.7.4.2 Prophylaxis of migraine 277
4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias 278
4.8 Antiepileptic drugs 279
4.8.1 Control of the epilepsies 279
4.8.2 Drugs used in status epilepticus 294
4.8.3 Febrile convulsions 297
4.9 Drugs used in parkinsonism and related disorders 297
4.9.1 Dopaminergic drugs used in Parkinson's disease 298
4.9.2 Antimuscarinic drugs used in parkinsonism 306
4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders 307
4.10 Drugs used in substance dependence 309
4.10.1 Alcohol dependence 310
4.10.2 Nicotine dependence 311
4.10.3 Opioid dependence 314
4.11 Drugs for dementia 317

4.1 Hypnotics and anxiolytics

4.1.1 Hypnotics
4.1.2 Anxiolytics
4.1.3 Barbiturates

Most anxiolytics ('sedatives') will induce sleep when given at night and most hypnotics will sedate when given during the day. Prescribing of these drugs is widespread but dependence (both physical and psychological) and tolerance occur. This may lead to difficulty in withdrawing the drug after the patient has been taking it regularly for more than a few weeks (see Dependence and Withdrawal, below). Hypnotics and anxiolytics should therefore be reserved for short courses to alleviate acute conditions after causal factors have been established.

Benzodiazepines are the most commonly used anxiolytics and hypnotics; they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors. Older drugs such as meprobamate and barbiturates are **not** recommended—they have more side-effects and interactions than benzodiazepines and are much more dangerous in overdosage.

Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

Driving Hypnotics and anxiolytics may impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day. See also Drugs and Driving under General Guidance, p. 3.

Dependence and withdrawal Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens. Abrupt withdrawal of a barbiturate is even more likely to have serious effects.

The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines.

A benzodiazepine can be withdrawn in steps of about one-eighth (range one-tenth to one-quarter) of the daily dose every fortnight. A suggested withdrawal protocol for patients who have difficulty is as follows:

1. Transfer patient to equivalent daily dose of diazepam[1] preferably taken at night
2. Reduce diazepam dose every 2–3 weeks in steps of 2 or 2.5 mg; if withdrawal symptoms occur, maintain this dose until symptoms improve
3. Reduce dose further, if necessary in smaller steps;[2] it is better to reduce too slowly rather than too quickly
4. Stop completely; period needed for withdrawal can vary from about 4 weeks to a year or more

Counselling may help; beta-blockers should **only** be tried if other measures fail; antidepressants should be used **only** where depression or panic disorder co-exist or emerge; **avoid** antipsychotics (which may aggravate withdrawal symptoms).

Important: benzodiazepine indications

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
2. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress.

4.1.1 Hypnotics

Before a hypnotic is prescribed the cause of the insomnia should be established and, where possible, underlying factors should be treated. However, it should be noted that some patients have unrealistic sleep expectations, and others understate their alcohol consumption which is often the cause of the insomnia. Short-acting hypnotics are preferable in patients with sleep onset insomnia, when sedation the following day is undesirable, or when prescribing for elderly patients (but see below). Long-acting hypnotics are indicated in patients with poor sleep maintenance (e.g. early morning waking) that causes daytime effects, when an anxiolytic effect is needed during the day, or when sedation the following day is acceptable; see also Important: Benzodiazepine Indications, above.

Transient insomnia may occur in those who normally sleep well and may be due to extraneous factors such as noise, shift work, and jet lag. If a hypnotic is indicated one that is rapidly eliminated should be chosen, and only one or two doses should be given.

Short-term insomnia is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A short-acting drug is usually appropriate.

Chronic insomnia is rarely benefited by hypnotics and is sometimes due to mild dependence caused by injudicious prescribing of hypnotics. Psychiatric disorders such as anxiety, depression, and abuse of drugs and alcohol are common causes. Sleep disturbance is very common in depressive illness and early wakening is often a useful pointer. The underlying psychiatric complaint should be treated, adapting the drug regimen to alleviate insomnia. For example, clomipramine or mirtazapine prescribed for depression will also help to promote sleep if taken at night. Other causes of insomnia include daytime cat-napping and physical causes such as pain, pruritus, and dyspnoea.

Hypnotics should **not** be prescribed indiscriminately and routine prescribing is undesirable. They should be reserved for short courses in the acutely distressed. Tolerance to their effects develops within 3 to 14 days of continuous use and long-term efficacy cannot be assured. A major drawback of long-term use is that withdrawal can cause rebound insomnia and a withdrawal syndrome (section 4.1).

Where prolonged administration is unavoidable hypnotics should be discontinued as soon as feasible and the patient warned that sleep may be disturbed for a few days before normal rhythm is re-established; broken sleep with vivid dreams may persist for several weeks.

Children The prescribing of hypnotics to children, except for occasional use such as for night terrors and somnambulism (sleep-walking), is not justified.

Elderly Hypnotics should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused, leading to falls and injury.

Dental procedures Some anxious patients may benefit from the use of a hypnotic the night before the dental appointment. Hypnotics do not relieve pain, and if pain interferes with sleep an appropriate analgesic should be given. **Diazepam** (section 4.1.2), **nitrazepam** or **temazepam** are used at night for dental patients. Temazepam is preferred when it is important to minimise any residual effect the following day. For information on anxiolytics for dental procedures, see section 15.1.4.1.

Benzodiazepines

Benzodiazepines used as hypnotics include **nitrazepam** and **flurazepam** which have a prolonged action and may give rise to residual effects on the following day; repeated doses tend to be cumulative.

Loprazolam, **lormetazepam**, and **temazepam** act for a shorter time and they have little or no hangover effect.

1. Approximate equivalent doses, diazepam 5 mg
   ≡ chlordiazepoxide 15 mg
   ≡ loprazolam 0.5–1 mg
   ≡ lorazepam 0.5–1 mg
   ≡ lormetazepam 0.5–1 mg
   ≡ nitrazepam 5 mg
   ≡ oxazepam 15 mg
   ≡ temazepam 10 mg
2. Steps may be adjusted according to initial dose and duration of treatment and can range from diazepam 500 micrograms (one-quarter of a 2-mg tablet) to 2.5 mg

Withdrawal phenomena are more common with the short-acting benzodiazepines.

If insomnia is associated with daytime anxiety then the use of a long-acting benzodiazepine anxiolytic such as **diazepam** given as a single dose at night may effectively treat both symptoms.

For general guidelines on benzodiazepine prescribing see section 4.1.2 and for benzodiazepine withdrawal see section 4.1.

Hepatic impairment Benzodiazepines can precipitate coma if used in hepatic impairment. If treatment is necessary, benzodiazepines with shorter half lives are safer, such as temazepam or oxazepam. Start with smaller initial doses or reduce dose; avoid in severe impairment.

Renal impairment Patients with renal impairment have increased cerebral sensitivity to benzodiazepines; start with small doses in severe impairment.

Pregnancy There is a risk of neonatal withdrawal symptoms when benzodiazepines are used during pregnancy. Avoid regular use and use only if there is a clear indication such as seizure control. High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

Breast-feeding Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

NITRAZEPAM

Indications insomnia (short-term use; see p. 208)

Cautions respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder; reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; not for use alone to treat depression (or anxiety associated with depression) or chronic psychosis

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur; dependence; see also under Diazepam (section 4.1.2); **overdosage:** see Emergency Treatment of Poisoning, p. 37

Dose

- 5–10 mg at bedtime; ELDERLY (or debilitated) 2.5–5 mg; CHILD 1 month–2 years (infantile spasms) see *BNF for Children*

Nitrazepam (Non-proprietary) PoM

Tablets, nitrazepam 5 mg, net price 28 = 98p. Label: 19

Brands include *Mogadon*® NHS

Dental prescribing on NHS Nitrazepam Tablets may be prescribed

Oral suspension, nitrazepam 2.5 mg/5 mL. Net price 150 mL = £5.09. Label: 19

Brands include *Somnite*® NHS

FLURAZEPAM

Indications insomnia (short-term use; see p. 208)

Cautions see under Nitrazepam

Contra-indications see under Nitrazepam

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Nitrazepam

Dose

- 15–30 mg at bedtime; ELDERLY (or debilitated) 15 mg; CHILD not recommended

Dalmane® (Meda) PoM NHS

Capsules, flurazepam (as hydrochloride), 15 mg (grey/yellow), net price 30-cap pack = £6.73; 30 mg (black/grey), 30-cap pack = £8.63. Label: 19

LOPRAZOLAM

Indications insomnia (short-term use; see p. 208)

Cautions see under Nitrazepam

Contra-indications see under Nitrazepam

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Nitrazepam; shorter acting

Dose

- 1 mg at bedtime, increased to 1.5 or 2 mg if required; ELDERLY (or debilitated) 0.5 or 1 mg; CHILD not recommended

Loprazolam (Non-proprietary) PoM

Tablets, loprazolam 1 mg (as mesilate). Net price 28-tab pack = £18.00. Label: 19

LORMETAZEPAM

Indications insomnia (short-term use; see p. 208)

Cautions see under Nitrazepam

Contra-indications see under Nitrazepam

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Nitrazepam; shorter acting

Dose

- 0.5–1.5 mg at bedtime; ELDERLY (or debilitated) 500 micrograms; CHILD not recommended

Lormetazepam (Non-proprietary) PoM

Tablets, lormetazepam 500 micrograms, net price 30-tab pack = £56.25; 1 mg, 30-tab pack = £54.60. Label: 19

TEMAZEPAM

Indications insomnia (short-term use; see p. 208); see also section 15.1.4.1 for peri-operative use

Cautions see under Nitrazepam

Contra-indications see under Nitrazepam

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see under Nitrazepam; shorter acting

Dose

- 10–20 mg at bedtime, exceptional circumstances 30–40 mg; ELDERLY (or debilitated) 10 mg at bedtime, exceptional circumstances 20 mg; CHILD not recommended

Temazepam (Non-proprietary) CD

Tablets, temazepam 10 mg, net price 28-tab pack = £3.42; 20 mg, 28-tab pack = £2.24. Label: 19

Dental prescribing on NHS Temazepam Tablets may be prescribed

Oral solution, temazepam 10 mg/5 mL, net price 300 mL = £33.44. Label: 19

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Temazepam Oral Solution may be prescribed

Zaleplon, zolpidem, and zopiclone

Zaleplon, **zolpidem** and **zopiclone** are non-benzodiazepine hypnotics, but they act at the benzodiazepine receptor. They are not licensed for long-term use; dependence has been reported in a small number of patients. Zolpidem and zopiclone have a short duration of action; zaleplon is very short acting.

ZALEPLON

Indications insomnia (short-term use—up to 2 weeks)

Cautions respiratory insufficiency (avoid if severe); muscle weakness and myasthenia gravis, history of drug or alcohol abuse; depression (risk of suicidal ideation); avoid prolonged use (risk of tolerance and withdrawal symptoms); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Contra-indications sleep apnoea syndrome, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Hepatic impairment can precipitate coma; reduce dose to 5 mg (avoid if severe impairment)

Pregnancy use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy

Breast-feeding present in milk but amount probably too small to be harmful

Side-effects amnesia, paraesthesia, drowsiness; dysmenorrhea; *less commonly* nausea, anorexia, asthenia, incoordination, confusion, impaired concentration, depression, depersonalisation, dizziness, hallucinations, disturbances of smell, hearing, speech, and vision; photosensitivity; paradoxical effects (see p. 207) and sleep-walking also reported

Dose

- ADULT over 18 years, 10 mg at bedtime or after going to bed if difficulty falling asleep; ELDERLY 5 mg

Note Patients should be advised not to take a second dose during a single night

Sonata® (Meda) PoM

Capsules, zaleplon 5 mg (white/light brown), net price 14-cap pack = £3.12; 10 mg (white), 14-cap pack = £3.76. Label: 2

ZOLPIDEM TARTRATE

Indications insomnia (short-term use—up to 4 weeks)

Cautions depression, muscle weakness and myasthenia gravis, history of drug or alcohol abuse; elderly; avoid prolonged use (and abrupt withdrawal thereafter); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications obstructive sleep apnoea, acute or severe respiratory depression, marked neuromuscular respiratory weakness including unstable myasthenia gravis, psychotic illness

Hepatic impairment can precipitate coma; reduce dose to 5 mg (avoid if severe impairment)

Renal impairment use with caution

Pregnancy avoid regular use (risk of neonatal withdrawal symptoms); high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression

Breast-feeding small amounts present in milk—avoid

Side-effects diarrhoea, nausea, vomiting, dizziness, headache, drowsiness, hallucination, agitation, asthenia, amnesia; dependence, memory disturbances, nightmares, depression, confusion, perceptual disturbances or diplopia, tremor, ataxia, falls, skin reactions, changes in libido; paradoxical effects (see p. 207), muscular weakness, and sleep-walking also reported

Dose

- ADULT over 18 years, 10 mg at bedtime; ELDERLY (or debilitated) 5 mg

Zolpidem (Non-proprietary) PoM

Tablets, zolpidem tartrate 5 mg, net price 28-tab pack = £1.41; 10 mg, 28-tab pack = £1.46. Label: 19

Stilnoct® (Sanofi-Aventis) PoM

Tablets, both f/c, zolpidem tartrate 5 mg, net price 28-tab pack = £2.96; 10 mg, 28-tab pack = £4.31. Label: 19

ZOPICLONE

Indications insomnia (short-term use—up to 4 weeks)

Cautions elderly; muscle weakness and myasthenia gravis, history of drug abuse, psychiatric illness; avoid prolonged use (risk of tolerance and withdrawal symptoms); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications marked neuromuscular respiratory weakness including unstable myasthenia gravis, respiratory failure, severe sleep apnoea syndrome

Hepatic impairment can precipitate coma; reduce dose (avoid if severe impairment)

Renal impairment start with small doses in severe impairment; increased cerebral sensitivity

Pregnancy avoid regular use (risk of neonatal withdrawal symptoms); high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression

Breast-feeding present in milk—avoid

Side-effects taste disturbance; *less commonly* nausea, vomiting; dizziness, drowsiness, dry mouth, headache;

rarely amnesia, confusion, depression, hallucinations, nightmares; *very rarely* light headedness, incoordination; paradoxical effects (see p. 207) and sleepwalking also reported

Dose

- ADULT over 18 years, 7.5 mg at bedtime; ELDERLY initially 3.75 mg at bedtime increased if necessary

Zopiclone (Non-proprietary) PoM

Tablets, zopiclone 3.75 mg, net price 28-tab pack = £1.34; 7.5 mg, 28-tab pack = £1.35. Label: 19

Zimovane® (Sanofi-Aventis) PoM

Tablets, f/c, zopiclone 3.75 mg (*Zimovane® LS*), net price 28-tab pack = £2.24; 7.5 mg (scored), 28-tab pack = £3.26. Label: 19

Chloral and derivatives

Chloral hydrate and derivatives were formerly popular hypnotics for children (but the use of hypnotics in children is not usually justified). There is no convincing evidence that they are particularly useful in the elderly and their role as hypnotics is now very limited.

CHLORAL HYDRATE

Indications insomnia (short-term use)

Cautions reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); avoid contact with skin and mucous membranes; **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications severe cardiac disease; gastritis; acute porphyria (section 9.8.2)

Hepatic impairment can precipitate coma; reduce dose in mild to moderate impairment; avoid in severe impairment

Renal impairment avoid in severe impairment

Pregnancy avoid

Breast-feeding risk of sedation in infant—avoid

Side-effects gastric irritation (nausea and vomiting reported), abdominal distention, flatulence, headache, tolerance, dependence, excitement, delirium (especially on abrupt withdrawal), ketonuria, and rash

Dose

- See under preparations below

Chloral Mixture, BP 2000 PoM

(Chloral Oral Solution)

Mixture, chloral hydrate 500 mg/5 mL in a suitable vehicle. Label: 19, 27

Dose 5–20 mL; CHILD 1–12 years 30–50 mg/kg (max. 1 g), taken well diluted with water at bedtime

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Chloral Elixir, Paediatric, BP 2000 PoM

(Chloral Oral Solution, Paediatric)

Elixir, chloral hydrate 200 mg/5 mL (4%) in a suitable vehicle with a black currant flavour. Label: 1, 27

Dose CHILD 1 month–1 year 30–50 mg/kg, taken well diluted with water at bedtime

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Cloral betaine

Welldorm® (Alphashow) PoM

Tablets, blue-purple, f/c, cloral betaine 707 mg (≡ chloral hydrate 414 mg), net price 30-tab pack = £12.10. Label: 19, 27

Dose ADULT and CHILD over 12 years, 1–2 tablets with water or milk at bedtime, max. 5 tablets (chloral hydrate 2 g) daily

Elixir, red, chloral hydrate 143.3 mg/5 mL, net price 150-mL pack = £8.70. Label: 19, 27

Dose 15–45 mL (chloral hydrate 0.4–1.3 g) with water or milk, at bedtime, max. 70 mL (chloral hydrate 2 g) daily; CHILD 2–12 years, 1–1.75 mL/kg (chloral hydrate 30–50 mg/kg), max. 35 mL (chloral hydrate 1 g) daily

Clomethiazole

Clomethiazole may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs. It is also licensed for use in acute alcohol withdrawal, but see section 4.10.1.

CLOMETHIAZOLE

(Chlormethiazole)

Indications see under Dose; alcohol withdrawal (section 4.10.1)

Cautions cardiac and respiratory disease (confusional state may indicate hypoxia), chronic pulmonary insufficiency, sleep apnoea syndrome; history of drug abuse; avoid prolonged use (and abrupt withdrawal thereafter); marked personality disorder; elderly; excessive sedation may occur (particularly with higher doses); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications acute pulmonary insufficiency; alcohol-dependent patients who continue to drink

Hepatic impairment can precipitate coma; reduce dose

Renal impairment start with small doses in severe impairment; increased cerebral sensitivity

Pregnancy avoid if possible—especially during first and third trimesters

Breast-feeding amount too small to be harmful

Side-effects nasal congestion and irritation (increased nasopharyngeal and bronchial secretions), conjunctival irritation, headache; *rarely* gastro-intestinal disturbances, paradoxical excitement, confusion, dependence, rash, urticaria, bullous eruption, anaphylaxis, alterations in liver enzymes

Dose

- Severe insomnia in the elderly (short-term use), 1–2 capsules at bedtime; CHILD not recommended
- Restlessness and agitation in the elderly, 1 capsule 3 times daily
- Alcohol withdrawal (but see section 4.10.1), initially 2–4 capsules, if necessary repeated after some hours; day 1 (first 24 hours), 9–12 capsules in 3–4 divided doses; day 2, 6–8 capsules in 3–4 divided doses; day 3, 4–6 capsules in 3–4 divided doses; then gradually reduced over days 4–6; total treatment for not more than 9 days

Heminevrin® (AstraZeneca) PoM

Capsules, grey-brown, clomethiazole base 192 mg in an oily basis. Net price 60-cap pack = £4.78. Label: 19

Antihistamines

Some **antihistamines** (section 3.4.1) such as promethazine are on sale to the public for occasional insomnia; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

Promethazine is also popular for use in children, but the use of hypnotics in children is not usually justified.

PROMETHAZINE HYDROCHLORIDE

Indications sedation (short-term use); allergy and urticaria (section 3.4.1); nausea and vomiting (section 4.6)

Cautions see Promethazine Hydrochloride, section 3.4.1

Contra-indications see notes in section 3.4.1

Hepatic impairment see notes in section 3.4.1

Renal impairment see Promethazine Hydrochloride, section 3.4.1

Pregnancy see notes in section 3.4.1

Breast-feeding see notes in section 3.4.1

Side-effects see Promethazine Hydrochloride, section 3.4.1

Dose

- By mouth, 25–50 mg; CHILD 2–5 years 15–20 mg, 5–10 years 20–25 mg
- By deep intramuscular injection, 25–50 mg; CHILD 5–10 years 6.25–12.5 mg

Preparations

Section 3.4.1

Alcohol

Alcohol is a poor hypnotic because the diuretic action interferes with sleep during the latter part of the night. Alcohol also disturbs sleep patterns, and so can worsen sleep disorders; **interactions:** Appendix 1 (alcohol).

Sodium oxybate

Sodium oxybate is a central nervous system depressant that is licensed for the treatment of narcolepsy with cataplexy.

SODIUM OXYBATE

Indications narcolepsy with cataplexy (under specialist supervision)

Cautions history of drug abuse or depression; epilepsy; elderly; respiratory disorders; heart failure and hypertension (high sodium content); risk of discontinuation effects including rebound cataplexy and withdrawal symptoms; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (sodium oxybate)

Hepatic impairment halve initial dose

Renal impairment caution—contains 3.96 mmol Na^+/mL

Pregnancy avoid

Breast-feeding no information available

Side-effects nausea, vomiting, diarrhoea, abdominal pain, anorexia; hypertension, peripheral oedema; dyspnoea; sleep disorders, confusion, disorientation, paraesthesia, hypoaesthesia, impaired attention, depression, drowsiness, anxiety, dizziness, headache, tremor, asthenia, fatigue; urinary incontinence, nocturnal enuresis; arthralgia, muscle cramps; blurred vision; sweating; *less commonly* faecal incontinence, myoclonus, psychosis, paranoia, hallucination, agitation, amnesia, and rash; respiratory depression, dependence, seizures, suicidal ideation, and urticaria also reported

Dose

- ADULT over 18 years, initially 2.25 g on retiring and repeated 2.5–4 hours later, increased according to response in steps of 1.5 g daily in 2 divided doses at intervals of 1–2 weeks; max. 9 g daily in two divided doses

  Note Dose titration should be repeated if restarting after interval of more than 14 days

  Counselling Dilute each dose with 60 mL water; prepare both doses before retiring. Observe the same time interval (2–3 hours) each night between the last meal and the first dose

Xyrem® (UCB Pharma) ▼ PoM

Oral solution, sugar-free, sodium oxybate 500 mg/mL, net price 180 mL (with graduated syringe) = £360.00. Label: 13, 19, counselling, administration

Electrolytes Na^+ 3.96 mmol/mL

Melatonin

Melatonin is a pineal hormone; it is licensed for the short-term treatment of insomnia in adults over 55 years. For information on the use of melatonin in children and adolescents, see *BNF for Children*.

MELATONIN

Indications insomnia (short-term use)

Cautions autoimmune disease (manufacturer advises avoid—no information available); **interactions:** Appendix 1 (melatonin)

Hepatic impairment clearance reduced—avoid

Renal impairment no information available—use with caution

Pregnancy no information available—avoid

Breast-feeding present in milk—avoid

Side-effects *less commonly* abdominal pain, dyspepsia, dry mouth, mouth ulceration, weight gain, hypertension, chest pain, malaise, dizziness, restlessness, nervousness, irritability, anxiety, migraine, proteinuria, glycosuria, pruritus, rash, dry skin; *rarely* thirst, flatulence, halitosis, salivation, vomiting, gastritis, hypertriglyceridaemia, angina, palpitation, syncope, hot flushes, aggression, impaired memory, restless legs syndrome, paraesthesia, mood changes, priapism, increased libido, prostatitis, polyuria, haematuria, leucopenia, thrombocytopenia, electrolyte disturbances, muscle spasm, arthritis, lacrimation, visual disturbances, nail disorder

Dose

- ADULT over 55 years, 2 mg once daily 1–2 hours before bedtime for up to 13 weeks; CHILD 1 month–18 years see *BNF for Children*

Circadin® (Lundbeck) ▼ PoM

Tablets, m/r, melatonin 2 mg, net price 21-tab pack = £10.77. Label: 2, 21, 25

4.1.2 Anxiolytics

Benzodiazepine anxiolytics can be effective in alleviating anxiety states. Although these drugs are sometimes prescribed for stress-related symptoms, unhappiness, or minor physical disease, their use in such conditions is inappropriate. Benzodiazepine anxiolytics should not be used as sole treatment for chronic anxiety, and they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines. In children, anxiolytic treatment should be used only to relieve acute anxiety (and related insomnia) caused by fear (e.g. before surgery).

Anxiolytic benzodiazepine treatment should be limited to the lowest possible dose for the shortest possible time (see p. 208). Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.

Some antidepressants (section 4.3) are licensed for use in anxiety and related disorders; see section 4.3 for a comment on their role in chronic anxiety. Some antipsychotics, in low doses, are also sometimes used in severe anxiety for their sedative action, but long-term use should be avoided because of the risk of adverse effects (section 4.2.1). The use of antihistamines (e.g. hydroxyzine) for their sedative effect in anxiety is not appropriate.

Beta-blockers (section 2.4) do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but they do reduce autonomic symptoms, such as palpitation and tremor; they do not reduce non-autonomic symptoms, such as muscle tension. Beta-blockers are therefore indicated for patients with predominantly somatic symptoms; this, in turn, may prevent the onset of worry and fear.

Benzodiazepines

Benzodiazepines are indicated for the *short-term relief of severe anxiety*; long-term use should be avoided (see p. 208). Diazepam, alprazolam, chlordiazepoxide, and clobazam have a sustained action. Shorter-acting compounds such as **lorazepam** and **oxazepam** may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

In *panic disorders* (with or without agoraphobia) resistant to antidepressant therapy (section 4.3), a benzodiazepine (lorazepam 3–5 mg daily or clonazepam 1–2 mg daily (section 4.8.1) [both unlicensed]) may be used; alternatively, a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam or lorazepam are very occasionally administered intravenously for the *control of panic attacks*. This route is the most rapid but the procedure is not without risk (section 4.8.2) and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

For guidelines on benzodiazepine withdrawal, see p. 207.

Hepatic impairment Benzodiazepines can precipitate coma if used in hepatic impairment. If treatment is necessary, benzodiazepines with shorter half lives are safer, such as temazepam or oxazepam. Start with smaller initial doses or reduce dose; avoid in severe impairment.

Renal impairment Patients with renal impairment have increased cerebral sensitivity to benzodiazepines; start with small doses in severe impairment.

Pregnancy There is a risk of neonatal withdrawal symptoms when benzodiazepines are used during pregnancy. Avoid regular use and use only if there is a clear indication such as seizure control. High doses administered during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.

Breast-feeding Benzodiazepines are present in milk, and should be avoided if possible during breast-feeding.

DIAZEPAM

Indications short-term use in anxiety or insomnia (see p. 208); adjunct in acute alcohol withdrawal; status epilepticus (section 4.8.2); febrile convulsions (section 4.8.3); muscle spasm (section 10.2.2); peri-operative use (section 15.1.4.1)

Cautions respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder; reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); special precautions for intravenous injection (section 4.8.2); acute porphyria (section 9.8.2); when given parenterally, close observation required until full recovery from sedation; **interactions:** Appendix 1 (anxiolytics and hypnotics) Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression (see also section 4.1); muscle weakness; *occasionally:* headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; on intravenous injection, pain, thrombophlebitis, and rarely apnoea; **overdosage:** see Emergency Treatment of Poisoning, p. 37

Dose

- By mouth, anxiety, 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; ELDERLY (or debilitated) half adult dose

  Insomnia associated with anxiety, 5–15 mg at bedtime
- By intramuscular injection *or* slow intravenous injection (into a large vein, at a rate of not more than

5 mg/minute), for severe acute anxiety, control of acute panic attacks, and acute alcohol withdrawal, 10 mg, repeated if necessary after not less than 4 hours

Note Only use intramuscular route when oral and intravenous routes not possible; emulsion formulation preferred for intravenous injection; special precautions for intravenous injection section 4.8.2

- By rectum as rectal solution, acute anxiety and agitation, 500 micrograms/kg repeated after 12 hours as required; ELDERLY 250 micrograms/kg; CHILD not recommended

  As suppositories, anxiety when oral route not appropriate, 10–30 mg (higher dose divided); dose form not appropriate for less than 10 mg

Diazepam (Non-proprietary) PoM

Tablets, diazepam 2 mg, net price 28-tab pack = 89p; 5 mg, 28-tab pack = 90p; 10 mg, 28-tab pack = 92p. Label: 2 or 19
Brands include *Rimapam®* NHS, *Tensium®* NHS

Dental prescribing on NHS Diazepam Tablets may be prescribed

Oral solution, diazepam 2 mg/5 mL, net price 100-mL pack = £6.08. Label: 2 or 19
Brands include *Dialar®* NHS

Dental prescribing on NHS Diazepam Oral Solution 2 mg/5 mL may be prescribed

Strong oral solution, diazepam 5 mg/5 mL, net price 100-mL pack = £6.38. Label: 2 or 19 NHS
Brands include *Dialar®* NHS

Injection (solution), diazepam 5 mg/mL, net price 2-mL amp = 45p
Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2), ethanol, propylene glycol
Note Do not dilute (except for intravenous infusion, see Appendix 6)

Injection (emulsion), diazepam 5 mg/mL, net price 2-mL amp = 91p
Brands include *Diazemuls®*
Note For intravenous injection or infusion, see Appendix 6

Rectal tubes (= rectal solution), diazepam 2 mg/mL, net price 1.25-mL (2.5-mg) tube = 90p, 2.5-mL (5-mg) tube = £1.41; 4 mg/mL, 2.5-mL (10-mg) tube = £1.88. Label: 2 or 19
Brands include *Diazepam Rectubes®*, *Stesolid®*

Suppositories, diazepam 10 mg, net price 6 = £10.20. Label: 2 or 19
Brands include *Valclair®*

ALPRAZOLAM

Indications short-term use in anxiety (see p. 208)
Cautions see under Diazepam
Contra-indications see under Diazepam
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Diazepam
Dose

- 250–500 micrograms 3 times daily (ELDERLY or debilitated 250 micrograms 2–3 times daily), increased if necessary to a total of 3 mg daily; CHILD not recommended

Alprazolam (Non-proprietary) PoM NHS

Tablets, alprazolam 250 micrograms, net price 60-tab pack = £2.97; 500 micrograms, 60-tab pack = £5.69. Label: 2
Brands include *Xanax®* NHS

CHLORDIAZEPOXIDE HYDROCHLORIDE

Indications short-term use in anxiety (see p. 208); adjunct in acute alcohol withdrawal (section 4.10.1)
Cautions see under Diazepam
Contra-indications see under Diazepam
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Diazepam
Dose

- Anxiety, 10 mg 3 times daily increased if necessary to 60–100 mg daily in divided doses; ELDERLY (or debilitated) half adult dose; CHILD not recommended
- Treatment of alcohol withdrawal in primary care, 10–50 mg 4 times daily, gradually reduced over 5–10 days

Chlordiazepoxide (Non-proprietary) PoM

Capsules, chlordiazepoxide hydrochloride 5 mg, net price 100-cap pack = £6.21; 10 mg, 100-cap pack = £13.13. Label: 2
Brands include *Librium®* NHS

Chlordiazepoxide Hydrochloride (Non-proprietary) PoM

Tablets, chlordiazepoxide hydrochloride 5 mg, net price 100 = £4.24; 10 mg, 100 = £11.34. Label: 2

LORAZEPAM

Indications short-term use in anxiety or insomnia (see p. 208); status epilepticus (section 4.8.2); peri-operative (section 15.1.4.1)
Cautions see under Diazepam; short acting; when given parenterally, facilities for managing respiratory depression with mechanical ventilation must be available
Contra-indications see under Diazepam
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Diazepam
Dose

- By mouth, anxiety, 1–4 mg daily in divided doses; ELDERLY (or debilitated) half adult dose

  Insomnia associated with anxiety, 1–2 mg at bedtime; CHILD not recommended
- By intramuscular *or* slow intravenous injection (into a large vein), acute panic attacks, 25–30 micrograms/kg (usual range 1.5–2.5 mg), repeated every 6 hours if necessary; CHILD not recommended

  Note Only use intramuscular route when oral and intravenous routes not possible

Lorazepam (Non-proprietary) PoM

Tablets, lorazepam 1 mg, net price 28-tab pack = £5.42; 2.5 mg, 28-tab pack = £7.11. Label: 2 or 19

Injection, lorazepam 4 mg/mL, net price 1-mL amp = 35p
Excipients include benzyl alcohol, propylene glycol (see Excipients, p. 2)
Brands include *Ativan®*
Note For intramuscular injection it should be diluted with an equal volume of water for injections or physiological saline (but only use when oral and intravenous routes not possible)

OXAZEPAM

Indications anxiety (short-term use; see p. 208)
Cautions see under Diazepam; short acting
Contra-indications see under Diazepam
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see under Diazepam
Dose

- Anxiety, 15–30 mg (elderly or debilitated 10–20 mg) 3–4 times daily; CHILD not recommended
- Insomnia associated with anxiety, 15–25 mg (max. 50 mg) at bedtime; CHILD not recommended

Oxazepam (Non-proprietary) PoM
Tablets, oxazepam 10 mg, net price 28-tab pack = £4.85; 15 mg, 28-tab pack = £5.16. Label: 2

Buspirone

Buspirone is thought to act at specific serotonin ($5HT_{1A}$) receptors. Response to treatment may take up to 2 weeks. It does not alleviate the symptoms of benzodiazepine withdrawal. Therefore a patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone. The dependence and abuse potential of buspirone is low; it is, however, licensed for short-term use only (but specialists occasionally use it for several months).

BUSPIRONE HYDROCHLORIDE

Indications anxiety (short-term use)
Cautions does not alleviate benzodiazepine withdrawal (see notes above); **interactions:** Appendix 1 (anxiolytics and hypnotics)
Driving May affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced
Contra-indications epilepsy; acute porphyria (section 9.8.2)
Hepatic impairment reduce dose in mild to moderate disease; avoid in severe disease
Renal impairment reduce dose; avoid if eGFR less than 20 mL/minute/1.73 m^2
Pregnancy avoid
Breast-feeding avoid
Side-effects nausea; dizziness, headache, nervousness, excitement; *rarely* dry mouth, tachycardia, palpitation, chest pain, drowsiness, confusion, seizures, fatigue, and sweating
Dose

- ADULT over 18 years, 5 mg 2–3 times daily, increased as necessary every 2–3 days; usual range 15–30 mg daily in divided doses; max. 45 mg daily

Buspirone Hydrochloride (Non-proprietary) PoM
Tablets, buspirone hydrochloride 5 mg, net price 30-tab pack = £13.01; 10 mg, 30-tab pack = £15.34. Counselling, driving

Meprobamate

Meprobamate is **less effective** than the benzodiazepines, more hazardous in overdosage, and can also induce dependence. It is **not** recommended.

Important: MHRA/CHM have advised that treatment with meprobamate should **not** be initiated.

MEPROBAMATE

Indications short-term use in anxiety, but see notes above
Cautions respiratory disease, muscle weakness, epilepsy (may induce seizures), history of drug or alcohol abuse, marked personality disorder; elderly and debilitated; avoid prolonged use, abrupt withdrawal (may precipitate convulsions); **interactions:** Appendix 1 (anxiolytics and hypnotics)
Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
Contra-indications acute pulmonary insufficiency; respiratory depression; acute porphyria (section 9.8.2)
Hepatic impairment can precipitate coma
Renal impairment start with small doses in severe impairment; increased cerebral sensitivity
Pregnancy avoid if possible
Breast-feeding avoid; concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant
Side-effects see under Diazepam, but incidence greater and drowsiness most common side-effect; also gastro-intestinal disturbances, hypotension, paraesthesia, weakness, CNS effects including headache, paradoxical excitement, disturbances of vision; rarely agranulocytosis and rashes
Dose

- 400 mg 3–4 times daily; ELDERLY half adult dose or less; CHILD not recommended
Note Meprobamate treatment should not be initiated in new patients, see notes above

Meprobamate (Non-proprietary) CD
Tablets, scored, meprobamate 400 mg, net price 84-tab pack = £19.95. Label: 2

4.1.3 Barbiturates

The intermediate-acting **barbiturates** have a place only in the treatment of severe intractable insomnia in patients **already taking** barbiturates; they should be **avoided** in the elderly. Intermediate-acting barbiturate preparations containing amobarbital sodium, butobarbital, and secobarbital sodium are available on a named-patient basis.

The long-acting barbiturate phenobarbital is still sometimes of value in epilepsy (section 4.8.1) but its use as a sedative is unjustified.

The very short-acting barbiturate thiopental is used in anaesthesia (section 15.1.1).

4.2 Drugs used in psychoses and related disorders

4.2.1 Antipsychotic drugs
4.2.2 Antipsychotic depot injections
4.2.3 Antimanic drugs

Advice of Royal College of Psychiatrists on doses of antipsychotic drugs above BNF upper limit. Unless otherwise stated, doses in the BNF are licensed doses—

any higher dose is therefore **unlicensed** (for an explanation of the significance of this, see p. 2).

1. Consider alternative approaches including adjuvant therapy and newer or atypical neuroleptics such as clozapine.
2. Bear in mind risk factors, including obesity—particular caution is indicated in older patients especially those over 70.
3. Consider potential for drug interactions—see **interactions:** Appendix 1 (antipsychotics).
4. Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse abnormality develops.
5. Increase dose slowly and not more often than once weekly.
6. Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
7. Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be **lower** than the corresponding oral dose (owing to absence of first-pass effect), particularly if the patient is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for **each route** and should **not** imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least **daily**.

4.2.1 Antipsychotic drugs

Antipsychotic drugs are also known as 'neuroleptics' and (misleadingly) as 'major tranquillisers'. Antipsychotic drugs generally tranquillise without impairing consciousness and without causing paradoxical excitement but they should not be regarded merely as tranquillisers. For conditions such as schizophrenia the tranquillising effect is of secondary importance.

In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia Antipsychotic drugs relieve psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse. Although they are usually less effective in apathetic withdrawn patients, they sometimes appear to have an activating influence. Patients with acute schizophrenia generally respond better than those with chronic symptoms. Patients should receive antipsychotic drugs for 4–6 weeks before the drug is deemed ineffective.

Long-term treatment of a patient with a definite diagnosis of schizophrenia may be necessary even after the first episode of illness in order to prevent the illness from becoming chronic. Withdrawal of drug treatment requires careful surveillance because the patient who appears well on medication may suffer a disastrous relapse if treatment is withdrawn inappropriately. In addition the need for continuation of treatment may not become immediately evident because relapse is often delayed for several weeks after cessation of treatment.

Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain by blocking dopamine D_2 receptors, which may give rise to the extrapyramidal effects described below, and also to hyperprolactinaemia. Antipsychotic drugs may also affect cholinergic, alpha-adrenergic, histaminergic, and serotonergic receptors.

Cautions Antipsychotic drugs should be used with **caution** in patients with cardiovascular disease; an ECG may be required (see individual drug monographs), particularly if physical examination identifies cardiovascular risk factors, if there is a personal history of cardiovascular disease, or if the patient is being admitted as an inpatient. Antipsychotic drugs should also be used with caution in Parkinson's disease (may be exacerbated by antipsychotics), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a susceptibility to angle-closure glaucoma. Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). As photosensitisation may occur with higher dosages, patients should avoid direct sunlight. Patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year. **Interactions:** Appendix 1 (antipsychotics).

Contra-indications Antipsychotic drugs may be **contra-indicated** in comatose states, CNS depression, and phaeochromocytoma.

Prescribing for the elderly

The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather.

It is recommended that:

- Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.
- Initial doses of antipsychotic drugs in elderly patients should be reduced (to half the adult dose or less), taking into account factors such as the patient's weight, co-morbidity, and concomitant medication.
- Treatment should be reviewed regularly.

Driving Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

Withdrawal There is a high risk of relapse if medication is stopped after 1–2 years. Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse. Patients should be monitored for 2 years after withdrawal of antipsychotic medication for signs and symptoms of relapse.

Hepatic impairment All antipsychotics can precipitate coma if used in hepatic impairment; phenothiazines are hepatotoxic. The manufacturer of zuclopenthixol (*Clopixol®*) advises that the dose should be halved in hepatic impairment, and serum-level monitoring should be considered.

Renal impairment Start with small doses of antipsychotic drugs in severe renal impairment because of increased cerebral sensitivity. Pericyazine should be avoided in renal impairment. The dose of zuclopenthixol should be halved in patients with renal failure.

Pregnancy Extrapyramidal effects have been reported occasionally in the neonate when antipsychotic drugs are taken during the third trimester of pregnancy.

Breast-feeding There is limited information available on the short- and long-term effects of antipsychotics on the breast-fed infant. *Animal* studies indicate possible adverse effects of antipsychotic medicines on the developing nervous system. Chronic treatment with antipsychotics whilst breast-feeding should be avoided unless absolutely necessary.

Side-effects Extrapyramidal symptoms are the most troublesome. They occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol and haloperidol), and the depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:

- *parkinsonian symptoms* (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
- *dystonia* (abnormal face and body movements) and *dyskinesia*, which occur more commonly in children or young adults and appear after only a few doses;
- *akathisia* (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated; and
- *tardive dyskinesia* (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

Parkinsonian symptoms remit if the drug is withdrawn and may be suppressed by the administration of **antimuscarinic** drugs (section 4.9.2). However, routine administration of such drugs is not justified because not all patients are affected and because they may unmask or worsen tardive dyskinesia.

Tardive dyskinesia is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermicular movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

Hypotension and interference with temperature regulation are dose-related side-effects and are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly.

Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of some drugs. Discontinuation of the antipsychotic is essential because there is no proven effective treatment, but cooling, bromocriptine, and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

Other side-effects include: drowsiness; apathy; agitation, excitement and insomnia; convulsions; dizziness; headache; confusion; gastro-intestinal disturbances; nasal congestion; antimuscarinic symptoms (such as dry mouth, constipation, difficulty with micturition, and blurred vision; *very rarely*, precipitation of angle-closure glaucoma); cardiovascular symptoms (such as hypotension, tachycardia, and arrhythmias); ECG changes (cases of sudden death have occurred); venous thromboembolism; endocrine effects such as menstrual disturbances, galactorrhoea, gynaecomastia, impotence, and weight gain; blood dyscrasias (such as agranulocytosis and leucopenia), photosensitisation, contact sensitisation and rashes, and jaundice (including cholestatic); corneal and lens opacities, and purplish pigmentation of the skin, cornea, conjunctiva, and retina.

Overdosage: for poisoning with phenothiazines and related compounds, see Emergency Treatment of Poisoning, p. 38.

Classification of antipsychotics The **phenothiazine** derivatives can be divided into 3 main groups.

Group 1: chlorpromazine, levomepromazine, and promazine, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.

Group 2: pericyazine and pipotiazine, generally characterised by moderate sedative effects, marked antimuscarinic effects, but fewer extrapyramidal side-effects than groups 1 or 3.

Group 3: fluphenazine, perphenazine, prochlorperazine, and trifluoperazine, generally characterised by fewer sedative effects, fewer antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Drugs of other chemical groups resemble the phenothiazines of *group 3* in their clinical properties. They include the **butyrophenones** (benperidol and haloperidol); **diphenylbutylpiperidines** (pimozide); **thioxanthenes** (flupentixol and zuclopenthixol); and the **substituted benzamides** (sulpiride).

For details of the newer antipsychotic drugs amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, and risperidone see under Atypical Antipsychotic Drugs, p. 222.

Choice As indicated above, the various drugs differ somewhat in predominant actions and side-effects. Selection is influenced by the degree of sedation required and the patient's susceptibility to extrapyramidal side-effects. However, the differences between antipsychotic drugs are less important than the great variability in patient response; moreover, tolerance to secondary effects such as sedation usually develops. The atypical antipsychotics may be appropriate if extrapyramidal side-effects are a particular concern (see

under Atypical Antipsychotic Drugs, below). Clozapine is used for schizophrenia when other antipsychotics are ineffective or not tolerated.

Prescribing of more than one antipsychotic drug at the same time is **not** recommended; it may constitute a hazard and there is no significant evidence that side-effects are minimised.

Chlorpromazine is still widely used despite the wide range of adverse effects associated with it. It has a marked sedating effect and is useful for treating violent patients without causing stupor. Agitated states in the elderly can be controlled without confusion, a dose of 10 to 25 mg once or twice daily usually being adequate.

Flupentixol and **pimozide** (see ECG monitoring, p. 220) are less sedating than chlorpromazine.

Sulpiride in high doses controls florid positive symptoms, but in lower doses it can have an alerting effect on apathetic withdrawn schizophrenics.

Fluphenazine, **haloperidol**, and **trifluoperazine** are also of value but their use is limited by the high incidence of extrapyramidal symptoms. Haloperidol may be preferred for the rapid control of hyperactive psychotic states; it causes less hypotension than chlorpromazine and is therefore also popular for agitation and restlessness in the elderly, despite the high incidence of extrapyramidal side-effects.

Promazine is not sufficiently active by mouth to be used as an antipsychotic drug; it has been used to treat agitation and restlessness in the elderly (see Other uses, below).

Other uses Nausea and vomiting (section 4.6), choreas, motor tics (section 4.9.3), and intractable hiccup (see under Chlorpromazine Hydrochloride and under Haloperidol). **Benperidol** is used in deviant antisocial sexual behaviour but its value is not established; see also section 6.4.2 for the role of cyproterone acetate.

Psychomotor agitation should be investigated for an underlying cause; it can be managed with low doses of chlorpromazine or haloperidol used for short periods. Antipsychotic drugs can be used with caution for the short-term treatment of severe agitation and restlessness in the elderly (but see p. 216).

Equivalent doses of oral antipsychotics

These equivalences are intended **only** as an approximate guide; individual dosage instructions should **also** be checked; patients should be carefully monitored after **any** change in medication

Antipsychotic drug	Daily dose
Chlorpromazine	100 mg
Clozapine	50 mg
Haloperidol	2–3 mg
Pimozide	2 mg
Risperidone	0.5–1 mg
Sulpiride	200 mg
Trifluoperazine	5 mg

Important These equivalences must **not** be extrapolated beyond the maximum dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate

Dosage
After an initial period of stabilisation, in most patients, the total daily oral dose can be given as a single dose. For the advice of The Royal College of Psychiatrists on doses above the BNF upper limit, see p. 215.

BENPERIDOL

Indications control of deviant antisocial sexual behaviour (but see notes above)

Cautions see notes above; also manufacturer advises regular blood counts and liver function tests during long-term treatment; risk factors for stroke

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- 0.25–1.5 mg daily in divided doses, adjusted according to response; ELDERLY (or debilitated) initially half adult dose; CHILD not recommended

Anquil® (Archimedes) PoM

Tablets, scored, benperidol 250 micrograms, net price 112-tab pack = £97.76. Label: 2

Note The proprietary name *Benquil®* has been used for benperidol tablets

CHLORPROMAZINE HYDROCHLORIDE

Warning Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

Indications see under Dose; antiemetic in palliative care (section 4.6)

Cautions see notes above; also diabetes; patients should remain supine, with blood pressure monitoring for 30 minutes after intramuscular injection; dose adjustment may be necessary if smoking started or stopped during treatment

Contra-indications see notes above; hypothyroidism

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also hyperglycaemia

Dose

- By mouth, schizophrenia and other psychoses, mania, short-term adjunctive management of severe anxiety, psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 25 mg 3 times daily (*or* 75 mg at night), adjusted according to response, to usual maintenance dose of 75–300 mg daily (but up to 1 g daily may be required in psychoses); ELDERLY (or debilitated) third to half adult dose; CHILD (childhood schizophrenia and autism) 1–6 years 500 micrograms/kg every 4–6 hours (max. 40 mg daily); 6–12 years 10 mg 3 times daily (max. 75 mg daily)

  Intractable hiccup, 25–50 mg 3–4 times daily

- By deep intramuscular injection, (for relief of acute symptoms but see also Cautions and Side-effects), 25–50 mg every 6–8 hours; CHILD 1–6 years 500 micrograms/kg every 6–8 hours (max. 40 mg daily); 6–12 years 500 micrograms/kg every 6–8 hours (max. 75 mg daily)
- By rectum in suppositories as chlorpromazine base 100 mg every 6–8 hours [unlicensed]

Note For equivalent therapeutic effect 100 mg chlorpromazine base given *rectally* as a suppository ≡ 20–25 mg chlorpromazine hydrochloride *by intramuscular injection* ≡ 40–50 mg of chlorpromazine base or hydrochloride *by mouth*

Chlorpromazine (Non-proprietary) PoM

Tablets, coated, chlorpromazine hydrochloride 25 mg, net price 28-tab pack = £1.77; 50 mg, 28-tab pack = £2.37; 100 mg, 28-tab pack = £2.31. Label: 2, 11

Brands include *Chloractil®*

Oral solution, chlorpromazine hydrochloride 25 mg/5 mL, net price 150 mL = £1.79, 100 mg/5 mL, 150 mL = £4.28. Label: 2, 11

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 1-mL amp = 60p; 2-mL amp = 63p

Suppositories, chlorpromazine 25 mg and 100 mg. Label: 2, 11

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Largactil® (Sanofi-Aventis) PoM

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 2-mL amp = 60p

FLUPENTIXOL
(Flupenthixol)

Indications schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity; depression (section 4.3.4)

Cautions see notes above; diabetes; avoid in acute porphyria (section 9.8.2)

Contra-indications see notes above; also excitable and overactive patients

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating but extrapyramidal symptoms frequent; hyperglycaemia

Dose

- Psychosis, initially 3–9 mg twice daily adjusted according to the response; max. 18 mg daily; ELDERLY (or debilitated) initially quarter to half adult dose; CHILD not recommended

Depixol® (Lundbeck) PoM

Tablets, yellow, s/c, flupentixol 3 mg (as dihydrochloride), net price 100 = £6.23. Label: 2

Fluanxol® (Lundbeck) PoM

Section 4.3.4 (depression)

Depot preparation

Section 4.2.2

HALOPERIDOL

Indications see under Dose; motor tics (section 4.9.3)

Cautions see notes above; also subarachnoid haemorrhage; metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia; thyrotoxicosis; arteriosclerosis; dose adjustment may be necessary if smoking started or stopped during treatment

Contra-indications see notes above; QT-interval prolongation (avoid concomitant administration of drugs that prolong QT interval); bradycardia

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above, but less sedating and fewer antimuscarinic or hypotensive symptoms; pigmentation and photosensitivity reactions rare; depression; weight loss; *less commonly* dyspnoea, oedema; *rarely* bronchospasm, hypoglycaemia, and inappropriate antidiuretic hormone secretion; hypertension, sweating, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported

Dose

- Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, ADULT and CHILD over 12 years, by mouth, initially 0.5–3 mg 2–3 times daily *or* 3–5 mg 2–3 times daily in severely affected or resistant patients; in resistant schizophrenia up to 30 mg daily may be needed; adjusted according to response to lowest effective maintenance dose (as low as 5–10 mg daily); ELDERLY (or debilitated) initially half adult dose

  By intramuscular *or* by intravenous injection, ADULT over 18 years, initially 2–10 mg, then every 4–8 hours according to response to total max. 18 mg daily; severely disturbed patients may require initial dose of up to 18 mg; ELDERLY (or debilitated) initially half adult dose
- Agitation and restlessness in the elderly, by mouth, initially 0.5–1.5 mg once or twice daily
- Short-term adjunctive management of severe anxiety, by mouth, ADULT over 18 years, 500 micrograms twice daily
- Motor tics, adjunctive treatment in choreas and Tourette syndrome, by mouth, 0.5–1.5 mg 3 times daily adjusted according to response; 10 mg daily or more may occasionally be necessary in Tourette syndrome; CHILD 5–12 years, Tourette syndrome, 12.5–25 microgram/kg twice daily, adjusted according to response up to max. 10 mg daily
- Intractable hiccup, by mouth, ADULT over 18 years, 1.5 mg 3 times daily adjusted according to response
- Nausea and vomiting, see Prescribing in Palliative Care, p. 22

  By intramuscular *or* intravenous injection, 1–2 mg

Haloperidol (Non-proprietary) PoM

Tablets, haloperidol 500 micrograms, net price 28-tab pack = 91p; 1.5 mg, 28-tab pack = £1.39; 5 mg, 28-tab pack = £2.15; 10 mg, 28-tab pack = £5.53; 20 mg, 28-tab pack = £14.07. Label: 2

Injection, haloperidol 5 mg/mL, net price 1-mL amp = 37p

Dozic® (Rosemont) PoM

Oral liquid, sugar-free, haloperidol 1 mg/mL, net price 100-mL pack = £6.86. Label: 2

Haldol® (Janssen-Cilag) PoM

Tablets, both scored, haloperidol 5 mg (blue), net price 100 = £7.21; 10 mg (yellow), 100 = £14.08. Label: 2

Oral liquid, sugar-free, haloperidol 2 mg/mL, net price 100-mL pack (with pipette) = £4.45. Label: 2

Injection, haloperidol 5 mg/mL, net price 1-mL amp = 37p

Serenace® (IVAX) PoM

Capsules, green, haloperidol 500 micrograms, net price 30-cap pack = 98p. Label: 2

Tablets, haloperidol 1.5 mg, net price 30-tab pack = £1.74; 5 mg (pink), 30-tab pack = £3.95; 10 mg (pale pink), 30-tab pack = £6.76. Label: 2

Oral liquid, sugar-free, haloperidol 2 mg/mL, net price 500-mL pack = £34.48. Label: 2

Depot preparation

Section 4.2.2

LEVOMEPROMAZINE
(Methotrimeprazine)

Indications see under Dose

Cautions see notes above; diabetes; patients receiving large initial doses should remain supine

Elderly Risk of postural hypotension; not recommended for ambulant patients over 50 years unless risk of hypotensive reaction assessed

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; occasionally raised erythrocyte sedimentation rate occurs; hyperglycaemia also reported

Dose

- Schizophrenia, by mouth initially 25–50 mg daily in divided doses increased as necessary; bedpatients initially 100–200 mg daily usually in 3 divided doses, increased if necessary to 1 g daily; ELDERLY, see Cautions
- Pain in palliative care, see p. 21
- Restlessness and confusion in palliative care, see p. 23; CHILD 1–18 years, see *BNF for Children*
- Nausea and vomiting in palliative care, by mouth, see p. 22, or by subcutaneous infusion, see p. 23; CHILD 1 month–18 years, see *BNF for Children*

Nozinan® (Sanofi-Aventis) PoM

Tablets, scored, levomepromazine maleate 25 mg, net price 84-tab pack = £20.26. Label: 2

Injection, levomepromazine hydrochloride 25 mg/mL, net price 1-mL amp = £2.01

PERICYAZINE
(Periciazine)

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; more sedating; hypotension common when treatment initiated; respiratory depression

Dose

- Schizophrenia and other psychoses, initially 75 mg daily in divided doses increased at weekly intervals by steps of 25 mg according to response; usual max. 300 mg daily (elderly initially 15–30 mg daily); CHILD and INFANT over 1 year (schizophrenia or behavioural disorders only), initially 500 micrograms daily for 10-kg child, increased by 1 mg for each additional 5 kg body-weight to max. total daily dose of 10 mg; dose may be gradually increased according to response but maintenance should not exceed twice initial dose
- Short-term adjunctive management of severe anxiety, psychomotor agitation, and violent or dangerously impulsive behaviour, initially 15–30 mg (elderly 5–10 mg) daily divided into 2 doses, taking the larger dose at bedtime, adjusted according to response; CHILD not recommended

Pericyazine (Non-proprietary) PoM

Tablets, yellow, scored, pericyazine 2.5 mg, net price 84-tab pack = £9.23; 10 mg, 84-tab pack = £24.95. Label: 2

Syrup, brown, pericyazine 10 mg/5 mL, net price 100-mL pack = £12.08. Label: 2

PERPHENAZINE

Indications see under Dose; antiemetic (section 4.6)

Cautions see notes above; hypothyroidism

Contra-indications see notes above; also agitation and restlessness in the elderly

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating; extrapyramidal symptoms, especially dystonia, more frequent, particularly at high dosage; rarely systemic lupus erythematosus

Dose

- Schizophrenia and other psychoses, mania, short-term adjunctive management of anxiety, severe psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 4 mg 3 times daily adjusted according to the response; max. 24 mg daily; ELDERLY quarter to half adult dose (but see Cautions); CHILD under 14 years not recommended

Fentazin® (Goldshield) PoM

Tablets, s/c, perphenazine 2 mg, net price 100 = £22.38; 4 mg, 100 = £26.34. Label: 2

PIMOZIDE

Indications see under Dose

Cautions see notes above

ECG monitoring Following reports of sudden unexplained death, an ECG is recommended before treatment. It is also recommended that patients taking pimozide should have an annual ECG (if the QT interval is prolonged, treatment should be reviewed and either withdrawn or dose reduced under close supervision) and that pimozide should **not** be given with other antipsychotic drugs (including depot preparations), tricyclic antidepressants or other drugs which prolong the QT interval, such as certain antimalarials, antiarrhythmic drugs and certain antihistamines and should **not** be given with drugs which cause electrolyte disturbances (especially diuretics)

Contra-indications see notes above; history of arrhythmias or congenital QT prolongation

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating; serious arrhythmias reported; glycosuria and, rarely, hyponatraemia reported

Dose

- Schizophrenia, ADULT and CHILD over 12 years, initially 2 mg daily, increased according to response in steps of 2–4 mg at intervals of not less than 1 week; usual dose range 2–20 mg daily; ELDERLY half usual starting dose
- Monosymptomatic hypochondriacal psychosis, paranoid psychosis, ADULT and CHILD over 12 years, initially 4 mg daily, increased according to response in steps of 2–4 mg at intervals of not less than 1 week; max. 16 mg daily; ELDERLY half usual starting dose

Orap® (Janssen-Cilag) PoM

Tablets, scored, green, pimozide 4 mg, net price 100 = £26.87. Label: 2

PROCHLORPERAZINE

Indications see under Dose; antiemetic (section 4.6)

Cautions see notes above; also hypotension more likely after intramuscular injection

Contra-indications see notes above; children, but see section 4.6 for use as antiemetic

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; less sedating; extrapyramidal symptoms, particularly dystonias, more frequent; respiratory depression may occur in susceptible patients

Dose

- By mouth, schizophrenia and other psychoses, mania, prochlorperazine maleate or mesilate, 12.5 mg twice daily for 7 days adjusted at intervals of 4–7 days to usual dose of 75–100 mg daily according to response; CHILD not recommended

  Short-term adjunctive management of severe anxiety, 15–20 mg daily in divided doses; max. 40 mg daily; CHILD not recommended
- By deep intramuscular injection, psychoses, mania, prochlorperazine mesilate 12.5–25 mg 2–3 times daily; CHILD not recommended

Preparations

Section 4.6

PROMAZINE HYDROCHLORIDE

Indications see under Dose

Cautions see notes above; also cerebral arteriosclerosis

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also haemolytic anaemia

Dose

- Short-term adjunctive management of psychomotor agitation, 100–200 mg 4 times daily; CHILD not recommended
- Agitation and restlessness in elderly, 25–50 mg 4 times daily

Promazine (Non-proprietary) PoM

Tablets, coated, promazine hydrochloride 25 mg, net price 100 = £12.38; 50 mg, 100 = £22.00. Label: 2

Oral solution, promazine hydrochloride 25 mg/5 mL, net price 150 mL = £4.65; 50 mg/5 mL, 150 mL = £4.80. Label: 2

SULPIRIDE

Indications schizophrenia

Cautions see notes above; also excited, agitated, or aggressive patients (even low doses may aggravate symptoms)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also hepatitis

Dose

- ADULT and CHILD over 14 years, 200–400 mg twice daily; max. 800 mg daily in predominantly negative symptoms, and 2.4 g daily in mainly positive symptoms; ELDERLY, lower initial dose, increased gradually according to response

Sulpiride (Non-proprietary) PoM

Tablets, sulpiride 200 mg, net price 30-tab pack = £8.09, 56-tab pack = £6.46; 400 mg, 30-tab pack = £18.57. Label: 2

Dolmatil® (Sanofi-Aventis) PoM

Tablets, both scored, sulpiride 200 mg, net price 100-tab pack = £13.31; 400 mg (f/c), 100-tab pack = £34.87. Label: 2

Sulpor® (Rosemont) PoM

Oral solution, sugar-free, lemon- and aniseed-flavoured, sulpiride 200 mg/5 mL, net price 150 mL = £25.38. Label: 2

TRIFLUOPERAZINE

Indications see under Dose; antiemetic (section 4.6)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; extrapyramidal symptoms more frequent, especially at doses exceeding 6 mg daily; anorexia; muscle weakness

Dose

- Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, ADULT and CHILD over 12 years, initially 5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to the response; ELDERLY reduce initial dose by at least half
- Short-term adjunctive management of severe anxiety, ADULT and CHILD over 12 years, 2–4 mg daily in divided doses, increased if necessary to 6 mg daily; CHILD 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily; ELDERLY reduce initial dose by at least half

Trifluoperazine (Non-proprietary) PoM

Tablets, coated, trifluoperazine (as hydrochloride) 1 mg, net price 112-tab pack = £6.57; 5 mg, 112-tab pack = £4.89. Label: 2

Oral solution, trifluoperazine (as hydrochloride) 5 mg/5 mL, net price 150-mL = £10.84. Label: 2

Stelazine® (Goldshield) PoM

Tablets, both blue, f/c, trifluoperazine (as hydrochloride) 1 mg, net price 112 = £3.43; 5 mg, 112 = £4.89. Label: 2

Syrup, sugar-free, yellow, trifluoperazine (as hydrochloride) 1 mg/5 mL, net price 200-mL pack = £2.95. Label: 2

ZUCLOPENTHIXOL ACETATE

Indications short-term management of acute psychosis, mania, or exacerbations of chronic psychosis

Cautions see notes above; avoid in acute porphyria (section 9.8.2)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- By deep intramuscular injection into the gluteal muscle or lateral thigh, 50–150 mg (ELDERLY 50–100 mg), if necessary repeated after 2–3 days (1 additional dose may be needed 1–2 days after the first injection); max. cumulative dose 400 mg per course and max. 4 injections; max. duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, *or* to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; CHILD not recommended

Clopixol Acuphase® (Lundbeck) PoM

Injection (oily), zuclopenthixol acetate 50 mg/mL, net price 1-mL amp = £2.17; 2-mL amp = £2.94

Depot preparation

Section 4.2.2

ZUCLOPENTHIXOL

Indications schizophrenia and other psychoses

Cautions see notes above; avoid in acute porphyria (section 9.8.2)

Contra-indications see notes above; apathetic or withdrawn states

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; urinary frequency or incontinence; weight loss (less common than weight gain)

Dose

- By mouth, initially 20–30 mg daily in divided doses, increasing to a max. of 150 mg daily if necessary; usual maintenance dose 20–50 mg daily; max. single dose 40 mg; ELDERLY (or debilitated) initially quarter to half adult dose; CHILD not recommended

Clopixol® (Lundbeck) PoM

Tablets, f/c, zuclopenthixol (as dihydrochloride) 2 mg (red), net price 100 = £3.14; 10 mg (light red-brown), 100 = £5.64; 25 mg (red-brown), 100 = £7.22. Label: 2

Depot preparation

Section 4.2.2

Atypical antipsychotic drugs

The 'atypical' antipsychotic drugs **amisulpride**, **aripiprazole**, **clozapine**, **olanzapine**, **paliperidone**, **quetiapine**, and **risperidone** may be better tolerated than other antipsychotic drugs; extrapyramidal symptoms may be less frequent than with older antipsychotic drugs.

Aripiprazole, clozapine, olanzapine, and quetiapine cause little or no elevation of prolactin concentration; when changing from other antipsychotic drugs, a reduction in prolactin may increase fertility.

Clozapine is licensed for the treatment of schizophrenia only in patients unresponsive to, or intolerant of, conventional antipsychotic drugs. It can cause agranulocytosis and its use is restricted to patients registered with a clozapine patient monitoring service (see under Clozapine).

The *Scottish Medicines Consortium* (p. 4) has advised (April 2009) that quetiapine (*Seroquel®*) is **not** recommended for use within NHS Scotland for the treatment of major depressive episodes associated with bipolar disorder.

NICE guidance

Atypical antipsychotics for schizophrenia (June 2002) and schizophrenia (March 2009)

NICE has recommended that:

- the atypical antipsychotics (amisulpride, olanzapine, quetiapine, risperidone, and zotepine) should be considered when choosing first-line treatment of *newly diagnosed schizophrenia*;
- an atypical antipsychotic is considered the treatment option of choice for managing an *acute schizophrenic episode* when discussion with the individual is not possible;
- an atypical antipsychotic should be considered for an individual who is suffering unacceptable side-effects from a conventional antipsychotic;
- an atypical antipsychotic should be considered for an individual in relapse whose symptoms were previously inadequately controlled;
- changing to an atypical antipsychotic is not necessary if a conventional antipsychotic controls symptoms adequately and the individual does not suffer unacceptable side-effects;
- clozapine should be introduced if schizophrenia is inadequately controlled despite the sequential use of two or more antipsychotics (one of which should be an atypical antipsychotic) each for at least 6–8 weeks.
- If symptoms do not respond adequately to an optimised dose of clozapine, measure clozapine plasma levels before adding a second antipsychotic to augment clozapine. If a second antipsychotic is added, there should be 8–10 weeks treatment duration to assess for response.

Cautions and contra-indications While atypical antipsychotic drugs have not generally been associated with clinically significant prolongation of the QT interval, they should be used with care if prescribed with other drugs that increase the QT interval. Atypical antipsychotic drugs should be used with caution in patients with cardiovascular disease, or a history of epilepsy; they should be used with great caution in the elderly (see p. 216); **interactions:** Appendix 1 (antipsychotics).

Driving Atypical antipsychotic drugs may affect performance of skilled tasks (e.g. driving); effects of alcohol are enhanced.

Withdrawal Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

Side-effects Side-effects of the atypical antipsychotic drugs include weight gain, dizziness, postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some patients, extrapyramidal symptoms (usually mild and transient and which respond to dose reduction or to an antimuscarinic drug), and occasionally tardive dyskinesia on long-term administration (discontinue drug on appearance of early signs); venous thromboembolism has been reported. Hyperglycaemia and sometimes diabetes can occur, particularly with clozapine, olanzapine, and risperidone; monitoring weight and plasma-glucose concentration may identify the development of hyperglycaemia. Neuroleptic malignant syndrome has been reported rarely. Hypersalivation associated with clozapine therapy can be treated with hyoscine hydrobromide [unlicensed indication] (p. 256), provided that the patient is not at particular risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

AMISULPRIDE

Indications schizophrenia

Cautions see notes above; also Parkinson's disease

Contra-indications see notes above; also phaeochromocytoma, prolactin-dependent tumours

Renal impairment halve dose if eGFR 30–60 mL/minute/1.73 m^2; use one-third dose if eGFR 10–30 mL/minute/1.73 m^2; no information available if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding avoid—no information available

Side-effects see notes above; also insomnia, anxiety, agitation, drowsiness, gastro-intestinal disorders such as constipation, nausea, vomiting, and dry mouth; hyperprolactinaemia; *occasionally* bradycardia; *rarely* seizures

Dose

- Acute psychotic episode, 400–800 mg daily in 2 divided doses, adjusted according to response; max. 1.2 g daily; CHILD under 15 years not recommended
- Predominantly negative symptoms, 50–300 mg daily; CHILD under 15 years not recommended

Amisulpride (Non-proprietary) PoM

Tablets, amisulpride 50 mg, net price 60-tab pack = £7.18; 100 mg, 60-tab pack = £31.74; 200 mg, 60-tab pack = £16.47; 400 mg, 60-tab pack = £105.68. Label: 2

Solian® (Sanofi-Aventis) PoM

Tablets, scored, amisulpride 50 mg, net price 60-tab pack = £22.76; 100 mg, 60-tab pack = £35.29; 200 mg, 60-tab pack = £58.99; 400 mg, 60-tab pack = £117.97. Label: 2

Solution, 100 mg/mL, net price 60 mL (caramel flavour) = £33.76. Label: 2

ARIPIPRAZOLE

Indications see under Dose

Cautions see notes above; cerebrovascular disease; elderly (reduce initial dose)

Contra-indications see notes above

Hepatic impairment use with caution in severe impairment

Pregnancy use only if potential benefit outweighs risk—no information available

Breast-feeding avoid—present in milk in *animal* studies

Side-effects see notes above; gastro-intestinal disturbances; tachycardia; fatigue, insomnia, akathisia, drowsiness, restlessness, tremor, headache, asthenia; blurred vision; *less commonly* depression; *very rarely* anorexia, dysphagia, oropharyngeal spasm, laryngospasm, hepatitis, jaundice, hypersalivation, pancreatitis, oedema, thromboembolism, arrhythmias, bradycardia, hypertension, chest pain, agitation, anxiety, speech disorder, suicidal ideation, seizures, hyponatraemia, stiffness, myalgia, rhabdomyolysis, priapism, urinary retention and incontinence, blood disorders, sweating, alopecia, photosensitivity reactions, rash, weight loss, and impaired temperature regulation; *with injection*, dry mouth

Dose

- Schizophrenia, by mouth, ADULT over 18 years 10–15 mg once daily, usual maintenance 15 mg once daily; max. 30 mg once daily; CHILD 15–18 years, initially 2 mg once daily for 2 days, then 5 mg once daily for 2 days, then 10 mg daily; thereafter increased if necessary in steps of 5 mg to max. 30 mg daily
- Treatment and prevention of mania, by mouth, ADULT over 18 years, 15 mg once daily, increased if necessary; max. 30 mg once daily
- Control of agitation and disturbed behaviour in schizophrenia, by intramuscular injection, ADULT over 18 years, initially 5.25–15 mg (usual dose 9.75 mg) as a single dose followed by 5.25–15 mg after 2 hours if necessary; max. 3 injections daily; max. daily combined oral and parenteral dose 30 mg

Abilify® (Bristol-Myers Squibb) PoM

Tablets, aripiprazole 5 mg (blue), net price 28-tab pack = £95.74; 10 mg (pink), 28-tab pack = £95.74; 15 mg (yellow), 28-tab pack = £95.74; 30 mg (pink), 28-tab pack = £191.47. Label: 2

Orodispersible tablets, aripiprazole 10 mg (pink), net price 28-tab pack = £95.74; 15 mg (yellow), 28-tab pack = £95.74. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed

Oral solution, aripiprazole 1 mg/mL, net price 150 mL with measuring cup = £102.57. Label: 2

Injection ▼, aripiprazole 7.5 mg/mL, net price 1.3-mL (9.75-mg) vial = £3.42

CLOZAPINE

Indications schizophrenia (including psychosis in Parkinson's disease) in patients unresponsive to, or intolerant of, conventional antipsychotic drugs

Cautions see notes above; elderly; monitor leucocyte and differential blood counts (see Agranulocytosis, below); prostatic hypertrophy, susceptibility to angle-closure glaucoma; taper off other antipsychotics

before starting; close medical supervision during initiation (risk of collapse because of hypotension); dose adjustment may be necessary if smoking started or stopped during treatment

Withdrawal On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe patient carefully

Agranulocytosis Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm^3 or if absolute neutrophil count below 1500/mm^3 discontinue permanently and refer to haematologist. Patients who have a low white blood cell count because of benign ethnic neutropenia may be started on clozapine with the agreement of a haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of infection, especially influenza-like illness

Myocarditis and cardiomyopathy Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported.

- Perform physical examination and take full medical history before starting
- Specialist examination required if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk
- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy
- If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist
- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

Gastro-intestinal obstruction Reactions resembling gastro-intestinal obstruction reported. Clozapine should be used cautiously with drugs which cause constipation (e.g. antimuscarinic drugs) or in history of colonic disease or bowel surgery. Monitor for constipation and prescribe laxative if required

Contra-indications severe cardiac disorders (e.g. myocarditis; see Cautions); history of neutropenia or agranulocytosis (see Cautions); bone-marrow disorders; paralytic ileus (see Cautions); alcoholic and toxic psychoses; history of circulatory collapse; drug intoxication; coma or severe CNS depression; uncontrolled epilepsy

Hepatic impairment monitor hepatic function regularly; avoid in symptomatic or progressive liver disease or hepatic failure

Renal impairment avoid in severe impairment

Pregnancy use with caution

Breast-feeding avoid

Side-effects see notes above; also constipation (see Cautions), hypersalivation, dry mouth, nausea, vomiting, anorexia; tachycardia, ECG changes, hypertension; drowsiness, dizziness, headache, tremor, seizures, fatigue, impaired temperature regulation; urinary incontinence and retention; leucopenia, eosinophilia, leucocytosis; blurred vision; sweating; *less commonly* agranulocytosis (**important:** see Cautions); *rarely* dysphagia, hepatitis, cholestatic jaundice, pancreatitis, circulatory collapse, arrhythmia, myocarditis (**important:** see Cautions), pericarditis, thromboembolism, agitation, confusion, delirium, anaemia; *very rarely* parotid gland enlargement, intestinal obstruction (see Cautions), cardiomyopathy, myocardial infarction, respiratory depression, priapism, interstitial nephritis, thrombocytopenia, thrombocythaemia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, angle-closure glaucoma, fulminant hepatic necrosis, and skin reactions

Dose

- Schizophrenia, ADULT over 16 years, 12.5 mg once or twice (ELDERLY 12.5 mg once) on first day then 25–50 mg (ELDERLY 25–37.5 mg) on second day then increased gradually (if well tolerated) in steps of 25–50 mg daily (ELDERLY max. increment 25 mg daily) over 14–21 days up to 300 mg daily in divided doses (larger dose at night, up to 200 mg daily may be taken as a single dose at bedtime); if necessary may be further increased in steps of 50–100 mg once (preferably) or twice weekly; usual dose 200–450 mg daily (max. 900 mg daily)

  Note *Restarting* after *interval of more than 2 days*, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

- Psychosis in Parkinson's disease, ADULT over 16 years, 12.5 mg at bedtime then increased according to response in steps of 12.5 mg up to twice weekly; usual dose range 25–37.5 mg at bedtime, usual max. 50 mg daily; exceptionally, dose may be increased further in steps of 12.5 mg weekly to max. 100 mg daily in 1–2 divided doses

Clozaril® (Novartis) PoM

Tablets, yellow, clozapine 25 mg (scored), net price 28-tab pack = £5.40, 84-tab pack (hosp. only) = £16.18, 100-tab pack (hosp. only) = £19.26; 100 mg, 28-tab pack = £21.56, 84-tab pack (hosp. only) = £64.68, 100-tab pack (hosp. only) = £77.00. Label: 2, 10, patient information leaflet

Note Patient, prescriber, and supplying pharmacist must be registered with the Clozaril Patient Monitoring Service—takes several days to do this

Denzapine® (Merz) PoM

Tablets, yellow, scored, clozapine 25 mg, net price 28-tab pack = £6.17, 84-tab pack = £16.64, 100-tab pack = £19.80; 50 mg, 50-tab pack = £19.80; 100 mg, 28-tab pack = £24.64, 84-tab pack = £66.53, 100-tab pack = £79.20; 200 mg, 50-tab pack = £79.20. Label: 2, 10, patient information leaflet

Suspension, clozapine 50 mg/mL, net price 100 mL = £39.60. Label: 2, 10, patient information leaflet, counselling, administration

Counselling Shake well for 90 seconds when dispensing or if visibly settled; otherwise shake well for 10 seconds before use

Note May be diluted with water

Note Patient, prescriber, and supplying pharmacist must be registered with the Denzapine Patient Monitoring Service—takes several days to do this

Zaponex® (TEVA UK) PoM

Tablets, yellow, scored, clozapine 25 mg, net price 84-tab pack = £8.28; 100 mg, 84-tab pack = £33.88. Label: 2, 10, patient information leaflet

Note Patient, prescriber, and supplying pharmacist must be registered with the Zaponex Treatment Access System—takes several days to do this

OLANZAPINE

Indications see under Dose

Cautions see notes above; also prostatic hypertrophy, susceptibility to angle-closure glaucoma, paralytic ileus, diabetes mellitus (risk of exacerbation or ketoacidosis), low leucocyte or neutrophil count, bone-

marrow depression, hypereosinophilic disorders, myeloproliferative disease, Parkinson's disease; dose adjustment may be necessary if smoking started or stopped during treatment

CNS and respiratory depression Blood pressure, pulse and respiratory rate should be monitored for at least 4 hours after intramuscular injection, particularly in those also receiving another antipsychotic or benzodiazepine

Contra-indications *for injection*, acute myocardial infarction, unstable angina, severe hypotension or bradycardia, sick sinus syndrome, recent heart surgery

Hepatic impairment consider initial dose of 5 mg daily

Renal impairment consider initial dose of 5 mg daily

Pregnancy use only if potential benefit outweighs risk; neonatal lethargy, tremor, and hypertonia reported when used in third trimester

Breast-feeding avoid—present in milk

Side-effects see notes above; also mild, transient antimuscarinic effects (*very rarely* precipitation of angle-closure glaucoma); drowsiness, speech difficulty, exacerbation of Parkinson's disease, abnormal gait, hallucinations, akathisia, asthenia, fatigue, increased appetite, increased body temperature, raised triglyceride concentration, oedema, hyperprolactinaemia (but clinical manifestations uncommon); eosinophilia; *less commonly* hypotension, bradycardia, QT-interval prolongation, urinary incontinence, and photosensitivity; *rarely* seizures, leucopenia, and rash; *very rarely* hepatitis, pancreatitis, thromboembolism, hypercholesterolaemia, hypothermia, urinary retention, priapism, thrombocytopenia, neutropenia, rhabdomyolysis, and alopecia; *with injection*, sinus pause and hypoventilation

Dose

- Schizophrenia, combination therapy for mania, preventing recurrence in bipolar disorder, by mouth, ADULT over 18 years, 10 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 10 mg daily only after reassessment; max. 20 mg daily; CHILD 12–18 years, see *BNF for Children*
- Monotherapy for mania, by mouth, ADULT over 18 years, 15 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 15 mg only after reassessment; max. 20 mg daily; CHILD 12–18 years, see *BNF for Children*
- Control of agitation and disturbed behaviour in schizophrenia or mania, by intramuscular injection, ADULT over 18 years, initially 5–10 mg (usual dose 10 mg) as a single dose followed by 5–10 mg after 2 hours if necessary; ELDERLY initially 2.5–5 mg as a single dose followed by 2.5–5 mg after 2 hours if necessary; max. 3 injections daily for 3 days; max. daily combined oral and parenteral dose 20 mg

Note When one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase

Zyprexa® (Lilly) PoM

Tablets, f/c, olanzapine 2.5 mg, net price 28-tab pack = £21.85; 5 mg, 28-tab pack = £43.70; 7.5 mg, 56-tab pack = £131.10; 10 mg, 28-tab pack = £87.40, 15 mg (blue), 28-tab pack = £119.18; 20 mg (pink), 28-tab pack = £158.90. Label: 2

Orodispersible tablet (*Velotab®*), yellow, olanzapine 5 mg, net price 28-tab pack = £48.07; 10 mg, 28-tab pack = £87.40; 15 mg, 28-tab pack = £131.10; 20 mg, 28-tab pack = £174.79. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling *Velotab®* may be placed on the tongue and allowed to dissolve, or dispersed in water, orange juice, apple juice, milk, or coffee

Injection ▼, powder for reconstitution, olanzapine 5 mg/mL, net price 10-mg vial = £3.48

Depot preparation

Section 4.2.2

PALIPERIDONE

Note Paliperidone is a metabolite of risperidone

Indications schizophrenia

Cautions see notes above; predisposition to gastrointestinal obstruction; elderly patients with dementia and risk factors for stroke; Parkinson's disease

Hepatic impairment caution in severe impairment—no information available

Renal impairment initially 3 mg once daily if eGFR 50–80 mL/minute/1.73 m^2 (max. 6 mg once daily); initially 1.5 mg once daily if eGFR 10–50 mL/minute/1.73 m^2 (max. 3 mg once daily); avoid if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy use only if potential benefit outweighs risk—toxicity in animal studies; if discontinuation during pregnancy is necessary, withdraw gradually

Breast-feeding avoid—present in milk

Side-effects see notes above; also abdominal pain, dry mouth, hypersalivation, vomiting; tachycardia, bradycardia, first-degree AV block, bundle branch block; drowsiness, agitation, headache, asthenia; *less commonly* palpitation, arrhythmias, ischaemia, oedema, seizures, nightmare, syncope, menstrual disturbances, erectile dysfunction, galactorrhoea, gynaecomastia, and rash; cerebrovascular accident also reported

Dose

- ADULT over 18 years, 6 mg once daily in the morning, adjusted if necessary in increments of 3 mg over at least 5 days; usual range 3–12 mg daily

Counselling Always take with breakfast or always take on an empty stomach

Invega® (Janssen-Cilag) ▼ PoM

Tablets, m/r, paliperidone 3 mg (white), net price 28-tab pack = £97.28; 6 mg (beige), 28-tab pack = £97.28; 9 mg (pink), 28-tab pack = £145.92. Label: 2, 25, counselling, administration

QUETIAPINE

Indications schizophrenia; mania, either alone or with mood stabilisers; depression in bipolar disorder; adjunctive treatment in major depressive disorder

Cautions see notes above; also cerebrovascular disease; patients at risk of aspiration pneumonia; treatment of depression in patients under 25 years (increased risk of suicide)

Hepatic impairment for *immediate-release tablets*, initially 25 mg daily, increased daily in steps of 25–50 mg; for *modified-release tablets*, initially 50 mg daily, increased daily in steps of 50 mg

Pregnancy use only if potential benefit outweighs risk

Breast-feeding avoid—no information available

Side-effects see notes above; also dry mouth, constipation, dyspepsia; tachycardia, hypertension, elevated plasma-triglyceride and -cholesterol concentrations, peripheral oedema; drowsiness, headache,

irritability, dysarthria, asthenia; hyperprolactinaemia; leucopenia, neutropenia; blurred vision; rhinitis; *less commonly* dysphagia, seizures, restless legs syndrome, and eosinophilia; *rarely* jaundice and priapism; *very rarely* hepatitis, angioedema, and Stevens-Johnson syndrome; suicidal behaviour (particularly on initiation) also reported

Dose

- Schizophrenia, ADULT over 18 years, 25 mg twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 150 mg twice daily on day 4, then adjusted according to response, usual range 300–450 mg daily in 2 divided doses; max. 750 mg daily; ELDERLY initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses; CHILD 12–18 years, see *BNF for Children*
- Treatment of mania in bipolar disorder, ADULT over 18 years, 50 mg twice daily on day 1, 100 mg twice daily on day 2, 150 mg twice daily on day 3, 200 mg twice daily on day 4, then adjusted according to response in steps of up to 200 mg daily to max. 800 mg daily; usual range 400–800 mg daily in 2 divided doses; ELDERLY initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses
- Treatment of depression in bipolar disorder, ADULT over 18 years, 50 mg once daily (at bedtime) on day 1, 100 mg once daily on day 2, 200 mg once daily on day 3, 300 mg once daily on day 4; adjust according to response, usual dose 300 mg once daily, max. 600 mg daily
- Prevention of mania and depression in bipolar disorder, ADULT over 18 years, continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual range 300–800 mg in 2 divided doses

Seroquel® (AstraZeneca) PoM

Tablets, f/c, quetiapine (as fumarate) 25 mg (peach), net price 60-tab pack = £33.83; 100 mg (yellow), 60-tab pack = £113.10; 150 mg (pale yellow), 60-tab pack = £113.10; 200 mg (white), 60-tab pack = £113.10; 300 mg (white), 60-tab pack = £170.00. Label: 2

Modified release

Seroquel® XL (AstraZeneca) ▼ PoM

Tablets, m/r, quetiapine (as fumarate) 50 mg (peach), net price 60-tab pack = £67.66; 150 mg (white) 60-tab pack = £113.10; 200 mg (yellow), 60-tab pack = £113.10; 300 mg (pale yellow), 60-tab pack = £170.00; 400 mg (white), 60-tab pack = £226.20. Label: 2, 23, 25

Dose schizophrenia, ADULT over 18 years, 300 mg once daily on day 1, then 600 mg once daily on day 2; adjust according to response, usual dose 600 mg once daily; max. 800 mg under specialist supervision; ELDERLY initially 50 mg once daily adjusted according to response in steps of 50 mg daily

Treatment of mania in bipolar disorder, ADULT over 18 years, 300 mg once daily on day 1, then 600 mg once daily on day 2, then adjusted according to response; dose range 400–800 mg once daily; ELDERLY initially 50 mg once daily adjusted according to response in steps of 50 mg daily

Treatment of depression in bipolar disorder, ADULT over 18 years, 50 mg once daily (at bedtime) on day 1, 100 mg once daily on day 2, 200 mg once daily on day 3, 300 mg once daily on day 4; adjust according to response, usual dose 300 mg once daily, max. 600 mg daily

Prevention of mania and depression in bipolar disorder, ADULT over 18 years, continue at the dose effective for treatment of bipolar disorder and adjust to lowest effective dose; usual range 300–800 mg once daily

Adjunctive treatment of major depression, ADULT over 18 years, 50 mg once daily at bedtime for 2 days, then 150 mg once daily for 2 days, then adjusted according to response, usual range 150–300 mg once daily; ELDERLY, initially 50 mg once daily for 3 days, then increase if necessary to 100 mg once daily for 4 days; thereafter adjusted in steps of 50 mg according to response, usual range 50–300 mg once daily (dose of 300 mg should not be reached before day 22 of treatment)

RISPERIDONE

Indications acute and chronic psychoses, mania; short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others; short-term treatment (up to 6 weeks) of persistent aggression in conduct disorder (under specialist supervision)

Cautions see notes above; Parkinson's disease; dementia with Lewy bodies; dehydration; avoid in acute porphyria (section 9.8.2)

Hepatic impairment initial and subsequent oral doses should be halved

Renal impairment initial and subsequent oral doses should be halved

Pregnancy use only if potential benefit outweighs risk; extrapyramidal effects reported in neonates when taken in third trimester

Breast-feeding use only if potential benefit outweighs risk—small amount present in milk

Side-effects see notes above; also gastro-intestinal disturbances (including diarrhoea, constipation, nausea and vomiting, dyspepsia, abdominal pain), dry mouth; dyspnoea; drowsiness, asthenia, tremor, sleep disturbances, agitation, anxiety, headache; urinary incontinence; arthralgia, myalgia; abnormal vision; epistaxis; rash; *less commonly* anorexia, ECG changes, hypoaesthesia, impaired concentration, hyperprolactinaemia (with galactorrhoea, menstrual disturbances, gynaecomastia), sexual dysfunction, blood disorders, tinnitus, angioedema; *rarely* intestinal obstruction, pancreatitis, jaundice, seizures, hyponatraemia, abnormal temperature regulation; oedema and priapism also reported

Dose

- Psychoses, 2 mg in 1–2 divided doses on first day *then* 4 mg in 1–2 divided doses on second day (slower titration appropriate in some patients); usual dose range 4–6 mg daily; doses above 10 mg daily only if benefit considered to outweigh risk (max. 16 mg daily); ELDERLY initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily; CHILD 12–18 years see *BNF for Children*
- Mania, initially 2 mg once daily, increased if necessary in steps of 1 mg daily; usual dose range 1–6 mg daily; ELDERLY initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily
- Persistent aggression in Alzheimer's dementia, initially 250 micrograms twice daily, increased according to response in steps of 250 micrograms twice daily on alternate days; usual dose 500 micrograms twice daily (up to 1 mg twice daily has been required)
- Persistent aggression in conduct disorder, CHILD over 5 years, body-weight under 50 kg, initially 250 micrograms once daily, increased according to response in steps of 250 micrograms on alternate days; usual dose 500 micrograms daily (up to 750 micrograms once daily has been required); CHILD over 5 years, body-

weight over 50 kg, initially 500 micrograms once daily, increased according to response in steps of 500 micrograms on alternate days; usual dose 1 mg daily (up to 1.5 mg once daily has been required)

Risperidone (Non-proprietary) ▼ PoM

Tablets, risperidone 500 micrograms, net price 20-tab pack = 97p; 1 mg, 20-tab pack = £1.18, 60-tab pack = £1.70; 2 mg, 60-tab pack = £2.13; 3 mg, 60-tab pack = £2.71; 4 mg, 60-tab pack = £31.52; 6 mg, 28-tab pack = £24.12. Label: 2

Orodispersible tablets, risperidone 0.5 mg, net price 28-tab pack = £16.88; 1 mg, 28-tab pack = £20.51; 2 mg, 28-tab pack = £37.72; 3 mg, 28-tab pack = £14.39; 4 mg, 28-tab pack = £15.20. Label: 2, counselling, administration

Counselling Tablets should be placed on the tongue, allowed to dissolve and swallowed

Liquid, risperidone 1 mg/mL, net price 100-mL pack = £57.40. Label: 2, counselling, use of dose syringe

Note Liquid may be diluted with any non-alcoholic drink, except tea

Risperdal® (Janssen-Cilag) ▼ PoM

Tablets, f/c, scored, risperidone 500 micrograms (brown-red), net price 20-tab pack = £5.08; 1 mg (white), 20-tab pack = £8.36, 60-tab pack = £25.08; 2 mg (orange), 60-tab pack = £49.46; 3 mg (yellow), 60-tab pack = £72.73; 4 mg (green), 60-tab pack = £96.00; 6 mg (yellow), 28-tab pack = £67.88. Label: 2

Orodispersible tablets (*Quicklet®*), pink, risperidone 500 micrograms, net price 28-tab pack = £8.23; 1 mg, 28-tab pack = £17.32; 2 mg, 28-tab pack = £32.65; 3 mg, 28-tab pack = £36.24; 4 mg, 28-tab pack = £46.68. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to dissolve and swallowed

Liquid, risperidone 1 mg/mL, net price 100 mL = £52.87. Label: 2, counselling, use of dose syringe

Note Liquid may be diluted with any non-alcoholic drink, except tea

Depot preparation

Section 4.2.2

4.2.2 Antipsychotic depot injections

Long-acting depot injections are used for maintenance therapy especially when compliance with oral treatment is unreliable. However, depot injections of conventional antipsychotics may give rise to a higher incidence of extrapyramidal reactions than oral preparations; extrapyramidal reactions occur less frequently with atypical antipsychotic depot preparations, such as risperidone and olanzapine embonate.

Administration Depot antipsychotics are administered by deep intramuscular injection at intervals of 1 to 4 weeks. When initiating therapy with sustained-release preparations of conventional antipsychotics, patients should first be given a small test-dose as undesirable side-effects are prolonged. In general not more than 2–3 mL of oily injection should be administered at any one site; correct injection technique (including the use of z-track technique) and rotation of injection sites are essential. If the dose needs to be reduced to alleviate side-effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose, therefore it may be a month or longer before side-effects subside.

Dosage Individual responses to neuroleptic drugs are very variable and to achieve optimum effect, dosage and dosage interval must be titrated according to the patient's response. For the advice of The Royal College of Psychiatrists on doses above the BNF upper limit, see p. 215.

Equivalent doses of depot antipsychotics

These equivalences are intended **only** as an approximate guide; individual dosage instructions should **also** be checked; patients should be carefully monitored after **any** change in medication

Antipsychotic drug	Dose (mg)	Interval
Flupentixol decanoate	40	2 weeks
Fluphenazine decanoate	25	2 weeks
Haloperidol (as decanoate)	100	4 weeks
Pipotiazine palmitate	50	4 weeks
Zuclopenthixol decanoate	200	2 weeks

Important These equivalences must **not** be extrapolated beyond the maximum dose for the drug

Choice There is no clear-cut division in the use of the conventional antipsychotics, but **zuclopenthixol** may be suitable for the treatment of agitated or aggressive patients whereas **flupentixol** can cause over-excitement in such patients. The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.

Cautions See section 4.2.1. Treatment requires careful monitoring for optimum effect. When transferring from oral to depot therapy, the dose by mouth should be reduced gradually.

Contra-indications See section 4.2.1. Do not use in children.

Side-effects See section 4.2.1. Pain may occur at injection site and occasionally erythema, swelling, and nodules. For side-effects of specific antipsychotics see under the relevant drug.

FLUPENTIXOL DECANOATE

(Flupenthixol Decanoate)

Indications maintenance in schizophrenia and other psychoses

Cautions see Flupentixol (section 4.2.1) and notes above; an alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear

Contra-indications see Flupentixol (section 4.2.1) and notes above

Hepatic impairment see section 4.2.1

Renal impairment see section 4.2.1

Pregnancy see section 4.2.1

Breast-feeding see section 4.2.1

Side-effects see Flupentixol (section 4.2.1) and notes above, but may have a mood elevating effect

Dose

- By deep intramuscular injection into the upper outer buttock or lateral thigh, test dose 20 mg, then after at least 7 days 20–40 mg repeated at intervals of 2–4 weeks, adjusted according to response; max. 400 mg weekly; usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; ELDERLY initially quarter to half adult dose; CHILD not recommended

Depixol® (Lundbeck) PoM
Injection (oily), flupentixol decanoate 20 mg/mL, net price 1-mL amp = £1.28; 2-mL amp = £2.49

Depixol Conc.® (Lundbeck) PoM
Injection (oily), flupentixol decanoate 100 mg/mL, net price 0.5-mL amp = £1.53; 1-mL amp = £1.84

Depixol Low Volume® (Lundbeck) PoM
Injection (oily), flupentixol decanoate 200 mg/mL, net price 1-mL amp = £3.01

FLUPHENAZINE DECANOATE

Indications maintenance in schizophrenia and other psychoses

Cautions see section 4.2.1 and notes above; dose adjustment may be necessary if smoking started or stopped during treatment; QT-interval prolongation (avoid concomitant drugs that prolong QT interval)

Contra-indications see section 4.2.1 and notes above; also marked cerebral atherosclerosis

Hepatic impairment see section 4.2.1; avoid in hepatic failure

Renal impairment see section 4.2.1; manufacturer advises caution; avoid in renal failure

Pregnancy see section 4.2.1

Breast-feeding see section 4.2.1

Side-effects see section 4.2.1 and notes above; less sedating and fewer antimuscarinic or hypotensive symptoms, but extrapyramidal symptoms, particularly dystonic reactions and akathisia, more frequent; systemic lupus erythematosus, inappropriate antidiuretic hormone secretion, and oedema also reported; extrapyramidal symptoms usually appear a few hours after injection and continue for about 2 days but may be delayed

Dose

- By deep intramuscular injection into the gluteal muscle, test dose 12.5 mg (6.25 mg in elderly), then after 4–7 days 12.5–100 mg repeated at intervals of 14–35 days, adjusted according to response; CHILD not recommended

Fluphenazine decanoate (Non-proprietary) PoM
Injection (oily), fluphenazine decanoate 25 mg/mL, net price 1-mL amp = £2.35; 100 mg/mL, 0.5-mL amp = £4.50, 1-mL amp = £8.79
Excipients include sesame oil

Modecate® (Sanofi-Aventis) PoM
Injection (oily), fluphenazine decanoate 25 mg/mL, net price 0.5-mL amp = £1.30, 1-mL amp = £2.26, 2-mL amp = £4.44
Excipients include sesame oil

Modecate Concentrate® (Sanofi-Aventis) PoM
Injection (oily), fluphenazine decanoate 100 mg/mL, net price 0.5-mL amp = £4.47, 1-mL amp = £8.75
Excipients include sesame oil

HALOPERIDOL

Indications maintenance in schizophrenia and other psychoses

Cautions see Haloperidol (section 4.2.1) and notes above

Contra-indications see Haloperidol (section 4.2.1) and notes above

Hepatic impairment see section 4.2.1

Renal impairment see section 4.2.1

Pregnancy see section 4.2.1

Breast-feeding see section 4.2.1

Side-effects see Haloperidol (section 4.2.1) and notes above

Dose

- By deep intramuscular injection into the gluteal muscle, initially 50 mg every 4 weeks, if necessary increasing by 50-mg increments to 300 mg every 4 weeks; higher doses may be needed in some patients; ELDERLY, initially 12.5–25 mg every 4 weeks; CHILD not recommended
  Note If 2-weekly administration preferred, doses should be halved

Haldol Decanoate® (Janssen-Cilag) PoM
Injection (oily), haloperidol (as decanoate) 50 mg/mL, net price 1-mL amp = £3.82; 100 mg/mL, 1-mL amp = £5.06
Excipients include sesame oil

OLANZAPINE EMBONATE
(Olanzapine Pamoate)

Indications maintenance in schizophrenia in patients tolerant to olanzapine by mouth

Cautions see under Olanzapine (section 4.2.1) and notes above; observe patient for at least 3 hours after injection

Contra-indications see under Olanzapine (section 4.2.1) and notes above

Hepatic impairment initially 150 mg every 4 weeks; increase with caution in moderate impairment

Renal impairment initially 150 mg every 4 weeks

Pregnancy see under Olanzapine (section 4.2.1)

Breast-feeding see under Olanzapine (section 4.2.1)

Side-effects see under Olanzapine (section 4.2.1) and notes above; post-injection reactions have been reported leading to signs and symptoms of overdose

Dose

- By deep intramuscular injection into the gluteal muscle, ADULT 18–75 years, *patients taking oral olanzapine 10 mg daily*, initially 210 mg every 2 weeks *or* 405 mg every 4 weeks, then maintenance dose after 2 months treatment, 150 mg every 2 weeks *or* 300 mg every 4 weeks; *patients taking oral olanzapine 15 mg daily*, initially 300 mg every 2 weeks, then maintenance dose after 2 months treatment, 210 mg every 2 weeks *or* 405 mg every 4 weeks; *patients taking oral olanzapine 20 mg daily*, initially 300 mg every 2 weeks, then maintenance dose after 2 months treatment 300 mg every 2 weeks; dose adjusted according to response; max. 300 mg every 2 weeks
  Note If supplementation with oral olanzapine required, consult product literature

ZypAdhera® (Lilly) ▼ PoM
Injection, powder for reconstitution, olanzapine embonate 210-mg vial, net price = £142.76, 300-mg vial = £222.64, 405-mg vial = £285.52 (all with diluent)

PIPOTIAZINE PALMITATE
(Pipothiazine Palmitate)

Indications maintenance in schizophrenia and other psychoses
Cautions see section 4.2.1 and notes above; also thyrotoxicosis; hypothyroidism
Contra-indications see section 4.2.1 and notes above
Hepatic impairment see section 4.2.1
Renal impairment see section 4.2.1
Pregnancy see section 4.2.1
Breast-feeding avoid unless essential
Side-effects see section 4.2.1 and notes above; respiratory depression also reported
Dose
- By deep intramuscular injection into the gluteal muscle, test dose 25 mg, then a further 25–50 mg after 4–7 days, then adjusted according to response at intervals of 4 weeks; usual maintenance range 50–100 mg (max. 200 mg) every 4 weeks; ELDERLY initially 5–10 mg; CHILD not recommended

Piportil Depot® (Sanofi-Aventis) PoM
Injection (oily), pipotiazine palmitate 50 mg/mL, net price 1-mL amp = £16.29; 2-mL amp = £26.65
Excipients include sesame oil

RISPERIDONE

Indications schizophrenia and other psychoses in patients tolerant to risperidone by mouth
Cautions see Risperidone (section 4.2.1) and notes above
Hepatic impairment if an oral dose of at least 2 mg daily tolerated, 25 mg as a depot injection can be given every 2 weeks
Renal impairment see Risperidone (section 4.2.1)
Pregnancy see Risperidone (section 4.2.1)
Breast-feeding see Risperidone (section 4.2.1)
Side-effects see Risperidone (section 4.2.1); also hypertension; depression, paraesthesia; *less commonly* apathy, weight loss, injection-site reactions, and pruritus
Dose
- By deep intramuscular injection into the deltoid or gluteal muscle, patients taking oral risperidone up to 4 mg daily, initially 25 mg every 2 weeks; patients taking oral risperidone over 4 mg daily, initially 37.5 mg every 2 weeks; dose adjusted at intervals of at least 4 weeks in steps of 12.5 mg to max. 50 mg every 2 weeks; CHILD under 18 years not recommended
Note During initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection

Risperdal Consta® (Janssen-Cilag) ▼ PoM
Injection, powder for reconstitution, risperidone 25-mg vial, net price = £79.69; 37.5-mg vial = £111.32; 50-mg vial = £142.76 (all with diluent)

ZUCLOPENTHIXOL DECANOATE

Indications maintenance in schizophrenia and paranoid psychoses
Cautions see section 4.2.1 and notes above; QT-interval prolongation (avoid concomitant use of drugs that prolong QT interval); avoid in acute porphyria (section 9.8.2)
Contra-indications see section 4.2.1 and notes above
Hepatic impairment see section 4.2.1
Renal impairment see section 4.2.1
Pregnancy see section 4.2.1
Breast-feeding see section 4.2.1
Side-effects see section 4.2.1 and notes above
Dose
- By deep intramuscular injection into the upper outer buttock or lateral thigh, test dose 100 mg, followed after at least 7 days by 200–500 mg or more, repeated at intervals of 1–4 weeks, adjusted according to response; max. 600 mg weekly; ELDERLY quarter to half usual starting dose; CHILD not recommended

Clopixol® (Lundbeck) PoM
Injection (oily), zuclopenthixol decanoate 200 mg/mL, net price 1-mL amp = £1.99

Clopixol Conc.® (Lundbeck) PoM
Injection (oily), zuclopenthixol decanoate 500 mg/mL, net price 1-mL amp = £3.65

4.2.3 Antimanic drugs

Antimanic drugs are used to control acute attacks and to prevent recurrence of episodes of mania or hypomania. Long-term treatment of bipolar disorder should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse.

An antidepressant drug (section 4.3) may also be required for the treatment of co-existing depression, but should be avoided in patients with rapid-cycling bipolar disorder, a recent history of hypomania, or with rapid mood fluctuations.

Benzodiazepines

Use of benzodiazepines (such as lorazepam) (section 4.1) may be helpful in the initial stages of treatment for behavioural disturbance or agitation; they should not be used for long periods because of the risk of dependence.

Antipsychotic drugs

Antipsychotic drugs (normally **olanzapine**, **quetiapine**, or **risperidone**) (section 4.2.1) are useful in acute episodes of mania and hypomania; if the response to antipsychotic drugs is inadequate, lithium or valproate may be added. An antipsychotic drug may be used concomitantly with lithium or valproate in the initial treatment of severe acute mania.

Olanzapine can be used for the long-term management of bipolar disorder [unlicensed use] either as monotherapy, or in combination with lithium or valproate if the patient has frequent relapses or continuing functional impairment.

When discontinuing antipsychotics, the dose should be reduced gradually over at least 4 weeks if the patient is continuing with other antimanic drugs; if the patient is not continuing with other antimanic drugs or if there is a history of manic relapse, a withdrawal period of up to 3 months should be considered.

High doses of haloperidol or flupentixol may be hazardous when used with lithium; irreversible toxic encephalopathy has been reported.

Carbamazepine

Carbamazepine (section 4.8.1) may be used under specialist supervision for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients unresponsive to a combination of other prophylactic drugs; it is used in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year). The dose of carbamazepine should not normally be increased if an acute episode of mania occurs.

When stopping treatment with carbamazepine, reduce the dose gradually over a period of at least 4 weeks.

Valproate

Valproic acid (as the semisodium salt) is licensed for the treatment of manic episodes associated with bipolar disorder. Sodium valproate (section 4.8.1) is unlicensed for the treatment of bipolar disorder.

Valproate is also used for the prophylaxis of bipolar disorder [unlicensed use]; however, it should not normally be prescribed for women of child-bearing potential. In patients with frequent relapse or continuing functional impairment, consider switching therapy to lithium or olanzapine, or adding lithium or olanzapine to valproate. If a patient taking valproate experiences an acute episode of mania that is not ameliorated by increasing the valproate dose, consider concomitant therapy with olanzapine, quetiapine, or risperidone.

If treatment with valproate is stopped, reduce the dose gradually over at least 4 weeks.

VALPROIC ACID

Indications treatment of manic episodes associated with bipolar disorder; migraine prophylaxis (section 4.7.4.2)

Cautions see Sodium Valproate, section 4.8.1; monitor closely if dose greater than 45 mg/kg daily

Contra-indications see Sodium Valproate, section 4.8.1

Hepatic impairment see Sodium Valproate, section 4.8.1

Renal impairment see Sodium Valproate, section 4.8.1

Pregnancy see Sodium Valproate, section 4.8.1

Breast-feeding see Sodium Valproate, section 4.8.1

Side-effects see Sodium Valproate, section 4.8.1

Dose

- Mania, initially 750 mg daily in 2–3 divided doses, increased according to response, usual dose 1–2 g daily; CHILD under 18 years not recommended
- Migraine prophylaxis [unlicensed], initially 250 mg twice daily, increased if necessary to 1 g daily in divided doses

Depakote® (Sanofi-Aventis) PoM

Tablets, e/c, valproic acid (as semisodium valproate) 250 mg, net price 90-tab pack = £12.17; 500 mg, 90-tab pack = £24.29. Label: 21, 25

Note Semisodium valproate comprises equimolar amounts of sodium valproate and valproic acid

Convulex® (Pharmacia) PoM

Section 4.8.1 (epilepsy)

Lithium

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder (manic-depressive disorder), as concomitant therapy with antidepressant medication in patients who have had an incomplete response to treatment for acute depression in bipolar disorder, and in the prophylaxis of recurrent depression (unipolar illness or unipolar depression). Lithium is also used as an augmenting agent in patients with treatment-resistant depression (section 4.3).

In acute mania, lithium should only be used in patients who have responded to lithium before and whose symptoms are not severe.

The decision to give prophylactic lithium usually requires *specialist advice*, and must be based on careful consideration of the likelihood of recurrence in the individual patient, and the benefit of treatment weighed against the risks. The full prophylactic effect of lithium may not occur for six to twelve months after the initiation of therapy. Olanzapine or valproate (given alone or as adjunctive therapy with lithium) are alternative prophylactic treatments in patients who experience frequent relapses or continued functional impairment.

Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid function every 6 months (more often if there is evidence of deterioration). Renal function should be monitored at baseline and every 6 months thereafter (more often if there is evidence of deterioration or if the patient has other risk factors, such as starting ACE inhibitors, NSAIDs, or diuretics). The need for continued therapy should be assessed regularly and patients should be maintained on lithium after 3–5 years only if benefit persists.

Serum concentrations Lithium salts have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring serum-lithium concentrations are available. Samples should be taken 12 hours after the dose to achieve a serum-lithium concentration of 0.4–1 mmol/litre (lower end of the range for maintenance therapy and elderly patients). A target serum-lithium concentration of 0.8–1 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have subsyndromal symptoms. It is important to determine the optimum range for each individual patient. Routine serum-lithium monitoring should be performed weekly after initiation and after each dose change until levels are stable, then every 3 months thereafter. Additional serum-lithium measurements should be made if a patient develops significant intercurrent disease or if there is a significant change in a patient's sodium or fluid intake.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre, may be fatal and toxic effects

include tremor, ataxia, dysarthria, nystagmus, renal impairment, and convulsions. If these potentially hazardous signs occur, treatment should be stopped, serum-lithium concentrations redetermined, and steps taken to reverse lithium toxicity. In mild cases withdrawal of lithium and administration of sodium salts and fluid will reverse the toxicity. A serum-lithium concentration in excess of 2 mmol/litre requires urgent treatment as described under Emergency Treatment of Poisoning, p. 38.

Interactions Lithium toxicity is made worse by sodium depletion, therefore concurrent use of diuretics (particularly thiazides) is hazardous and should be avoided. For other **interactions** with lithium, see Appendix 1 (lithium).

Withdrawal While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of at least 4 weeks (preferably over a period of up to 3 months). Patients should be warned of the risk of relapse if lithium is discontinued abruptly. If lithium is stopped or is to be discontinued abruptly, consider changing therapy to an atypical antipsychotic or valproate.

Lithium treatment packs

A lithium treatment pack may be given to patients on initiation of treatment with lithium. The pack consists of a patient information booklet, lithium alert card, and a record book for tracking serum-lithium concentration.
Packs may be purchased from 3M.
Tel: 0845 610 1112
nhsforms@spsl.uk.com

LITHIUM CARBONATE

Indications treatment and prophylaxis of mania, bipolar disorder, and recurrent depression (see also notes above); aggressive or self-mutilating behaviour

Cautions see notes above; also measure serum-lithium concentration regularly (every 3 months on stabilised regimens), measure renal function and thyroid function every 6 months on stabilised regimens and advise patient to seek attention if symptoms of hypothyroidism develop (women at greater risk) e.g. lethargy, feeling cold; maintain adequate sodium and fluid intake; test renal function before initiating and if evidence of toxicity; cardiac disease; QT-interval prolongation; conditions with sodium imbalance such as Addison's disease; reduce dose or discontinue in diarrhoea, vomiting, and intercurrent infection (especially if sweating profusely); psoriasis (risk of exacerbation); elderly (reduce dose); diuretic treatment; myasthenia gravis; surgery (section 15.1); avoid abrupt withdrawal (see notes above); **interactions:** Appendix 1 (lithium)
Counselling Patients should maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake; lithium treatment packs are available (see above)

Renal impairment avoid if possible or reduce dose and monitor serum-lithium concentration carefully

Pregnancy avoid if possible in the first trimester (risk of teratogenicity, including cardiac abnormalities); dose requirements increased during the second and third trimesters (but on delivery return abruptly to normal); close monitoring of serum-lithium concentration advised (risk of toxicity in neonate)

Breast-feeding present in milk and risk of toxicity in infant—avoid

Side-effects gastro-intestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, leucocytosis; also weight gain and oedema (may respond to dose reduction); hyperparathyroidism, hyperthyroidism, hyperglycaemia, hypermagnesaemia, and hypercalcaemia reported; signs of intoxication are blurred vision, increasing gastro-intestinal disturbances (anorexia, vomiting, diarrhoea), muscle weakness, increased CNS disturbances (mild drowsiness and sluggishness increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria), and require withdrawal of treatment; with severe **overdosage** (serum-lithium concentration above 2 mmol/litre) hyperreflexia and hyperextension of limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, and occasionally, death; goitre, raised antidiuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, and kidney changes may also occur; see also Emergency Treatment of Poisoning, p. 38

Dose

- See under preparations below, adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter; doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised
  Note **Preparations vary widely in bioavailability**; changing the preparation requires the same precautions as initiation of treatment

Camcolit® (Norgine) PoM

Camcolit 250® tablets, f/c, scored, lithium carbonate 250 mg (Li^+ 6.8 mmol), net price 100-tab pack = £3.09. Label: 10, lithium card, counselling, see above

Camcolit 400® tablets, m/r, f/c, scored, lithium carbonate 400 mg (Li^+ 10.8 mmol), net price 100-tab pack = £4.13. Label: 10, lithium card, 25, counselling, see above

Dose (see Dose above for advice on bioavailability and serum monitoring):
ADULT and CHILD over 12 years, treatment, initially 1–1.5 g daily; prophylaxis, initially 300–400 mg daily
Note *Camcolit 400®* also available as *Lithonate®* (TEVA UK)

Liskonum® (GSK) PoM

Tablets, m/r, f/c, scored, lithium carbonate 450 mg (Li^+ 12.2 mmol), net price 60-tab pack = £2.88. Label: 10, lithium card, 25, counselling, see above

Dose (see Dose above for advice on bioavailability and serum monitoring):
ADULT and CHILD over 12 years, treatment, initially 450–675 mg twice daily (elderly initially 225 mg twice daily); prophylaxis, initially 450 mg twice daily (elderly 225 mg twice daily)

Priadel® (Sanofi-Aventis) PoM

Tablets, m/r, both scored, lithium carbonate 200 mg (Li^+ 5.4 mmol), net price 100-tab pack= £2.30; 400 mg (Li^+ 10.8 mmol), 100-tab pack = £3.35. Label: 10, lithium card, 25, counselling, see above

Dose (see Dose above for advice on bioavailability and serum monitoring):
Treatment and prophylaxis, initially 0.4–1.2 g daily as a single dose or in 2 divided doses (elderly or patients less than 50 kg, 400 mg daily); CHILD not recommended

Liquid, see under Lithium Citrate below

LITHIUM CITRATE

Indications see under Lithium Carbonate and notes above

Cautions see under Lithium Carbonate and notes above

Counselling Patients should maintain an adequate fluid intake and should avoid dietary changes which might reduce or increase sodium intake; lithium treatment cards are available from pharmacies (see above)

Renal impairment see Lithium Carbonate

Pregnancy see Lithium Carbonate

Breast-feeding see Lithium Carbonate

Side-effects see under Lithium Carbonate and notes above

Dose

- See under preparations below, adjusted to achieve serum-lithium concentration of 0.4–1 mmol/litre as described under Lithium Carbonate

Note **Preparations vary widely in bioavailability**; changing the preparation requires the same precautions as initiation of treatment

Li-Liquid® (Rosemont) PoM

Oral solution, lithium citrate 509 mg/5 mL (Li^+ 5.4 mmol/5 mL), yellow, net price 150-mL pack = £5.79; 1.018 g/5 mL (Li^+ 10.8 mmol/5 mL), orange, 150-mL pack = £11.58. Label: 10, lithium card, counselling, see above

Dose (see Dose above for advice on bioavailability and serum monitoring):
Treatment and prophylaxis, initially 1.018–3.054 g daily in 2 divided doses (elderly or patients less than 50 kg, initially 509 mg twice daily); CHILD not recommended

Note 5-mL dose of 509 mg/5 mL oral solution is equivalent to 200 mg lithium carbonate

Priadel® (Sanofi-Aventis) PoM

Tablets, see under Lithium Carbonate

Liquid, sugar-free, lithium citrate 520 mg/5 mL (approx. Li^+ 5.4 mmol/5 mL), net price 150-mL pack = £5.61. Label: 10, lithium card, counselling, see above

Dose (see Dose above for advice on bioavailability and serum monitoring):
Treatment and prophylaxis, initially 1.04–3.12 g daily in 2 divided doses (elderly or patients less than 50 kg, 520 mg twice daily); CHILD not recommended

Note 5-mL dose is equivalent to 204 mg lithium carbonate

4.3 Antidepressant drugs

4.3.1 Tricyclic and related antidepressant drugs
4.3.2 Monoamine-oxidase inhibitors
4.3.3 Selective serotonin re-uptake inhibitors
4.3.4 Other antidepressant drugs

Antidepressant drugs are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as loss of appetite and sleep disturbance; improvement in sleep is usually the first benefit of therapy. Ideally, patients with moderate to severe depression should be treated with psychological therapy in addition to drug therapy. Antidepressant drugs are also effective for dysthymia (lower grade chronic depression (typically of at least 2 years duration)).

Antidepressant drugs should not be used routinely in mild depression, and psychological therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in patients with a history of moderate or severe depression.

Choice The major classes of antidepressant drugs include the tricyclic and related antidepressants (section 4.3.1), the selective serotonin re-uptake inhibitors (SSRIs) (section 4.3.3), and the monoamine oxidase inhibitors (MAOIs) (section 4.3.2). A number of antidepressant drugs cannot be accommodated easily into this classification; these are included in section 4.3.4.

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. Since there may be an interval of 2 weeks before the antidepressant action takes place, electroconvulsive treatment may be required in severe depression when delay is hazardous or intolerable. During the first few weeks of treatment, there is an increased potential for agitation, anxiety, and suicidal ideation (see p. 233).

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. In patients with unstable angina or who have had a recent myocardial infarction, sertraline has been shown to be safe.

Tricyclic antidepressants have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects; toxicity in overdosage is also a problem. See section 4.3.1 for more details.

MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists.

Although anxiety is often present in depressive illness (and may be the presenting symptom), the use of an antipsychotic or an anxiolytic may mask the true diagnosis. Anxiolytics (section 4.1.2) or antipsychotic drugs (section 4.2.1) should therefore be used with caution in depression but they are useful adjuncts in agitated patients. Augmenting antidepressants with antipsychotics under specialist supervision may also be necessary in patients who have depression with psychotic symptoms.

See section 4.2.3 for notes on the management of bipolar disorder.

St John's wort (*Hypericum perforatum*) is a popular herbal remedy on sale to the public for treating mild depression. It should not be prescribed or recommended for depression because St John's wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs, including conventional antidepressants, have been identified (see Appendix 1, St John's wort). Furthermore, the amount of active ingredient varies between different preparations of St John's wort and switching from one to another can change the degree of enzyme induction. If a patient stops taking St John's wort, concentrations of interacting drugs may increase, leading to toxicity.

Hyponatraemia and antidepressant therapy
Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressants. Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

Suicidal behaviour and antidepressant therapy
The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

Management Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2–4 weeks (elderly patients may take longer to respond).

Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should receive maintenance treatment for at least 2 years.

Failure to respond Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or mirtazapine. Other second-line choices include lofepramine, moclobemide, and reboxetine. Other tricyclic antidepressants and venlafaxine should be considered for more severe forms of depression; irreversible MAOIs should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or use of an augmenting agent (such as lithium (section 4.2.3), aripiprazole [unlicensed], olanzapine [unlicensed], quetiapine, or risperidone [unlicensed] (section 4.2.1)), but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.

Withdrawal Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. Drugs with a shorter half-life, such as paroxetine (p. 241) and venlafaxine (p. 244), are associated with a higher risk of withdrawal symptoms. The risk of withdrawal symptoms is also increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). See also section 4.3.1, section 4.3.2, and section 4.3.3.

Anxiety disorders and obsessive-compulsive disorder Management of acute anxiety generally involves the use of a benzodiazepine or buspirone (section 4.1.2). For chronic anxiety (of longer than 4 weeks' duration) it may be appropriate to use an antidepressant. Combined therapy with a benzodiazepine may be required until the antidepressant takes effect. *Generalised anxiety disorder*, a form of chronic anxiety, is treated with an SSRI such as escitalopram or paroxetine; pregabalin and venlafaxine are also licensed for the treatment of generalised anxiety disorder.

Panic disorder, *obsessive-compulsive disorder*, *post-traumatic stress disorder*, and phobic states such as *social anxiety disorder* are treated with SSRIs. Clomipramine or imipramine can be used second-line in panic disorder [unlicensed]; clomipramine can also be used second-line for obsessive-compulsive disorder. Moclobemide is licensed for the treatment of social anxiety disorder.

4.3.1 Tricyclic and related antidepressant drugs

This section covers tricyclic antidepressants and also 1-, 2-, and 4-ring structured drugs with broadly similar properties.

Some tricyclic antidepressants are used in the management of *panic* and other *anxiety disorders* (section 4.3). For reference to the role of some tricyclic antidepressants in some forms of *neuralgia*, see section 4.7.3, and in *nocturnal enuresis* in children, see section 7.4.2.

Cautions Tricyclic and related antidepressant drugs should be used with caution in patients with cardiovascular disease (see also Contra-indications, below); because of the risk of arrhythmias, patients with concomitant conditions such as hyperthyroidism and phaeochromocytoma should be treated with care. Care is also needed in patients with epilepsy and diabetes.

Tricyclic antidepressant drugs have antimuscarinic activity, and therefore caution is needed in patients with prostatic hypertrophy, chronic constipation, increased intra-ocular pressure, urinary retention, or those with a susceptibility to angle-closure glaucoma. Tricyclic and related antidepressant drugs should be used with caution in patients with a significant risk of suicide, or a history of psychosis or bipolar disorder, because antidepressant therapy may aggravate these conditions; treatment should be stopped if the patient enters a manic phase.

Elderly patients are particularly susceptible to many of the side-effects of tricyclic antidepressants; low initial doses should be used, with close monitoring, particularly for psychiatric and cardiac side-effects.

Overdosage Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage. In particular, overdosage with dosulepin and amitriptyline is associated with a relatively high rate of fatality. Lofepramine is associated with the lowest risk of fatality in overdosage, in comparison with other tricyclic antidepressant drugs. For advice on **overdosage** see Emergency Treatment of Poisoning, p. 37.

Withdrawal Amitriptyline and imipramine are the tricyclic antidepressants most commonly associated with withdrawal symptoms. These symptoms include influenza-like symptoms (chills, myalgia, sweating, headache, nausea), insomnia, vivid dreams, and may occasionally include movement disorders, mania, and cardiac arrhythmia. If possible tricyclic and related antidepressants should be withdrawn slowly (see also section 4.3).

Interactions A tricyclic or related antidepressant (or an SSRI or related antidepressant) should not be started until 2 weeks after stopping an MAOI (3 weeks if starting clomipramine or imipramine). Conversely, an MAOI should not be started until at least 7–14 days after a tricyclic or related antidepressant (3 weeks in the case of clomipramine or imipramine) has been stopped. For guidance relating to the reversible monoamine oxidase inhibitor, moclobemide, see p. 239. For other tricyclic antidepressant **interactions**, see Appendix 1 (antidepressants, tricyclic and antidepressants, tricyclic (related)).

Driving Drowsiness may affect the performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Contra-indications Tricyclic and related antidepressants are contra-indicated in the immediate recovery period after myocardial infarction, in arrhythmias (particularly heart block), and in the manic phase of bipolar disorder. Avoid treatment with tricyclic antidepressant drugs in acute porphyria (section 9.8.2).

Hepatic impairment Tricyclic antidepressants are preferable to MAOIs in hepatic impairment but sedative effects are increased. They should be avoided in severe liver disease.

Breast-feeding The amount of tricyclic antidepressants (including related drugs such as mianserin and trazodone) secreted into breast milk is too small to be harmful (but see Doxepin, p. 236).

Side-effects Arrhythmias and heart block occasionally follow the use of tricyclic antidepressants, particularly amitriptyline, and may be a factor in the sudden death of patients with cardiac disease; other cardiovascular side-effects include postural hypotension, tachycardia, and ECG changes. The tricyclic-related antidepressant drugs may be associated with a lower risk of cardiotoxicity in overdosage.

Central nervous system side-effects are common, particularly in the elderly, and include anxiety, dizziness, agitation, confusion, sleep disturbances, irritability, and paraesthesia; drowsiness is associated with some of the tricyclic antidepressants (see under Choice, below). Convulsions, hallucinations, delusions, mania, and hypomania may occur (see also under Cautions, above), and, *rarely*, extrapyramidal symptoms including tremor and dysarthria.

Antimuscarinic side-effects include dry mouth, blurred vision (*very rarely* precipitation of angle-closure glaucoma), constipation (*rarely* leading to paralytic ileus, particularly in the elderly), and urinary retention. Tricyclic-related antidepressant drugs have a lower incidence of antimuscarinic side-effects than older tricyclics.

Endocrine effects include breast enlargement, galactorrhoea, and gynaecomastia. Sexual dysfunction may occur. Changes in blood sugar, increased appetite, and weight gain can accompany treatment with tricyclic antidepressant drugs, but anorexia and weight loss are also seen. Hepatic and haematological reactions may occur and have been particularly associated with mianserin. Another side-effect to which the elderly are particularly susceptible is hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233). Other class side-effects include nausea, vomiting, taste disturbance, tinnitus, rash, urticaria, pruritus, photosensitivity, alopecia, and sweating.

The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible.

Neuroleptic malignant syndrome (section 4.2.1) may, very rarely, occur in the course of antidepressant drug treatment.

Suicidal behaviour has been linked with antidepressants (see p. 233).

Dosage About 10 to 20% of patients fail to respond to tricyclic and related antidepressant drugs and inadequate dosage may account for some of these failures. It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment in the **elderly** (see under Side-effects, below).

In most patients the long half-life of tricyclic antidepressant drugs allows **once-daily** administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Choice Tricyclic and related antidepressants block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, clomipramine is more selective for serotonergic transmission, and imipramine is more selective for noradrenergic transmission. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties and those that are less sedating. Agitated and anxious patients tend to respond best to the sedative compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones. Those with **sedative** properties include amitriptyline, clomipramine, dosulepin, doxepin, mianserin, trazodone, and trimipramine. Those with **less sedative** properties include imipramine, lofepramine, and nortriptyline.

Tricyclic and related antidepressants also have varying degrees of antimuscarinic side-effects and cardiotoxicity in overdosage, which may be important in individual patients. **Lofepramine** has a lower incidence of side-effects and is less dangerous in overdosage but is infrequently associated with hepatic toxicity. **Imipramine** is also well established, but has more marked antimuscarinic side-effects than other tricyclic and related antidepressants. **Amitriptyline** and **dosulepin** are effective but they are particularly dangerous in overdosage (see Overdosage, above) and are not recommended for the treatment of depression; dosulepin should only be prescribed by specialists.

Children and adolescents Studies have shown that tricyclic antidepressants are not effective for treating depression in children; see also Depressive Illness in Children and Adolescents, p. 239.

Tricyclic antidepressants

AMITRIPTYLINE HYDROCHLORIDE

Indications depressive illness (but not recommended, see notes above); nocturnal enuresis in children (section 7.4.2); neuropathic pain [unlicensed] (section 4.7.3); migraine prophylaxis [unlicensed] (section 4.7.4.2)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding see notes above

Side-effects see notes above; also abdominal pain, stomatitis, palpitation, oedema, hypertension, restlessness, fatigue, mydriasis, and increased intra-ocular pressure; high rate of fatality in overdose—see notes above

Dose

- Depression (but not recommended, see notes above), ADULT and CHILD over 16 years, initially 75 mg (elderly and adolescents 30–75 mg) daily in divided doses *or* as a single dose at bedtime increased gradually as necessary to 150–200 mg
- Nocturnal enuresis, CHILD 7–11 years 10–20 mg at night, 11–16 years 25–50 mg at night; max. period of treatment (including gradual withdrawal) 3 months—full physical examination, including ECG, before further course
- Neuropathic pain [unlicensed indication], initially 10 mg daily at night, gradually increased if necessary to 75 mg daily; higher doses under specialist supervision
- Migraine prophylaxis [unlicensed indication], initially 10 mg at night, increased if necessary to maintenance of 50–75 mg at night; max. 150 mg at night

Amitriptyline (Non-proprietary) PoM

Tablets, coated, amitriptyline hydrochloride 10 mg, net price 28-tab pack = 90p; 25 mg, 28-tab pack = 90p; 50 mg, 28-tab pack = £1.00. Label: 2

Oral solution, amitriptyline hydrochloride 25 mg/5 mL, net price 150 mL = £15.47; 50 mg/5 mL, 150 mL = £16.82. Label: 2

Compound preparations

Triptafen® (Goldshield) PoM

Tablets, pink, s/c, amitriptyline hydrochloride 25 mg, perphenazine 2 mg, net price 100-tab pack = £25.49. Label: 2

Dose depression with anxiety, ADULT and CHILD over 14 years, 1 tablet 3 times daily; an additional tablet may be taken at bedtime when required

CLOMIPRAMINE HYDROCHLORIDE

Indications depressive illness, phobic and obsessional states; adjunctive treatment of cataplexy associated with narcolepsy

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy neonatal withdrawal symptoms reported if used during third trimester

Breast-feeding see notes above

Side-effects see notes above; also abdominal pain, diarrhoea, hypertension, flushing, restlessness, fatigue, aggression, impaired memory, muscle weakness, muscle hypertonia, myoclonus, mydriasis, and yawning; *very rarely* allergic alveolitis

Dose

- Depressive illness, ADULT over 18 years, initially 10 mg daily, increased gradually as necessary to 30–150 mg daily in divided doses *or* as a single dose at bedtime; max. 250 mg daily; ELDERLY initially 10 mg daily increased carefully over approx. 10 days to 30–75 mg daily
- Phobic and obsessional states, ADULT over 18 years, initially 25 mg daily (ELDERLY 10 mg daily) increased over 2 weeks to 100–150 mg daily; max. 250 mg daily
- Adjunctive treatment of cataplexy associated with narcolepsy, ADULT over 18 years, initially 10 mg daily, gradually increased until satisfactory response (range 10–75 mg daily)

Clomipramine (Non-proprietary) PoM

Capsules, clomipramine hydrochloride 10 mg, net price 28-cap pack = £1.71; 25 mg, 28-cap pack = £2.01; 50 mg, 28-cap pack = £2.75. Label: 2

Anafranil® (Novartis) PoM

Capsules, clomipramine hydrochloride 10 mg (yellow/caramel), net price 84-cap pack = £3.23; 25 mg (orange/caramel), 84-cap pack = £6.35; 50 mg (grey/caramel), 56-cap pack = £8.06. Label: 2

Modified release

Anafranil SR® (Novartis) PoM

Tablets, m/r, grey-red, f/c, clomipramine hydrochloride 75 mg, net price 28-tab pack = £8.83. Label: 2, 25

Dose see above; to be taken once daily

DOSULEPIN HYDROCHLORIDE

(Dothiepin hydrochloride)

Indications depressive illness, particularly where sedation is required

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding see notes above

Side-effects see notes above; also increased intra-ocular pressure; high rate of fatality in overdose—see notes above

Dose

- Initially 75 mg (ELDERLY 50–75 mg) daily in divided doses *or* as a single dose at bedtime, increased gradually as necessary to 150 mg daily (ELDERLY 75 mg may be sufficient); up to 225 mg daily in some circumstances (e.g. hospital use); CHILD not recommended

Dosulepin (Non-proprietary) PoM

Capsules, dosulepin hydrochloride 25 mg, net price 28-cap pack = £1.11. Label: 2

Tablets, dosulepin hydrochloride 75 mg, net price 28-tab pack = £1.34. Label: 2

Prothiaden® (Teofarma) PoM

Capsules, red/red-brown, dosulepin hydrochloride 25 mg, net price 28-cap pack = £1.70. Label: 2

Tablets, red, s/c, dosulepin hydrochloride 75 mg, net price 28-tab pack = £2.97. Label: 2

DOXEPIN

Indications depressive illness, particularly where sedation is required; pruritus in eczema (section 13.3)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution

Pregnancy use with caution—limited information available

Breast-feeding see notes above; accumulation of metabolite may cause sedation and respiratory depression in neonate

Side-effects see notes above; also abdominal pain, stomatitis, diarrhoea, flushing, and oedema

Dose

- ADULT and CHILD over 12 years, initially 75 mg daily in divided doses *or* as a single dose at bedtime, adjusted according to response; usual maintenance 30–300 mg daily (doses above 100 mg given in 3 divided doses); ELDERLY initially 10–50 mg daily adjusted according to response (usual maintenance 30–50 mg daily)

Sinepin® (Marlborough) PoM

Capsules, doxepin (as hydrochloride) 25 mg, net price 28-cap pack = £3.77; 50 mg, 28-cap pack = £5.71. Label: 2

IMIPRAMINE HYDROCHLORIDE

Indications depressive illness; nocturnal enuresis in children (section 7.4.2)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment use with caution in severe impairment

Pregnancy colic, tachycardia, dyspnoea, irritability, and muscle spasms reported in neonates when used in the third trimester

Breast-feeding see notes above

Side-effects see notes above; also palpitation, flushing, restlessness, headache, fatigue; *very rarely* abdominal pain, stomatitis, hypertension, oedema, cardiac decompensation, allergic alveolitis, aggression, myoclonus, peripheral vasospasm, and mydriasis

Dose

- Depression, initially up to 75 mg daily in divided doses increased gradually to 150–200 mg (up to 300 mg in hospital patients); up to 150 mg may be given as a single dose at bedtime; ELDERLY initially 10 mg daily, increased gradually to 30–50 mg daily; CHILD not recommended for depression
- Nocturnal enuresis, CHILD 7–8 years 25 mg, 8–11 years 25–50 mg, over 11 years 50–75 mg at bedtime; max. period of treatment (including gradual withdrawal) 3 months—full physical examination before further course

Imipramine (Non-proprietary) PoM

Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.30; 25 mg, 28-tab pack = £1.24. Label: 2

Oral solution, imipramine hydrochloride 25 mg/5 mL, net price 150-mL = £20.00. Label: 2

LOFEPRAMINE

Indications depressive illness

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment avoid in severe impairment

Pregnancy neonatal withdrawal symptoms and respiratory depression reported if used during third trimester

Breast-feeding see notes above

Side-effects see notes above; also oedema and hepatic disorders reported

Dose

- 140–210 mg daily in divided doses; ELDERLY may respond to lower doses; CHILD under 18 years not recommended

Lofepramine (Non-proprietary) PoM

Tablets, lofepramine 70 mg (as hydrochloride), net price 56-tab pack = £5.69. Label: 2
Brands include *Feprapax®*

Oral suspension, lofepramine 70 mg/5 mL (as hydrochloride), net price 150 mL = £22.22. Label: 2
Brands include *Lomont®* (sugar-free)

NORTRIPTYLINE

Indications depressive illness; nocturnal enuresis in children (section 7.4.2); neuropathic pain [unlicensed] (section 4.7.3)

Cautions see notes above; manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily, but evidence of practical value uncertain

Contra-indications see notes above

Hepatic impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding see notes above

Side-effects see notes above; also abdominal pain, stomatitis, diarrhoea, hypertension, oedema, flushing, restlessness, fatigue, and mydriasis

Dose

- Depression, low dose initially increased as necessary to 75–100 mg daily in divided doses *or* as a single dose (max. 150 mg daily); ADOLESCENT and ELDERLY 30–50 mg daily in divided doses; CHILD not recommended for depression
- Nocturnal enuresis, CHILD 7 years 10 mg, 8–11 years 10–20 mg, over 11 years 25–35 mg, 30 minutes before bedtime; max period of treatment (including gradual withdrawal) 3 months—full physical examination and ECG before further course
- Neuropathic pain [unlicensed], initially 10 mg daily at night, gradually increased if necessary to 75 mg daily; higher doses under specialist supervision

Allegron® (King) PoM

Tablets, nortriptyline (as hydrochloride) 10 mg, net price 100-tab pack = £12.06; 25 mg (orange, scored), 100-tab pack = £24.02. Label: 2

TRIMIPRAMINE

Indications depressive illness, particularly where sedation required

Cautions see notes above

Contra-indications see notes above
Hepatic impairment see notes above
Pregnancy use only if potential benefit outweighs risk
Breast-feeding see notes above
Side-effects see notes above
Dose

- Initially 50–75 mg daily in divided doses *or* as a single dose at bedtime, increased as necessary to 150–300 mg daily; ELDERLY initially 10–25 mg 3 times daily, maintenance half adult dose may be sufficient; CHILD not recommended

Surmontil® (Sanofi-Aventis) PoM
Capsules, green/white, trimipramine 50 mg (as maleate), net price 28-cap pack = £7.60. Label: 2
Tablets, trimipramine (as maleate) 10 mg, net price 28-tab pack = £3.43, 84-tab pack = £10.27; 25 mg, 28-tab pack = £4.53, 84-tab pack = £13.55. Label: 2

Tricyclic-related antidepressants

MIANSERIN HYDROCHLORIDE

Indications depressive illness, particularly where sedation is required
Cautions see notes above
Blood counts A full **blood count** is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if *fever, sore throat, stomatitis*, or other signs of infection develop
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment caution in renal impairment
Pregnancy avoid
Breast-feeding see notes above
Side-effects see notes above; also jaundice, oedema, blood dyscrasias, arthritis, and arthralgia
Dose

- ADULT over 18 years, initially 30–40 mg (elderly 30 mg) daily in divided doses *or* as a single dose at bedtime, increased gradually as necessary; usual dose range 30–90 mg

Mianserin (Non-proprietary) PoM
Tablets, mianserin hydrochloride 10 mg, net price 28-tab pack = £8.05; 30 mg, 28-tab pack = £14.05. Label: 2, 25

TRAZODONE HYDROCHLORIDE

Indications depressive illness, particularly where sedation is required; anxiety
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment use with caution in severe impairment
Pregnancy avoid during first trimester—limited information available
Breast-feeding see notes above
Side-effects see notes above; *rarely* priapism (discontinue immediately)
Dose

- Depression, initially 150 mg (elderly 100 mg) daily in divided doses after food *or* as a single dose at bedtime; may be increased to 300 mg daily; hospital patients up to max. 600 mg daily in divided doses; CHILD not recommended
- Anxiety, 75 mg daily, increasing if necessary to 300 mg daily; CHILD not recommended

Trazodone (Non-proprietary) PoM
Capsules, trazodone hydrochloride 50 mg, net price 84-cap pack = £4.72; 100 mg, 56-cap pack = £4.85. Label: 2, 21
Tablets, trazodone hydrochloride 150 mg, net price 28-tab pack = £4.57. Label: 2, 21

Molipaxin® (Sanofi-Aventis) PoM
Capsules, trazodone hydrochloride 50 mg (violet/green), net price 84-cap pack = £23.92; 100 mg (violet/fawn), 56-cap pack = £28.14. Label: 2, 21
Tablets, pink, f/c, trazodone hydrochloride 150 mg, net price 28-tab pack = £16.08. Label: 2, 21
Liquid, sugar-free, trazodone hydrochloride 50 mg/5 mL, net price 120 mL = £13.37. Label: 2, 21

4.3.2 Monoamine-oxidase inhibitors (MAOIs)

Monoamine-oxidase inhibitors are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions and the fact that it is easier to prescribe MAOIs when tricyclic antidepressants have been unsuccessful than vice versa. **Tranylcypromine** is the most **hazardous** of the MAOIs because of its stimulant action. The drugs of choice are **phenelzine** or **isocarboxazid** which are less stimulant and therefore safer.

Phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to MAOIs. However, MAOIs should be tried in any patients who are refractory to treatment with other antidepressants as there is occasionally a dramatic response. Response to treatment may be delayed for 3 weeks or more and may take an additional 1 or 2 weeks to become maximal.

Withdrawal MAOIs are associated with withdrawal symptoms on cessation of therapy. Symptoms include agitation, irritability, ataxia, movement disorders, insomnia, drowsiness, vivid dreams, cognitive impairment, and slowed speech. Withdrawal symptoms occasionally experienced when discontinuing MAOIs include hallucinations and paranoid delusions. If possible MAOIs should be withdrawn slowly (see also section 4.3).

Hepatic impairment MAOIs may cause idiosyncratic hepatotoxicity if used in patients with hepatic impairment. See also individual monographs.

Pregnancy There is an increased risk of neonatal malformations when phenelzine, isocarboxazid, or tranylcypromine is used during pregnancy. The safety of moclobemide in pregnancy has not been established. Manufacturers advise avoid use unless there are compelling reasons.

Interactions MAOIs inhibit monoamine oxidase, thereby causing an accumulation of amine neurotransmitters. The metabolism of some amine drugs such as *indirect-acting sympathomimetics* (present in many cough and decongestant preparations, section 3.10) is also inhibited and their pressor action may be potentiated; the pressor effect of tyramine (in some foods, such as mature cheese, pickled herring, broad bean pods, and *Bovril®*, *Oxo®*, *Marmite®* or any similar meat or yeast extract or fermented soya bean extract) may also be dangerously potentiated. These interactions may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or 'going off'. This is especially important with meat, fish, poultry or offal; game should be avoided. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Patients should also avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.

Other antidepressants should **not** be started for 2 weeks after treatment with MAOIs has been stopped (3 weeks if starting clomipramine or imipramine). Some psychiatrists use selected tricyclics in conjunction with MAOIs but this is hazardous, indeed potentially lethal, except in experienced hands and there is no evidence that the combination is more effective than when either constituent is used alone. The combination of tranylcypromine with clomipramine is particularly **dangerous**.

Conversely, an MAOI should not be started until at least 7–14 days after a tricyclic or related antidepressant (3 weeks in the case of clomipramine or imipramine) has been stopped.

In addition, an MAOI should not be started for at least 2 weeks after a previous MAOI has been stopped (then started at a reduced dose).

For other interactions with MAOIs including those with opioid analgesics (notably pethidine), see Appendix 1 (MAOIs). For guidance on interactions relating to the reversible monoamine oxidase inhibitor, moclobemide, see p. 239; for guidance on interactions relating to SSRIs, see p. 240.

PHENELZINE

Indications depressive illness

Cautions diabetes mellitus, cardiovascular disease, epilepsy, blood disorders, concurrent electroconvulsive therapy; elderly (great caution); monitor blood pressure (risk of postural hypotension and hypertensive responses—discontinue if palpitations or frequent headaches); if possible avoid abrupt withdrawal; severe hypertensive reactions to certain drugs and foods; avoid in agitated patients; acute porphyria (section 9.8.2); surgery (section 15.1); **interactions:** Appendix 1 (MAOIs)
Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications cerebrovascular disease, phaeochromocytoma; not indicated in manic phase

Hepatic impairment avoid in hepatic impairment or if abnormal liver function tests; see also notes above

Pregnancy see notes above

Breast-feeding avoid—no information available

Side-effects commonly postural hypotension (especially in elderly) and dizziness; less common side-effects include drowsiness, insomnia, headache, weakness and fatigue, dry mouth, constipation and other gastro-intestinal disturbances, oedema, myoclonic movement, hyperreflexia, elevated liver enzymes; agitation and tremors, nervousness, euphoria, arrhythmias, blurred vision, nystagmus, difficulty in micturition, sweating, convulsions, rashes, purpura, leucopenia, sexual disturbances, and weight gain with inappropriate appetite may also occur; psychotic episodes with hypomanic behaviour, confusion, and hallucinations may be induced in susceptible persons; suicidal behaviour (see p. 233); jaundice has been reported and, on rare occasions, fatal progressive hepatocellular necrosis; paraesthesia, peripheral neuritis, peripheral neuropathy may be due to pyridoxine deficiency; hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233)

Dose

- 15 mg 3 times daily, increased if necessary to 4 times daily after 2 weeks (hospital patients, max. 30 mg 3 times daily), then reduced gradually to lowest possible maintenance dose (15 mg on alternate days may be adequate); CHILD not recommended

Nardil® (Archimedes) PoM
Tablets, orange, f/c, phenelzine (as sulphate) 15 mg, net price 100-tab pack = £18.75. Label: 3, 10, patient information leaflet

ISOCARBOXAZID

Indications depressive illness

Cautions see under Phenelzine

Contra-indications see under Phenelzine

Hepatic impairment avoid in hepatic impairment; see also notes above

Renal impairment use with caution

Pregnancy see notes above

Breast-feeding avoid

Side-effects see under Phenelzine

Dose

- Initially 30 mg daily in single or divided doses until improvement occurs (increased after 4 weeks if necessary to max. 60 mg daily for 4–6 weeks under close supervision), then reduced to usual maintenance dose 10–20 mg daily (but up to 40 mg daily may be required); ELDERLY 5–10 mg daily; CHILD not recommended

Isocarboxazid (Non-proprietary) PoM
Tablets, pink, scored, isocarboxazid 10 mg, net price 56-tab pack = £55.06. Label: 3, 10, patient information leaflet

TRANYLCYPROMINE

Indications depressive illness

Cautions see under Phenelzine

Contra-indications see under Phenelzine; hyperthyroidism

Hepatic impairment see notes above

Pregnancy see notes above

Breast-feeding present in milk in *animal* studies

Side-effects see under Phenelzine; insomnia; hypertensive crises with throbbing headache requiring discontinuation of treatment more frequent than with other MAOIs; liver damage less frequent than with phenelzine; blood dyscrasias also reported

Dose

- Initially 10 mg twice daily not later than 3 p.m., increasing the second daily dose to 20 mg after 1 week if necessary; doses above 30 mg daily under close supervision only; usual maintenance dose 10 mg daily; CHILD not recommended

Tranylcypromine (Non-proprietary) PoM

Tablets, tranylcypromine (as sulphate) 10 mg, net price 28-tab pack = £46.24. Label: 3, 10, patient information leaflet

Reversible MAOIs

Moclobemide is indicated for major depression and social anxiety disorder; it is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line treatment.

Interactions Moclobemide is claimed to cause less potentiation of the pressor effect of tyramine than the traditional (irreversible) MAOIs, but patients should avoid consuming large amounts of tyramine-rich food (such as mature cheese, yeast extracts and fermented soya bean products).

The risk of drug interactions is also claimed to be less but patients still need to avoid sympathomimetics such as ephedrine and pseudoephedrine. In addition, moclobemide should not be given with another antidepressant. Owing to its short duration of action no treatment-free period is required after it has been stopped but it should not be started until at least a week after a tricyclic or related antidepressant or an SSRI or related antidepressant has been stopped (2 weeks in the case of sertraline, and at least 5 weeks in the case of fluoxetine), or for at least a week after an MAOI has been stopped. For other interactions, see Appendix 1 (moclobemide).

MOCLOBEMIDE

Indications depressive illness; social anxiety disorder

Cautions avoid in agitated or excited patients (or give with sedative for up to 2–3 weeks), thyrotoxicosis, may provoke manic episodes in bipolar disorders; **interactions:** see notes above and Appendix 1 (moclobemide)

Contra-indications acute confusional states, phaeochromocytoma

Hepatic impairment reduce dose in severe disease

Pregnancy see notes above, p. 237

Breast-feeding amount too small to be harmful, but patient information leaflet advises avoid

Side-effects sleep disturbances, dizziness, gastrointestinal disorders, headache, restlessness, agitation; paraesthesia, dry mouth, visual disturbances, oedema, skin reactions, confusional states reported; *rarely* raised liver enzymes, galactorrhoea; hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233)

Dose

- Depression, initially 300 mg daily usually in divided doses after food, adjusted according to response; usual range 150–600 mg daily; CHILD not recommended
- Social anxiety disorder, initially 300 mg daily increased on fourth day to 600 mg daily in 2 divided doses, continued for 8–12 weeks to assess efficacy; CHILD not recommended

Moclobemide (Non-proprietary) PoM

Tablets, moclobemide 150 mg, net price 30-tab pack = £3.76; 300 mg, 30-tab pack = £5.86. Label: 10, patient information leaflet, 21

Manerix® (Meda) PoM

Tablets, yellow, f/c, scored, moclobemide 150 mg, net price 30-tab pack = £9.33; 300 mg, 30-tab pack = £13.99. Label: 10, patient information leaflet, 21

4.3.3 Selective serotonin re-uptake inhibitors

Citalopram, **escitalopram**, **fluoxetine**, **fluvoxamine**, **paroxetine**, and **sertraline** selectively inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT); they are termed selective serotonin re-uptake inhibitors (SSRIs). For a general comment on the management of depression and on the comparison between *tricyclic and related antidepressants* and the *SSRIs and related antidepressants*, see section 4.3.

Depressive illness in children and adolescents

The balance of risks and benefits for the treatment of depressive illness in individuals under 18 years is considered unfavourable for the SSRIs citalopram, escitalopram, paroxetine, and sertraline, and for mirtazapine and venlafaxine. Clinical trials have failed to show efficacy and have shown an increase in harmful outcomes. However, it is recognised that specialists may sometimes decide to use these drugs in response to individual clinical need; children and adolescents should be monitored carefully for suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment.

Only fluoxetine has been shown in clinical trials to be effective for treating depressive illness in children and adolescents. However, it is possible that, in common with the other SSRIs, it is associated with a small risk of self-harm and suicidal thoughts. Overall, the balance of risks and benefits for fluoxetine in the treatment of depressive illness in individuals under 18 years is considered favourable, but children and adolescents must be carefully monitored as above.

Cautions SSRIs should be used with caution in patients with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used with other drugs that increase the risk of bleeding. They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). SSRIs may also impair performance of skilled tasks (e.g. driving). **Interactions:** see below and Appendix 1 (antidepressants, SSRI).

Withdrawal The risk of withdrawal reactions is higher with paroxetine (see also Withdrawal, section 4.3). Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most com-

mon features of abrupt withdrawal of an SSRI or marked reduction of the dose; palpitation and visual disturbances can occur less commonly. The dose should be tapered over a few weeks to avoid these effects. For some patients, it may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist.

Interactions An SSRI or related antidepressant should not be started until 2 weeks after stopping an MAOI. Conversely, an MAOI should not be started until at least a week after an SSRI or related antidepressant has been stopped (2 weeks in the case of sertraline, at least 5 weeks in the case of fluoxetine). For guidance relating to the reversible monoamine oxidase inhibitor, moclobemide, see above. For other SSRI antidepressant interactions, see Appendix 1 (antidepressants, SSRI).

Contra-indications SSRIs should not be used if the patient enters a manic phase.

Pregnancy Manufacturers advise that SSRIs should not be used during pregnancy unless the potential benefit outweighs the risk. There is a small increased risk of congenital heart defects when SSRIs are taken during early pregnancy. If SSRIs are used during the third trimester there is a risk of neonatal withdrawal symptoms, and persistent pulmonary hypertension in the newborn has been reported; see also individual monographs.

Side-effects SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressants (section 4.3.1). Side-effects of the SSRIs include gastro-intestinal effects (dose-related and fairly common—include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation), anorexia with weight loss (increased appetite and weight gain also reported) and hypersensitivity reactions including rash (consider discontinuation—may be sign of impending serious systemic reaction, possibly associated with vasculitis), urticaria, angioedema, anaphylaxis, arthralgia, myalgia and photosensitivity; other side-effects include dry mouth, nervousness, anxiety, headache, insomnia, tremor, dizziness, asthenia, hallucinations, drowsiness, convulsions (see Cautions above), galactorrhoea, sexual dysfunction, urinary retention, sweating, hypomania or mania (see Cautions above), movement disorders and dyskinesias, visual disturbances, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233), and bleeding disorders including ecchymoses and purpura. Suicidal behaviour has been linked with antidepressants (see p. 233). Studies have shown an increased risk of bone fractures in patients receiving SSRIs. Angle-closure glaucoma may very rarely be precipitated by treatment with SSRIs.

CITALOPRAM

Indications depressive illness, panic disorder

Cautions see notes above

Contra-indications see notes above

Hepatic impairment use doses at lower end of range

Renal impairment no information available for eGFR less than 20 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; also hepatitis, palpitation, tachycardia, oedema, bradycardia, postural hypotension, coughing, yawning, confusion, impaired concentration, aggression, malaise, amnesia, migraine, paraesthesia, abnormal dreams, mydriasis, taste disturbance, increased salivation, rhinitis, tinnitus, polyuria, micturition disorders, euphoria, pruritus; paradoxical increased anxiety during initial treatment of panic disorder (reduce dose)

Dose

- By mouth as tablets, depressive illness, 20 mg once daily increased if necessary in steps of 20 mg daily at intervals of 3–4 weeks; max. 60 mg daily (ELDERLY over 65 years, max. 40 mg daily); CHILD under 18 years see *BNF for Children* and Depressive Illness in Children and Adolescents, p. 239

  Panic disorder, ADULT over 18 years, initially 10 mg daily increased gradually if necessary in steps of 10 mg daily, usual dose 20–30 mg daily; max. 60 mg daily (ELDERLY over 65 years, max. 40 mg daily)
- By mouth as oral drops, depressive illness, 16 mg daily as a single dose increased if necessary in steps of 16 mg daily at intervals of 3–4 weeks; max. 48 mg daily (ELDERLY over 65 years, max. 32 mg daily); CHILD under 18 years see *BNF for Children* and Depressive Illness in Children and Adolescents, p. 239

  Panic disorder, ADULT over 18 years, initially 8 mg daily as a single dose increased gradually if necessary in steps of 8 mg, usual dose 16–24 mg daily; max. 48 mg daily (ELDERLY over 65 years, max. 32 mg daily)

Citalopram (Non-proprietary) PoM

Tablets, citalopram (as hydrobromide) 10 mg, net price 28-tab pack = £1.03; 20 mg, 28-tab pack = £1.30; 40 mg, 28-tab pack = £1.37. Counselling, driving

Oral drops, citalopram (as hydrochloride) 40 mg/mL, net price 15 mL = £17.92. Counselling, driving, administration

Note 4 drops (8 mg) is equivalent in therapeutic effect to 10-mg tablet

Mix with water, orange juice, or apple juice before taking

Cipramil® (Lundbeck) PoM

Tablets, f/c, citalopram (as hydrobromide) 10 mg, net price 28-tab pack = £5.38; 20 mg (scored), 28-tab pack = £8.95; 40 mg, 28-tab pack = £15.12. Counselling, driving

Oral drops, sugar-free, citalopram (as hydrochloride) 40 mg/mL, net price 15 mL = £10.08. Counselling, driving, administration

Excipients include alcohol

Note 4 drops (8 mg) is equivalent in therapeutic effect to 10-mg tablet

Mix with water, orange juice, or apple juice before taking

ESCITALOPRAM

Note Escitalopram is the active enantiomer of citalopram

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Hepatic impairment initial dose 5 mg daily for 2 weeks, thereafter increased to 10 mg daily according to response; particular caution in severe impairment

Renal impairment caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding present in milk; avoid

Side-effects see notes above; also sinusitis, yawning; fatigue, restlessness, abnormal dreams, paraesthesia; pyrexia; *less commonly* taste disturbance, bruxism, syncope, tachycardia, oedema, confusion, menstrual disturbances, epistaxis, mydriasis, tinnitus, pruritus, and alopecia; *rarely* bradycardia, aggression, and depersonalisation; hepatitis, postural hypotension, QT interval prolongation, and thrombocytopenia also reported; paradoxical increased anxiety during initial treatment of panic disorder (reduce dose)

Dose

- ADULT over 18 years, depressive illness, generalised anxiety disorder, and obsessive-compulsive disorder, 10 mg once daily increased if necessary to max. 20 mg daily; ELDERLY initially half adult dose, lower maintenance dose may be sufficient; CHILD not recommended (see Depressive Illness in Children and Adolescents, p. 239)
- ADULT over 18 years, panic disorder, initially 5 mg once daily increased to 10 mg daily after 7 days; max. 20 mg daily; ELDERLY initially half adult dose, lower maintenance dose may be sufficient
- ADULT over 18 years, social anxiety disorder, initially 10 mg once daily adjusted after 2–4 weeks; usual dose 5–20 mg daily

Cipralex® (Lundbeck) PoM

Tablets, f/c, escitalopram (as oxalate) 5 mg, net price 28-tab pack = £8.97; 10 mg (scored), 28-tab pack = £14.91; 20 mg (scored), 28-tab pack = £25.20. Counselling, driving

Oral drops, sugar-free, escitalopram (as oxalate) 10 mg/mL, net price 28 mL = £18.82; 20 mg/mL, 15 mL = £20.16. Counselling, driving, administration

Note Can be mixed with water, orange juice, or apple juice before taking

FLUOXETINE

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Hepatic impairment reduce dose or increase dose interval

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; also vasodilatation, postural hypotension, pharyngitis, dyspnoea, chills, taste disturbance, sleep disturbances, euphoria, confusion, yawning, impaired concentration, changes in blood sugar, alopecia, urinary frequency; *rarely* pulmonary inflammation and fibrosis; *very rarely* hepatitis, toxic epidermal necrolysis, and neuroleptic malignant syndrome-like event

Dose

- Major depression, 20 mg once daily increased after 3–4 weeks if necessary, and at appropriate intervals thereafter; max. 60 mg once daily (ELDERLY usual max. 40 mg once daily but 60 mg can be used); CHILD 8–18 years, 10 mg once daily increased after 1–2 weeks if necessary, max. 20 mg once daily (but see also Depressive Illness in Children and Adolescents, p. 239)
- Bulimia nervosa, ADULT over 18 years, 60 mg once daily
- Obsessive-compulsive disorder, ADULT over 18 years, 20 mg once daily; increased gradually if necessary to max. 60 mg once daily (ELDERLY usual max. 40 mg once daily but 60 mg can be used); review treatment if inadequate response after 10 weeks

Long duration of action Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage)

Fluoxetine (Non-proprietary) PoM

Capsules, fluoxetine (as hydrochloride) 20 mg, net price 30-cap pack = £1.90; 60 mg, 30-cap pack = £54.43. Counselling, driving

Brands include *Oxactin®*

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £5.04. Counselling, driving

Brands include *Prozep®*

Prozac® (Lilly) PoM

Capsules, fluoxetine (as hydrochloride) 20 mg (green/yellow), net price 30-cap pack = £1.50 Counselling, driving

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £11.12. Counselling, driving

FLUVOXAMINE MALEATE

Indications depressive illness, obsessive-compulsive disorder

Cautions see notes above

Contra-indications see notes above

Hepatic impairment start with low dose

Renal impairment start with low dose

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; palpitation, tachycardia, malaise; *less commonly* postural hypotension, confusion, ataxia; *rarely* abnormal liver function, usually symptomatic (discontinue treatment); *also reported* paraesthesia, taste disturbance, neuroleptic malignant syndrome-like event

Dose

- Depression, ADULT over 18 years, initially 50–100 mg daily in the evening, increased gradually if necessary to max. 300 mg daily (over 150 mg in divided doses); usual maintenance dose 100 mg daily
- Obsessive-compulsive disorder, initially 50 mg in the evening increased gradually if necessary after some weeks to max. 300 mg daily (over 150 mg in divided doses); usual maintenance dose 100–300 mg daily; CHILD over 8 years initially 25 mg daily increased if necessary in steps of 25 mg every 4–7 days to max. 200 mg daily (over 50 mg in 2 divided doses)

Note If no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

Fluvoxamine (Non-proprietary) PoM

Tablets, fluvoxamine maleate 50 mg, net price 60-tab pack = £10.81; 100 mg, 30-tab pack = £11.67. Counselling, driving

Faverin® (Abbott Healthcare) PoM

Tablets, f/c, scored, fluvoxamine maleate 50 mg, net price 60-tab pack = £17.10; 100 mg, 30-tab pack = £17.10. Counselling, driving

PAROXETINE

Indications major depression, obsessive-compulsive disorder, panic disorder; social anxiety disorder; post-traumatic stress disorder; generalised anxiety disorder

Cautions see notes above; also achlorhydria or high gastric pH (reduced absorption of oral suspension)

Contra-indications see notes above

Hepatic impairment reduce dose

Renal impairment reduce dose if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy increased risk of congenital malformations, especially if used in the first trimester; see also notes above

Breast-feeding present in milk but amount too small to be harmful

Side-effects see notes above; also yawning; abnormal dreams; raised cholesterol; *less commonly* arrhythmias, confusion, urinary incontinence; *rarely* panic attacks and paradoxical increased anxiety during initial treatment of panic disorder (reduce dose), depersonalisation, and neuroleptic malignant syndrome-like event; *rarely* restless legs syndrome; *very rarely* peripheral oedema, acute glaucoma, hepatic disorders (e.g. hepatitis), and priapism; *also reported* tinnitus, extrapyramidal reactions (including orofacial dystonias) and withdrawal reactions (see notes above)

Dose

- Major depression, social anxiety disorder, post-traumatic stress disorder, generalised anxiety disorder, ADULT over 18 years, recommended dose 20 mg each morning (no evidence of greater efficacy at higher doses); max. 50 mg daily (ELDERLY 40 mg daily); CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)
- Obsessive-compulsive disorder, ADULT over 18 years, initially 20 mg each morning, increased gradually in steps of 10 mg to recommended dose of 40 mg daily (no evidence of greater efficacy at higher doses); max. 60 mg daily (ELDERLY 40 mg daily)
- Panic disorder, ADULT over 18 years, initially 10 mg each morning, increased gradually in steps of 10 mg to recommended dose of 40 mg daily (no evidence of greater efficacy at higher doses); max. 60 mg daily (ELDERLY 40 mg daily)

Paroxetine (Non-proprietary) PoM

Tablets, paroxetine (as hydrochloride) 20 mg, net price 30-tab pack = £2.29; 30 mg, 30-tab pack = £3.17. Label: 21, counselling, driving

Seroxat® (GSK) PoM

Tablets, f/c, scored, paroxetine (as hydrochloride) 10 mg, net price 28-tab pack = £11.84; 20 mg, 30-tab pack = £12.69; 30 mg (blue), 30-tab pack = £22.28. Label: 21, counselling, driving

Oral suspension, orange, sugar-free, paroxetine (as hydrochloride) 10 mg/5 mL, net price 150-mL pack = £9.12. Label: 5, 21, counselling, driving

SERTRALINE

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Hepatic impairment reduce dose or increase dose interval in mild or moderate impairment; avoid in severe impairment

Renal impairment use with caution

Pregnancy see notes above

Breast-feeding not known to be harmful but consider discontinuing breast-feeding

Side-effects see notes above; pancreatitis, hepatitis, jaundice, liver failure, stomatitis, palpitation, hypertension, hypercholesterolaemia, tachycardia, postural hypotension, bronchospasm, amnesia, paraesthesia, aggression, hypoglycaemia, hypothyroidism, hyperprolactinaemia, urinary incontinence, menstrual irregularities, leucopenia, and tinnitus also reported

Dose

- Depressive illness, initially 50 mg daily, increased if necessary by increments of 50 mg at intervals of at least 1 week to max. 200 mg daily; usual maintenance dose 50 mg daily; CHILD under 18 years, see *BNF for Children* and Depressive Illness in Children and Adolescents, p. 239
- Obsessive-compulsive disorder, ADULT and CHILD over 12 years initially 50 mg daily, increased if necessary in steps of 50 mg at intervals of at least 1 week; max. 200 mg daily; CHILD 6–12 years initially 25 mg daily, increased to 50 mg daily after 1 week, further increased if necessary in steps of 50 mg at intervals of at least 1 week; max. 200 mg daily
- Panic disorder, post-traumatic stress disorder, or social anxiety disorder, ADULT over 18 years, initially 25 mg daily, increased after 1 week to 50 mg daily; if response is partial and if drug tolerated, dose increased in steps of 50 mg at intervals of at least 1 week to max. 200 mg daily

Sertraline (Non-proprietary) PoM

Tablets, sertraline (as hydrochloride) 50 mg, net price 28-tab pack = £1.15; 100 mg, 28-tab pack = £1.53. Counselling, driving

Lustral® (Pfizer) PoM

Tablets, f/c, sertraline (as hydrochloride) 50 mg (scored), net price 28-tab pack = £17.82; 100 mg, 28-tab pack = £29.16. Counselling, driving

4.3.4 Other antidepressant drugs

Agomelatine is a melatonin receptor agonist and a selective serotonin-receptor antagonist; it does not affect the uptake of serotonin, noradrenaline, or dopamine.

Duloxetine inhibits the re-uptake of both serotonin and noradrenaline and is licensed to treat major depressive disorder.

The thioxanthene **flupentixol** (*Fluanxol®*) has antidepressant properties when given by mouth in low doses. Flupentixol is also used for the treatment of psychoses (section 4.2.1 and section 4.2.2)

Mirtazapine, a presynaptic alpha$_2$-adrenoreceptor antagonist, increases central noradrenergic and serotonergic neurotransmission. It has few antimuscarinic effects, but causes sedation during initial treatment.

Reboxetine, a selective inhibitor of noradrenaline re-uptake, has been introduced for the treatment of depressive illness.

Tryptophan is licensed as adjunctive therapy for depression resistant to standard antidepressants; it has been associated with eosinophilia-myalgia syndrome. Tryptophan should be initiated under specialist supervision.

Venlafaxine is a serotonin and noradrenaline re-uptake inhibitor; it lacks the sedative and antimuscarinic effects of the tricyclic antidepressants. Treatment with venlafaxine is associated with a higher risk of withdrawal effects compared with other antidepressants.

AGOMELATINE

Indications major depression

Cautions elderly; mania or hypomania; concomitant use of drugs associated with hepatic injury; excessive alcohol consumption; monitor liver function before treatment and after 6, 12 and 24 weeks of treatment, then as appropriate (discontinue if serum transaminases exceed 3 times the upper limit of reference range); **interactions**: Appendix 1 (agomelatine)

Contra-indications dementia

Hepatic impairment avoid

Renal impairment caution in moderate to severe impairment

Pregnancy caution

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, diarrhoea, constipation, abdominal pain, increased serum transaminases (see Cautions); headache, dizziness, drowsiness, insomnia, fatigue, anxiety; back pain; sweating; *less commonly* paraesthesia, blurred vision, and eczema; *rarely* hepatitis and rash; suicidal behaviour (see Suicidal Behaviour and Antidepressant Therapy, p. 233) also reported

Dose

- ADULT over 18 years, 25 mg at bedtime, increased if necessary after 2 weeks to 50 mg at bedtime

Valdoxan® (Servier) ▼ PoM

Tablets, orange-yellow, f/c, agomelatine 25 mg, net price 28-tab pack = £43.77

DULOXETINE

Indications major depressive disorder; generalised anxiety disorder; diabetic neuropathy (section 6.1.5); stress urinary incontinence (section 7.4.2)

Cautions section 7.4.2

Contra-indications section 7.4.2

Hepatic impairment section 7.4.2

Renal impairment section 7.4.2

Pregnancy toxicity in *animal* studies—use only if potential benefit outweighs risk; risk of neonatal withdrawal symptoms if used near term

Breast-feeding section 7.4.2

Side-effects section 7.4.2

Dose

- Major depression, ADULT over 18 years, 60 mg once daily
- Generalised anxiety disorder, ADULT over 18 years, initially 30 mg daily, increased if necessary to 60 mg once daily; max. 120 mg daily
- Diabetic neuropathy, ADULT over 18 years, 60 mg once daily; max. 120 mg daily in divided doses
  Note In diabetic neuropathy, discontinue if inadequate response after 2 months; review treatment at least every 3 months

Cymbalta® (Lilly) ▼ PoM

Capsules, duloxetine (as hydrochloride) 30 mg (white/blue), net price 28-cap pack = £22.40; 60 mg (green/blue), 28-cap pack = £27.72. Label: 2

Note The *Scottish Medicines Consortium* has advised (September 2006) that duloxetine (*Cymbalta®*) should be restricted for use by specialists when other treatments for diabetic peripheral neuropathic pain are unsuitable or inadequate

Yentreve® (Lilly) ▼ PoM

Section 7.4.2 (stress urinary incontinence)

FLUPENTIXOL

(Flupenthixol)

Indications depressive illness; psychoses (section 4.2.1)

Cautions cardiovascular disease (including cardiac disorders and cerebral arteriosclerosis), QT-interval prolongation (avoid concomitant administration of drugs that prolong QT interval); diabetes; senile confusional states, parkinsonism; elderly; acute porphyria (section 9.8.2); see also section 4.2.1; **interactions**: Appendix 1 (antipsychotics)

Contra-indications excitable and overactive patients; impaired consciousness; circulatory collapse; coma

Hepatic impairment can precipitate coma; consider serum-flupentixol concentration monitoring

Renal impairment increased cerebral sensitivity in severe impairment; manufacturer advises caution in renal failure

Pregnancy avoid unless potential benefit outweighs risk

Breast-feeding present in milk—avoid

Side-effects section 4.2.1; also hypersalivation, dyspnoea, asthenia, hyperglycaemia, myalgia; torsade de pointes and sudden death also reported

Dose

- ADULT over 18 years, initially 1 mg (ELDERLY 500 micrograms) in the morning, increased after 1 week to 2 mg (ELDERLY 1 mg) if necessary; max. 3 mg (ELDERLY 1.5 mg) daily, doses above 2 mg (ELDERLY 1 mg) in divided doses, last dose before 4 pm; discontinue if no response after 1 week at max. dosage
  Counselling Although drowsiness may occur, can also have an alerting effect so should not be taken in the evening

Fluanxol® (Lundbeck) PoM

Tablets, yellow, s/c, flupentixol (as dihydrochloride) 500 micrograms, net price 60-tab pack = £2.63; 1 mg, 60-tab pack = £2.72. Label: 2, counselling, administration

Depixol® (Lundbeck) PoM

Section 4.2.1 (psychoses)

MIRTAZAPINE

Indications major depression

Cautions elderly, cardiac disorders, hypotension, history of urinary retention, susceptibility to angle-closure glaucoma, diabetes mellitus, psychoses (may aggravate psychotic symptoms), history of seizures or bipolar depression; **interactions:** Appendix 1 (mirtazapine)

Blood disorders Patients should be advised to report any fever, sore throat, stomatitis or other signs of infection during treatment. Blood count should be performed and the drug stopped immediately if blood dyscrasia suspected

Withdrawal Nausea, vomiting, dizziness, agitation, anxiety, and headache are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks

Hepatic impairment use with caution

Renal impairment clearance reduced by 30% if eGFR less than 40 mL/minute/1.73 m^2; clearance reduced by 50% if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy use with caution—limited experience; monitor neonate for withdrawal effects

Breast-feeding present in milk; use only if potential benefit outweighs risk

Side-effects increased appetite, weight gain, dry mouth; postural hypotension, peripheral oedema;

drowsiness, fatigue, tremor, dizziness, abnormal dreams, confusion, anxiety, insomnia; arthralgia, myalgia; *less commonly* syncope, hypotension, mania, hallucinations, movement disorders; *rarely* myoclonus; *very rarely* blood disorders (see Cautions), convulsions, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233), suicidal behaviour (see p. 233), and angle-closure glaucoma

Dose

- Initially 15–30 mg daily at bedtime increased within 2–4 weeks according to response; max. 45 mg daily as a single dose at bedtime or in 2 divided doses; CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)

Mirtazapine (Non-proprietary) PoM

Tablets, mirtazapine 15 mg, net price 28-tab pack = £3.36; 30 mg, 28-tab pack = £2.04; 45 mg, 28-tab pack = £3.71. Label: 2, 25

Orodispersible tablets, mirtazapine 15 mg, net price 30-tab pack = £2.59; 30 mg, 30-tab pack = £2.94; 45 mg, 30-tab pack = £2.98. Label: 2, counselling, administration

Oral solution, mirtazapine 15 mg/mL, net price 66 mL = £47.00. Label: 2

Zispin SolTab® (Organon) PoM

Orodispersible tablets, mirtazapine 15 mg, net price 6-tab pack = £3.84, 30-tab pack = £15.06; 30 mg, 30-tab pack = £15.06; 45 mg, 30-tab pack = £15.06. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling *Zispin SolTab®* should be placed on the tongue, allowed to disperse and swallowed

REBOXETINE

Indications major depression

Cautions history of cardiovascular disease and epilepsy; bipolar disorder; urinary retention; prostatic hypertrophy; susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; **interactions:** Appendix 1 (reboxetine)

Hepatic impairment initial dose 2 mg twice daily, increased according to tolerance

Renal impairment initial dose 2 mg twice daily, increased according to tolerance

Pregnancy use only if potential benefit outweighs risk—limited information available

Breast-feeding small amount present in milk—use only if potential benefit outweighs risk

Side-effects nausea, dry mouth, constipation, anorexia; tachycardia, palpitation, vasodilation, postural hypotension; headache, insomnia, dizziness; chills; impotence; urinary retention; impaired visual accommodation; sweating; lowering of plasma-potassium concentration on prolonged administration in the elderly; *very rarely* angle-closure glaucoma; *also reported* vomiting, hypertension, paraesthesia, agitation, anxiety, irritability, hallucinations, aggression, hyponatraemia, testicular pain, cold extremities, and rash; suicidal behaviour (see p. 233)

Dose

- 4 mg twice daily increased if necessary after 3–4 weeks to 10 mg daily in divided doses, max. 12 mg daily; CHILD under 18 years and ELDERLY not recommended

Edronax® (Pharmacia) PoM

Tablets, scored, reboxetine (as mesilate) 4 mg, net price 60-tab pack = £18.91. Counselling, driving

TRYPTOPHAN

(L-Tryptophan)

Indications see notes above

Cautions eosinophilia-myalgia syndrome has been reported (withhold treatment if increased eosinophil count, myalgia, arthralgia, fever, dyspnoea, neuropathy, oedema or skin lesions develop until possibility of eosinophilia-myalgia syndrome excluded); **interactions:** Appendix 1 (tryptophan)

Contra-indications history of eosinophilia-myalgia syndrome following use of tryptophan

Pregnancy no information available

Breast-feeding no information available

Side-effects drowsiness, nausea, headache, lightheadedness, suicidal behaviour (see p. 233); eosinophilia-myalgia syndrome, see Cautions

Dose

- 1 g 3 times daily; max. 6 g daily; ELDERLY lower dose may be appropriate especially in renal or hepatic impairment; CHILD not recommended

Optimax® (Merck Serono) PoM

Tablets, scored, tryptophan 500 mg, net price 84-tab pack = £23.47. Label: 3

VENLAFAXINE

Indications major depression, generalised anxiety disorder

Cautions heart disease (monitor blood pressure); diabetes; history of epilepsy; history or family history of mania; susceptibility to angle-closure glaucoma; concomitant use of drugs that increase risk of bleeding, history of bleeding disorders; **interactions:** Appendix 1 (venlafaxine)

Driving May affect performance of skilled tasks (e.g. driving)

Withdrawal Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, tremor, sleep disturbances, and sweating are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks

Contra-indications conditions associated with high risk of cardiac arrhythmia, uncontrolled hypertension

Hepatic impairment consider reducing dose by 50% in mild or moderate impairment; use with caution and reduce dose by at least 50% in severe impairment

Renal impairment use with caution; use half normal dose (immediate-release tablets may be given once daily) if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid unless potential benefit outweighs risk—toxicity in *animal* studies; risk of withdrawal effects in neonate

Breast-feeding present in milk—avoid

Side-effects constipation, nausea, anorexia, weight changes, vomiting; hypertension, palpitation, vasodilatation, changes in serum cholesterol; chills, yawning; dizziness, dry mouth, insomnia, nervousness, drowsiness, asthenia, headache, abnormal dreams, anxiety, confusion, hypertonia, sensory disturbances, tremor; difficulty with micturition, sexual dysfunction, menstrual disturbances; visual disturbances, mydriasis (*very rarely* angle-closure glaucoma); sweating; *less commonly* bruxism, diarrhoea, taste disturbance, postural hypotension, arrhythmias, agitation, apathy, incoordination, hallucinations, myoclonus, urinary

retention, bleeding disorders (including ecchymosis and gastro-intestinal haemorrhage), tinnitus, alopecia, photosensitivity, and rash; *rarely* mania, hypomania, seizures, and extrapyramidal symptoms including akathisia; *also reported* hepatitis, pancreatitis, hypotension, QT-interval prolongation, aggression, neuroleptic malignant syndrome, delirium, syndrome of inappropriate anti-diuretic hormone secretion (see Hyponatraemia and Antidepressant Therapy, p. 233), hyperprolactinaemia, blood dyscrasias, rhabdomyolysis, pruritus, urticaria, Stevens-Johnson syndrome; suicidal behaviour (see p. 233)

Dose

- Depression, ADULT over 18 years, initially 75 mg daily in 2 divided doses increased if necessary at intervals of at least 2 weeks; max. 375 mg daily; CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)
  Note Faster dose titration may be necessary in some patients
- Generalised anxiety disorder and social anxiety disorder, see under preparations below

Venlafaxine (Non-proprietary) PoM

Tablets, venlafaxine (as hydrochloride) 37.5 mg, net price 56-tab pack = £3.60; 75 mg, 56-tab pack = £4.71. Label: 3, counselling, driving

Modified release

Venlafaxine m/r preparations PoM

Capsules, m/r, venlafaxine (as hydrochloride) 75 mg; 150 mg. Label: 3, 25, counselling, driving

Brands include *Bonilux XL®*, *Depefex® XL*, *Foraven XL®*, *Politid XL®*, *Ranfaxine XL®*, *Tifaxin XL®*, *Venaxx XL®*, *Vensir XL®*, *Winfex® XL*

Dose depression, ADULT over 18 years, 75 mg once daily, increased if necessary at intervals of at least 2 weeks; max. 375 mg once daily; CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)

Note Faster dose titration may be necessary in some patients

Generalised anxiety disorder, ADULT over 18 years, 75 mg once daily, increased if necessary at intervals of at least 2 weeks; max. 225 mg once daily

Social anxiety disorder, ADULT over 18 years, recommended dose 75 mg once daily (no evidence of greater efficacy at higher doses); dose may be increased at intervals of at least 2 weeks; max. 225 mg once daily

Tablets, m/r, venlafaxine (as hydrochloride) 75 mg; 150 mg; 225 mg. Label: 3, 25, counselling, driving

Brands include *Venlalic® XL*

Dose depression, ADULT over 18 years, 75 mg once daily, increased if necessary at intervals of at least 2 weeks; max. 375 mg once daily; CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)

Note Faster dose titration may be necessary in some patients

Efexor® XL (Wyeth) PoM

Capsules, m/r, venlafaxine (as hydrochloride) 75 mg (peach), net price 28-cap pack = £22.50; 150 mg (orange), 28-cap pack = £37.51. Label: 3, 25, counselling, driving

Dose depression, ADULT over 18 years, 75 mg once daily, increased if necessary at intervals of at least 2 weeks; max. 375 mg once daily; CHILD under 18 years not recommended (see Depressive Illness in Children and Adolescents, p. 239)

Note Faster dose titration may be necessary in some patients

Generalised anxiety disorder, ADULT over 18 years, 75 mg once daily, increased if necessary at intervals of at least 2 weeks; max. 225 mg once daily

Social anxiety disorder, ADULT over 18 years, recommended dose 75 mg once daily (no evidence of greater efficacy at higher doses); dose may be increased at intervals of at least 2 weeks; max. 225 mg once daily

4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder

Central nervous system stimulants include the **amfetamines** (notably dexamfetamine) **and related drugs** (e.g. methylphenidate). They have very few indications and in particular, should **not** be used to treat depression, obesity, senility, debility, or for relief of fatigue.

CNS stimulants should be prescribed for children with severe and persistent symptoms of *attention deficit hyperactivity disorder* (ADHD), when the diagnosis has been confirmed by a specialist; children with moderate symptoms of ADHD can be treated with CNS stimulants when psychological interventions have been unsuccessful or are unavailable. Prescribing of CNS stimulants may be continued by general practitioners, under a shared-care arrangement. Treatment of ADHD often needs to be continued into adolescence, and may need to be continued into adulthood. Initiating treatment in adulthood is unlicensed.

Drug treatment of ADHD should be part of a comprehensive treatment programme. The choice of medication should take into consideration co-morbid conditions (such as tic disorders, Tourette syndrome, and epilepsy), the adverse effect profile, potential for drug misuse, and preferences of the patient and carers. **Methylphenidate** and **atomoxetine** are used for the management of ADHD; **dexamfetamine** is an alternative in children who do not respond to these drugs. Before initiation of drug therapy, and every 6 months thereafter, pulse, blood pressure, weight, and height should be measured.

The need to continue drug treatment for ADHD should be reviewed at least annually. This may involve suspending treatment.

Modafinil is used for the treatment of daytime sleepiness associated with narcolepsy or obstructive sleep apnoea syndrome; dependence with long-term use cannot be excluded and it should therefore be used with caution.

Dexamfetamine and methylphenidate [unlicensed indication] are also used to treat narcolepsy.

ATOMOXETINE

Indications attention deficit hyperactivity disorder (initiated by a specialist physician experienced in managing the condition)

Cautions see notes above; also cardiovascular disease including hypertension and tachycardia; structural cardiac abnormalities; QT-interval prolongation (avoid concomitant administration of drugs that prolong QT interval); psychosis or mania; history of seizures; aggressive behaviour, hostility, or emotional lability; susceptibility to angle-closure glaucoma; **interactions:** Appendix 1 (atomoxetine)

Hepatic disorders Following rare reports of hepatic disorders, patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine, or jaundice

Suicidal ideation Following reports of suicidal thoughts and behaviour, patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression

Hepatic impairment halve dose in moderate impairment; quarter dose in severe impairment; see also Hepatic Disorders above

Pregnancy no information available; avoid unless potential benefit outweighs risk

Breast-feeding avoid—present in milk in *animal* studies

Side-effects anorexia, dry mouth, nausea, vomiting, abdominal pain, constipation, dyspepsia, flatulence; palpitation, tachycardia, increased blood pressure, postural hypotension, hot flushes; sleep disturbance, dizziness, headache, fatigue, lethargy, depression, psychotic or manic symptoms, aggression, hostility, emotional lability, drowsiness, anxiety, irritability, tremor, rigors; urinary retention, enuresis, prostatitis, sexual dysfunction, menstrual disturbances; mydriasis, conjunctivitis; dermatitis, pruritus, rash, sweating, weight changes; *less commonly* suicidal ideation (see Suicidal Ideation, above), cold extremities; *very rarely* hepatic disorders (see Hepatic Disorders, above), seizures, angle-closure glaucoma, and Raynaud's phenomenon

Dose

- ADULT over 18 years, body-weight over 70 kg, initially 40 mg daily for 7 days, increased according to response; usual maintenance 80–100 mg daily, but may be increased to max. 120 mg daily [unlicensed] under the direction of a specialist; CHILD 6–18 years, body-weight over 70 kg, initially 40 mg daily for 7 days, increased according to response; usual maintenance 80 mg daily, but may be increased to max. 120 mg daily [unlicensed] under the direction of a specialist; ADULT and CHILD over 6 years, body-weight under 70 kg, initially 500 micrograms/kg daily for 7 days, increased according to response; usual maintenance 1.2 mg/kg daily, but may be increased to 1.8 mg/kg daily (max. 120 mg daily) [unlicensed] under the direction of a specialist
  Note Total daily dose may be given *either* as a single dose in the morning *or* in 2 divided doses with last dose no later than early evening

Strattera® (Lilly) ▼ PoM

Capsules, atomoxetine (as hydrochloride) 10 mg (white), net price 7-cap pack = £15.62, 28-cap pack = £62.46; 18 mg (gold/white), 7-cap pack = £15.62, 28-cap pack = £62.46; 25 mg (blue/white), 7-cap pack = £15.62, 28-cap pack = £62.46; 40 mg (blue), 7-cap pack = £15.62, 28-cap pack = £62.46; 60 mg (blue/gold), 28-cap pack = £62.46; 80 mg (brown/white), 28-cap pack = £83.28. Label: 3

DEXAMFETAMINE SULPHATE
(Dexamphetamine sulphate)

Indications narcolepsy; refractory attention deficit hyperactivity disorder (under specialist supervision)

Cautions see notes above; also anorexia; mild hypertension (contra-indicated if moderate or severe); psychosis or bipolar disorder; monitor for aggressive behaviour or hostility during initial treatment; history of epilepsy (discontinue if convulsions occur); tics and Tourette syndrome (use with caution)—discontinue if tics occur; monitor growth in children (see also below); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; data on safety and efficacy of long-term use not complete; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (sympathomimetics)

Special cautions in children Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity)

Driving May affect performance of skilled tasks (e.g. driving); effects of alcohol unpredictable

Contra-indications cardiovascular disease including moderate to severe hypertension, structural cardiac abnormalities, advanced arteriosclerosis, hyperexcitability or agitated states, hyperthyroidism, history of drug or alcohol abuse

Renal impairment use with caution

Pregnancy avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity)

Breast-feeding significant amount in milk—avoid

Side-effects insomnia, restlessness, irritability and excitability, night terrors, euphoria, tremor, dizziness, aggression, paranoia, anxiety, confusion, depression, fatigue, headache; seizures (see also Cautions); dependence and tolerance, psychosis; anorexia, gastrointestinal symptoms, growth restriction in children (see also under Cautions); dry mouth, sweating, tachycardia (and anginal pain), palpitation, myocardial infarction, hypertension, hypotension; impotence; visual disturbances; alopecia, rash; cardiomyopathy reported with chronic use; cardiovascular collapse; cerebral vasculitis; central stimulants have provoked choreoathetoid movements and dyskinesia, tics and Tourette syndrome in predisposed individuals (see also Cautions); *very rarely* angle-closure glaucoma; **overdosage:** see Emergency Treatment of Poisoning, p. 38

Dose

- Narcolepsy, initially 10 mg (ELDERLY 5 mg) daily in divided doses increased at weekly intervals by 10 mg (ELDERLY 5 mg) daily to a max. of 60 mg daily
- Refractory attention deficit hyperactivity disorder, ADULT over 18 years [unlicensed use], initially 5 mg twice daily, increased at weekly intervals according to response; max. 60 mg daily; CHILD 6–18 years, initially 5–10 mg daily, increased if necessary at weekly intervals by 5 mg daily, usual max. 1 mg/kg (up to 20 mg) daily (40 mg daily has been required in some children)
  Note Maintenance dose given in 2–4 divided doses

Dexamfetamine (Non-proprietary) CD

Tablets, scored, dexamfetamine sulphate 5 mg, net price 28-tab pack = £15.60. Counselling, driving

METHYLPHENIDATE HYDROCHLORIDE

Indications attention deficit hyperactivity disorder (under specialist supervision); narcolepsy [unlicensed indication]

Cautions see notes above; also monitor for psychiatric disorders; anxiety or agitation; tics or a family history of Tourette syndrome; epilepsy (discontinue if increased seizure frequency); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; **interactions:** Appendix 1 (sympathomimetics)

Contra-indications severe depression, suicidal ideation; anorexia nervosa; drug or alcohol dependence; psychosis; uncontrolled bipolar disorder; hyperthyroidism; cardiovascular disease (including heart

failure, cardiomyopathy, severe hypertension, and arrhythmias), structural cardiac abnormalities; phaeochromocytoma; vasculitis; cerebrovascular disorders

Pregnancy limited experience—avoid unless potential benefit outweighs risk

Breast-feeding limited information available—avoid

Side-effects abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, dry mouth, anorexia, reduced weight gain; tachycardia, palpitation, arrhythmias, changes in blood pressure; cough, nasopharyngitis; tics (*very rarely* Tourette syndrome), insomnia, nervousness, asthenia, depression, irritability, aggression, headache, drowsiness, dizziness, movement disorders; fever; arthralgia; rash, pruritus, alopecia; growth restriction; *less commonly* constipation, dyspnoea, abnormal dreams, confusion, suicidal ideation, urinary frequency, haematuria, muscle cramps, epistaxis; *rarely* angina, sweating, and visual disturbances; *very rarely* hepatic dysfunction, myocardial infarction, cerebral arteritis, psychosis, neuroleptic malignant syndrome, tolerance and dependence, blood disorders including leucopenia and thrombocytopenia, angle-closure glaucoma, exfoliative dermatitis, and erythema multiforme; supraventricular tachycardia, bradycardia, and convulsions *also reported*

Dose

- Attention deficit hyperactivity disorder, ADULT over 18 years [unlicensed use], 5 mg 2–3 times daily increased if necessary at weekly intervals according to response, max. 100 mg daily in 2–3 divided doses; CHILD 6–18 years, initially 5 mg 1–2 times daily, increased if necessary at weekly intervals by 5–10 mg daily; usual max. 60 mg daily in 2–3 divided doses but may be increased to 2.1 mg/kg daily in 2–3 divided doses (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month; CHILD 4–6 years see *BNF for Children*
  Evening dose If effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose)
  Note Treatment may be started using a modified-release preparation
- Narcolepsy [unlicensed indication], 10–60 mg (usually 20–30 mg) daily in divided doses before meals

Methylphenidate Hydrochloride (Non-proprietary) CD

Tablets, methylphenidate hydrochloride 5 mg, net price 30-tab pack = £2.67; 10 mg, 30-tab pack = £6.74; 20 mg, 30-tab pack = £9.59
Brands include *Medikinet®*

Ritalin® (Novartis) CD

Tablets, scored, methylphenidate hydrochloride 10 mg, net price 30-tab pack = £5.57

Modified release

Concerta® XL (Janssen-Cilag) CD

Tablets, m/r, methylphenidate hydrochloride 18 mg (yellow), net price 30-tab pack = £31.19; 27 mg (grey), 30-tab pack = £36.81; 36 mg (white), 30-tab pack = £42.45. Label: 25

Note *Concerta® XL* tablets consist of an immediate-release component (22% of the dose) and a modified-release component (78% of the dose)

Counselling Tablet membrane may pass through gastro-intestinal tract unchanged

Cautions dose form not appropriate for use in dysphagia or if gastro-intestinal lumen restricted

Dose attention deficit hyperactivity disorder, ADULT over 18 years [unlicensed use], initially 18 mg once daily in the morning, adjusted at weekly intervals according to response, max. 108 mg daily; CHILD 6–18 years, initially 18 mg once daily (in the morning), increased if necessary at weekly intervals by 18 mg according to response, usual max. 54 mg once daily, but may be increased to 2.1 mg/kg daily (max. 108 mg daily) [unlicensed] under the direction of a specialist; discontinue if no response after 1 month

Note Total daily dose of 15 mg of standard-release formulation is equivalent to *Concerta® XL* 18 mg once daily

Equasym XL® (Shire) CD

Capsules, m/r, methylphenidate hydrochloride 10 mg (white/green), net price 30-cap pack = £25.00; 20 mg (white/blue), 30-cap pack = £30.00; 30 mg (white/brown), 30-cap pack = £35.00. Label: 25

Note *Equasym XL®* capsules consist of an immediate-release component (30% of the dose) and a modified-release component (70% of the dose)

Dose attention deficit hyperactivity disorder, ADULT over 18 years [unlicensed use], initially 10 mg once daily in the morning before breakfast, increased gradually at weekly intervals if necessary, max. 100 mg daily; CHILD 6–18 years, initially 10 mg once daily in the morning before breakfast, increased gradually at weekly intervals if necessary, usual max. 60 mg daily but may be increased to 2.1 mg/kg daily (max. 90 mg daily) [unlicensed] under the direction of a specialist; discontinue if no response after 1 month

Note Contents of capsule can be sprinkled on a tablespoon of apple sauce (then swallowed immediately without chewing)

Medikinet XL® (Flynn) CD

Capsules, m/r, methylphenidate hydrochloride 10 mg (lilac/white), net price 28-cap pack = £20.18; 20 mg (lilac), 28-cap pack = £26.91; 30 mg (purple/light grey), 28-cap pack = £31.39; 40 mg (purple/grey), 28-cap pack = £43.20. Label: 25

Note *Medikinet XL®* capsules consist of an immediate-release component (50% of the dose) and a modified-release component (50% of the dose)

Dose attention deficit hyperactivity disorder, ADULT over 18 years [unlicensed use], initially 10 mg once daily in the morning with breakfast, adjusted at weekly intervals according to response, max. 100 mg daily; CHILD 6–18 years, initially 10 mg once daily in the morning with breakfast, adjusted at weekly intervals according to response, usual max. 60 mg daily but may be increased to 2.1 mg/kg daily (max. 90 mg daily) [unlicensed] under the direction of a specialist; discontinue if no response after 1 month

Note Contents of capsule can be sprinkled on a tablespoon of apple sauce (then swallowed immediately without chewing)

MODAFINIL

Indications daytime sleepiness associated with narcolepsy, obstructive sleep apnoea syndrome, and chronic shift work

Cautions monitor blood pressure and heart rate in hypertensive patients (but see Contra-indications); history of psychosis, depression, mania, alcohol or drug abuse; discontinue treatment if psychiatric symptoms develop; possibility of dependence; discontinue treatment if rash develops; **interactions:** Appendix 1 (modafinil)

Contra-indications moderate to severe uncontrolled hypertension, arrhythmia; history of left ventricular hypertrophy, cor pulmonale, or of clinically significant signs of CNS stimulant-induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias)

Hepatic impairment halve dose in severe impairment

Renal impairment halve dose in severe impairment

Pregnancy avoid

Breast-feeding avoid—present in milk in *animal* studies

Side-effects dry mouth, appetite changes, gastro-intestinal disturbances (including nausea, diarrhoea, constipation, and dyspepsia), abdominal pain; tachycardia, vasodilatation, chest pain, palpitation; head-

ache (uncommonly migraine), anxiety, sleep disturbances, dizziness, drowsiness, depression, confusion, paraesthesia, asthenia; visual disturbances; *less commonly* flatulence, reflux, vomiting, mouth ulcers, glossitis, dysphagia, taste disturbance, weight changes, hypertension, hypotension, bradycardia, arrhythmia, peripheral oedema, hypercholesterolaemia, rhinitis, dyspnoea, epistaxis, dyskinesia, amnesia, emotional lability, tremor, decreased libido, agitation, aggression, hyperglycaemia, thirst, urinary frequency, menstrual disturbances, eosinophilia, leucopenia, myasthenia, muscle cramps, hypertonia, myalgia, arthralgia, dry eye, sinusitis, acne, sweating, rash, and pruritus; *also reported* psychosis, mania, delusions, hallucinations, suicidal ideation, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

- Narcolepsy and obstructive sleep apnoea syndrome, ADULT over 12 years, initially 200 mg daily, *either* in 2 divided doses morning and at noon *or* as a single dose in the morning, dose adjusted according to response to 200–400 mg daily in 2 divided doses or as a single dose; ELDERLY initiate at 100 mg daily; CHILD 5–12 years, see *BNF for Children*
- Chronic shift work sleep disorder, 200 mg taken 1 hour before the start of the work shift

Provigil® (Cephalon) ▼ PoM
Tablets, modafinil 100 mg, net price 30-tab pack = £52.60; 200 mg (scored), 30 tab-pack = £105.20

4.5 Drugs used in the treatment of obesity

4.5.1 Anti-obesity drugs acting on the gastro-intestinal tract
4.5.2 Centrally acting appetite suppressants

Obesity is associated with many health problems including cardiovascular disease, diabetes mellitus, gallstones and osteoarthritis. Factors that aggravate obesity may include depression, other psychosocial problems, and some drugs.

The main treatment of the obese individual is a suitable diet, carefully explained to the individual, with appropriate support and encouragement; the individual should also be advised to increase physical activity. Smoking cessation (while maintaining body weight) may be worthwhile before attempting supervised weight loss since cigarette smoking may be more harmful than obesity. Attendance at groups (e.g. 'weight-watchers') helps some individuals.

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity; the individual should receive advice on diet and lifestyle modification and be monitored for changes in weight as well as in blood pressure, blood lipids and other associated conditions.

An anti-obesity drug should be considered only for those with a body mass index (BMI, individual's bodyweight divided by the square of the individual's height) of 30 kg/m^2 or greater in whom at least 3 months of managed care involving supervised diet, exercise and behaviour modification fails to achieve a realistic reduction in weight. In the presence of risk factors (such as diabetes, coronary heart disease, hypertension, and obstructive sleep apnoea), it may be appropriate to prescribe a drug to individuals with a BMI of 27 kg/m^2 or greater, provided that such use is permitted by the drug's marketing authorisation. Drugs should **never** be used as the sole element of treatment. The individual should be monitored on a regular basis; drug treatment should be discontinued if the individual regains weight at any time whilst receiving drug treatment.

Combination therapy involving more than one anti-obesity drug is **contra-indicated** by the manufacturers; there is no evidence-base to support such treatment.

Thyroid hormones have **no** place in the treatment of obesity except in biochemically proven hypothyroid patients. The use of diuretics, chorionic gonadotrophin, or amfetamines is **not** appropriate for weight reduction.

4.5.1 Anti-obesity drugs acting on the gastro-intestinal tract

Orlistat, a lipase inhibitor, reduces the absorption of dietary fat. It is used in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m^2 or more *or* in individuals with a BMI of 28 kg/m^2 in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia.

Orlistat should be used in conjunction with other lifestyle measures to manage obesity (section 4.5); treatment should only be continued beyond 12 months after discussing potential benefits and risks with the patient. On stopping orlistat, there may be a gradual reversal of weight loss.

Some of the weight loss in those taking orlistat probably results from individuals reducing their fat intake to avoid severe gastro-intestinal effects including steatorrhoea. Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins.

Methylcellulose is claimed to reduce food intake by producing a feeling of satiety, but there is little evidence to support its use in the management of obesity.

ORLISTAT

Indications adjunct in obesity (see notes above)

Cautions may impair absorption of fat-soluble vitamins; epilepsy; **interactions:** Appendix 1 (orlistat)
Multivitamins If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime

Contra-indications chronic malabsorption syndrome; cholestasis

Pregnancy use with caution

Breast-feeding avoid—no information available

Side-effects oily leakage from rectum, flatulence, faecal urgency, liquid or oily stools, faecal incontinence, abdominal distension and pain (gastro-intestinal effects minimised by reduced fat intake), tooth and gingival disorders; respiratory infections; fatigue, anxiety, headache; menstrual disturbances, urinary-

tract infection; hypoglycaemia; *rarely* rectal bleeding, hypothyroidism; *very rarely* diverticulitis, cholelithiasis, hepatitis, and bullous eruptions; oxalate nephropathy also reported

Dose

- ADULT over 18 years, 120 mg taken immediately before, during, or up to 1 hour after each main meal (up to max. 360 mg daily); continue treatment beyond 12 weeks only if weight loss since start of treatment exceeds 5% (target for initial weight loss may be lower in patients with type 2 diabetes); CHILD over 12 years, initiated by specialist only [unlicensed use]

  Note If a meal is missed or contains no fat, the dose of orlistat should be omitted

[1] **Xenical®** (Roche) PoM

Capsules, turquoise, orlistat 120 mg, net price 84-cap pack = £31.63

1. Orlistat can be sold to the public for the treatment of obesity in adults over 18 years with a body mass index of 28 kg/m^2 or more, taken in conjunction with a mildly hypocaloric, lower-fat diet (max. daily dose 180 mg)

4.5.2 Centrally acting appetite suppressants

Phentermine and **diethylpropion** are central stimulants; they are not recommended for the treatment of obesity. Phentermine has been associated with a risk of pulmonary hypertension.

Sibutramine, dexfenfluramine, and fenfluramine have been withdrawn from the market because the benefit of treatment does not outweigh the risk of serious adverse effects.

4.6 Drugs used in nausea and vertigo

Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis, particularly in children. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or antiepileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting.

Antihistamines are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of adverse effects (drowsiness and antimuscarinic effects) differ.

The **phenothiazines** are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They are of considerable value for the prophylaxis and treatment of nausea and vomiting associated with diffuse neoplastic disease, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytotoxics. **Prochlorperazine**, **perphenazine**, and **trifluoperazine** are less sedating than **chlorpromazine**; severe dystonic reactions sometimes occur with phenothiazines, especially in children. Some phenothiazines are available as rectal suppositories, which can be useful in patients with persistent vomiting or with severe nausea; prochlorperazine can also be administered as a buccal tablet which is placed between the upper lip and the gum.

Droperidol is a butyrophenone, structurally related to haloperidol, which blocks dopamine receptors in the chemoreceptor trigger zone.

Other antipsychotic drugs including **haloperidol** and **levomepromazine** are used for the relief of nausea and vomiting in terminal illness (see Palliative Care, p. 22).

Metoclopramide is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease. In postoperative nausea and vomiting, metoclopramide in a dose of 10 mg has limited efficacy. High-dose metoclopramide injection is now less commonly used for cytotoxic-induced nausea and vomiting. As with the phenothiazines, metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine (section 4.9.2) will abort dystonic attacks.

Domperidone acts at the chemoreceptor trigger zone; it is used for the relief of nausea and vomiting, especially when associated with cytotoxic therapy. It has the advantage over metoclopramide and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. In Parkinson's disease, it is used to prevent nausea and vomiting during treatment with apomorphine and also to treat nausea caused by other dopaminergic drugs (section 4.9.1). Domperidone is also used to treat vomiting due to emergency hormonal contraception (section 7.3.5).

Granisetron, **ondansetron**, and **palonosetron** are specific 5HT$_3$-receptor antagonists which block 5HT$_3$ receptors in the gastro-intestinal tract and in the CNS. Granisetron and ondansetron are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting. Palonosetron is licensed for prevention of nausea and vomiting associated with moderately or highly emetogenic cytotoxic chemotherapy.

Dexamethasone (section 6.3.2) has antiemetic effects and it is used in vomiting associated with cancer chemotherapy. It can be used alone or with metoclopramide, prochlorperazine, lorazepam, or a 5HT$_3$ antagonist (section 8.1).

Aprepitant and **fosaprepitant** are neurokinin 1 receptor antagonists licensed for the prevention of acute and delayed nausea and vomiting associated with cisplatin-based cytotoxic chemotherapy; they are given with dexamethasone and a 5HT$_3$ antagonist.

Nabilone is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics. Side-effects such as drowsiness and dizziness occur frequently with standard doses.

Vomiting during pregnancy

Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as **promethazine**, may be required. **Prochlorperazine** or **metoclopramide** may be considered as second-line treatments. If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought. Hyperemesis gravidarum is a more serious condition, which requires intravenous fluid and electrolyte replacement and sometimes nutritional support. Supplementation with thiamine must be considered in order to reduce the risk of Wernicke's encephalopathy.

Postoperative nausea and vomiting

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, and the type and duration of surgery. Other risk factors include female sex, a history of postoperative nausea and vomiting or motion sickness, and intraoperative and postoperative use of opioids. Therapy to prevent postoperative nausea and vomiting should be based on the assessed risk of postoperative nausea and vomiting in each patient. Drugs used include **$5HT_3$-receptor antagonists**, **droperidol**, **dexamethasone** (section 6.3.2), some **phenothiazines** (e.g. prochlorperazine), and **antihistamines** (e.g. cyclizine). A combination of two or more antiemetic drugs that have different mechanisms of action is often indicated in those at high risk of postoperative nausea and vomiting or where postoperative vomiting presents a particular danger (e.g. in some types of surgery). When a prophylactic antiemetic drug has failed, postoperative nausea and vomiting should be treated with one or more drugs from a different class.

Motion sickness

Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is **hyoscine**. A transdermal hyoscine patch provides prolonged activity but it needs to be applied several hours before travelling. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative effect is desired **promethazine** is useful, but generally a slightly less sedating antihistamine such as **cyclizine** or **cinnarizine** is preferred. The $5HT_3$ antagonists, domperidone, metoclopramide, and the phenothiazines (except the antihistamine phenothiazine promethazine) are **ineffective** in motion sickness.

Other vestibular disorders

Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. Vertigo and nausea associated with Ménière's disease and middle-ear surgery can be difficult to treat.

Betahistine is an analogue of histamine and is claimed to reduce endolymphatic pressure by improving the microcirculation. Betahistine is licensed for vertigo, tinnitus, and hearing loss associated with Ménière's disease.

A **diuretic** alone or combined with salt restriction may provide some benefit in vertigo associated with Ménière's disease; **antihistamines** (such as cinnarizine), and **phenothiazines** (such as prochlorperazine) are also used. Where possible, prochlorperazine should be reserved for the treatment of acute symptoms.

For advice to avoid the inappropriate prescribing of drugs (notably phenothiazines) for dizziness in the elderly, see Prescribing for the Elderly, p. 24.

Cytotoxic chemotherapy

For the management of nausea and vomiting induced by cytotoxic chemotherapy, see section 8.1.

Palliative care

For the management of nausea and vomiting in palliative care, see p. 22 and p. 23.

Migraine

For the management of nausea and vomiting associated with migraine, see p. 277.

Antihistamines

CINNARIZINE

Indications vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière's disease; motion sickness

Cautions section 3.4.1; also Parkinson's disease

Contra-indications section 3.4.1

Hepatic impairment section 3.4.1

Renal impairment use with caution—no information available

Pregnancy section 3.4.1

Breast-feeding section 3.4.1

Side-effects section 3.4.1; also *rarely* weight gain, sweating, lichen planus, and lupus-like skin reactions

Dose

- Vestibular disorders, 30 mg 3 times daily; CHILD 5–12 years 15 mg 3 times daily
- Motion sickness, 30 mg 2 hours before travel then 15 mg every 8 hours during journey if necessary; CHILD 5–12 years, 15 mg 2 hours before travel then 7.5 mg every 8 hours during journey if necessary

Cinnarizine (Non-proprietary)
Tablets, cinnarizine 15 mg, net price 84-tab pack = £8.84. Label: 2

Stugeron® (Janssen-Cilag)
Tablets, scored, cinnarizine 15 mg, net price 15-tab pack = £1.55, 100-tab pack = £4.18. Label: 2

With dimenhydrinate

Arlevert® (Hampton) PoM
Tablets, cinnarizine 20 mg, dimenhydrinate 40 mg, net price 100-tab pack = £24.00. Label: 2
Dose ADULT over 18 years, 1 tablet 3 times daily

CYCLIZINE

Indications nausea, vomiting, vertigo, motion sickness, labyrinthine disorders

Cautions section 3.4.1; severe heart failure; may counteract haemodynamic benefits of opioids; **interactions:** Appendix 1 (antihistamines)

Contra-indications section 3.4.1

Hepatic impairment section 3.4.1

Pregnancy section 3.4.1

Breast-feeding no information available

Side-effects section 3.4.1; also hypertension, paraesthesia, and twitching

Dose

- By mouth, cyclizine hydrochloride 50 mg up to 3 times daily; CHILD 6–12 years 25 mg up to 3 times daily
  Note For motion sickness, take 1–2 hours before departure
- By intramuscular *or* intravenous injection, cyclizine lactate 50 mg 3 times daily

Valoid® (Amdipharm)

Tablets, scored, cyclizine hydrochloride 50 mg, net price 100-tab pack = £7.41. Label: 2

Injection PoM, cyclizine lactate 50 mg/mL, net price 1-mL amp = 51p

PROMETHAZINE HYDROCHLORIDE

Indications nausea, vomiting, vertigo, labyrinthine disorders, motion sickness; allergy and urticaria (section 3.4.1); sedation (section 4.1.1)

Cautions see Promethazine Hydrochloride, section 3.4.1

Contra-indications see notes in section 3.4.1

Hepatic impairment see notes in section 3.4.1

Renal impairment see Promethazine Hydrochloride, section 3.4.1

Pregnancy see notes in section 3.4.1

Breast-feeding see notes in section 3.4.1

Side-effects see Promethazine Hydrochloride, section 3.4.1

Dose

- By mouth, 20–25 mg at bedtime on night before travel, repeat following morning if necessary; CHILD 2–5 years 5 mg at night, and following morning if necessary, 5–10 years 10 mg at night, and following morning if necessary

Preparations

Section 3.4.1

PROMETHAZINE TEOCLATE

Indications nausea, vertigo, labyrinthine disorders, motion sickness (acts longer than the hydrochloride)

Cautions section 3.4.1; severe coronary artery disease; asthma, bronchitis, bronchiectasis; Reye's syndrome

Contra-indications section 3.4.1

Hepatic impairment section 3.4.1

Renal impairment use with caution

Pregnancy section 3.4.1

Breast-feeding section 3.4.1

Side-effects section 3.4.1

Dose

- 25–75 mg, max. 100 mg, daily; CHILD 5–10 years, 12.5–37.5 mg daily
- Motion sickness prevention, ADULT and CHILD over 10 years, 25 mg at bedtime on night before travel *or* 25 mg 1–2 hours before travel; CHILD 5–10 years, 12.5 mg at bedtime on night before travel *or* 12.5 mg 1–2 hours before travel
- Motion sickness treatment, ADULT and CHILD over 10 years, 25 mg at onset, then 25 mg at bedtime for 2 days; CHILD 5–10 years, 12.5 mg at onset, then 12.5 mg at bedtime for 2 days
- Severe vomiting during pregnancy [unlicensed], 25 mg at bedtime, increased if necessary to max. 100 mg daily (but see also Vomiting During Pregnancy, p. 250)

Avomine® (Manx)

Tablets, scored, promethazine teoclate 25 mg, net price 10-tab pack = £1.13; 28-tab pack = £3.13. Label: 2

Phenothiazines and related drugs

CHLORPROMAZINE HYDROCHLORIDE

Indications nausea and vomiting of terminal illness (where other drugs have failed or are not available); other indications (section 4.2.1)

Cautions see Chlorpromazine Hydrochloride, section 4.2.1

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Chlorpromazine Hydrochloride, section 4.2.1

Dose

- By mouth, 10–25 mg every 4–6 hours; CHILD 500 micrograms/kg every 4–6 hours (1–5 years max. 40 mg daily, 6–12 years max. 75 mg daily)
- By deep intramuscular injection initially 25 mg then 25–50 mg every 3–4 hours until vomiting stops; CHILD 500 micrograms/kg every 6–8 hours (1–5 years max. 40 mg daily, 6–12 years max. 75 mg daily)
- By rectum in suppositories, chlorpromazine 100 mg every 6–8 hours [unlicensed]

Preparations

Section 4.2.1

DROPERIDOL

Indications prevention and treatment of postoperative nausea and vomiting

Cautions section 4.2.1; also chronic obstructive pulmonary disease or respiratory failure; electrolyte disturbances; history of alcohol abuse; continuous pulse oximetry required if risk of ventricular arrhythmia—continue for 30 minutes following administration; **interactions**: Appendix 1 (droperidol)

Contra-indications section 4.2.1; QT-interval prolongation (avoid concomitant administration of drugs

that prolong QT interval); hypokalaemia; hypomagnesaemia; bradycardia

Hepatic impairment in postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required; for nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose

Renal impairment in postoperative nausea and vomiting, max. 625 micrograms repeated every 6 hours as required; for nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia, reduce dose

Pregnancy section 4.2.1

Breast-feeding limited information available—avoid repeated administration

Side-effects section 4.2.1; also anxiety, cardiac arrest, hallucinations, and inappropriate antidiuretic hormone secretion

Dose

- Prevention and treatment of postoperative nausea and vomiting, ADULT over 18 years, by intravenous injection, 0.625–1.25 mg (ELDERLY 625 micrograms) 30 minutes before end of surgery, repeated every 6 hours as required; CHILD over 2 years (second-line use only) 20–50 micrograms/kg (max. 1.25 mg)
- Prevention of nausea and vomiting caused by opioid analgesics in postoperative patient-controlled analgesia (PCA), ADULT over 18 years, by intravenous injection, 15–50 micrograms of droperidol for every 1 mg of morphine in PCA (max. 5 mg droperidol daily); ELDERLY reduce dose

Xomolix® (ProStrakan) ▼ PoM

Injection, droperidol 2.5 mg/mL, net price 1–mL amp = £3.94

PERPHENAZINE

Indications severe nausea, vomiting (see notes above); other indications (section 4.2.1)

Cautions see notes in section 4.2.1

Contra-indications see Perphenazine, section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Perphenazine, section 4.2.1

Dose

- 4 mg 3 times daily, adjusted according to response; max. 24 mg daily (chemotherapy-induced); ELDERLY quarter to half adult dose; CHILD under 14 years not recommended

Preparations

Section 4.2.1

PROCHLORPERAZINE

Indications severe nausea, vomiting, vertigo, labyrinthine disorders (see notes above); other indications section 4.2.1

Cautions see Prochlorperazine, section 4.2.1; oral route only for children (avoid if under 10 kg); elderly (see notes above)

Contra-indications see Prochlorperazine, section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Prochlorperazine, section 4.2.1

Dose

Note Doses are expressed as prochlorperazine maleate or mesilate; 1 mg prochlorperazine maleate ≡ 1 mg prochlorperazine mesilate

- By mouth, nausea and vomiting, acute attack, 20 mg initially then 10 mg after 2 hours; prevention 5–10 mg 2–3 times daily; CHILD (over 10 kg only) 250 micrograms/kg 2–3 times daily

  Labyrinthine disorders, 5 mg 3 times daily, gradually increased if necessary to 30 mg daily in divided doses, then reduced after several weeks to 5–10 mg daily; CHILD not recommended
- By deep intramuscular injection, nausea and vomiting, 12.5 mg when required followed if necessary after 6 hours by an oral dose, as above; CHILD and ADOLESCENT under 18 years, see *BNF for Children*

Prochlorperazine (Non-proprietary) PoM

Tablets, prochlorperazine maleate 5 mg, net price 28-tab pack = £1.25, 84-tab pack = £2.28. Label: 2

Injection, prochlorperazine mesilate 12.5 mg/mL, net price 1-mL amp = 52p

Stemetil® (Sanofi-Aventis) PoM

Tablets, prochlorperazine maleate 5 mg (off-white), net price 28-tab pack = £1.98, 84-tab pack = £5.94. Label: 2

Syrup, straw-coloured, prochlorperazine mesilate 5 mg/5 mL, net price 100-mL pack = £3.34. Label: 2

Injection, prochlorperazine mesilate 12.5 mg/mL, net price 1-mL amp = 52p

Buccal preparation

[1] **Buccastem®** (Alliance) PoM

Tablets (buccal), pale yellow, prochlorperazine maleate 3 mg, net price 5 × 10-tab pack = £5.89. Label: 2, counselling, administration, see under Dose below

Dose ADULT and CHILD over 12 years, 1–2 tablets twice daily; tablets are placed high between upper lip and gum and left to dissolve

1. Prochlorperazine maleate can be sold to the public for adults over 18 years (provided packs do not contain more than 24 mg) for the treatment of nausea and vomiting in previously diagnosed migraine only (max. daily dose 12 mg)

TRIFLUOPERAZINE

Indications severe nausea and vomiting (see notes above); other indications (section 4.2.1)

Cautions see notes in section 4.2.1

Contra-indications see notes in section 4.2.1

Hepatic impairment see notes in section 4.2.1

Renal impairment see notes in section 4.2.1

Pregnancy see notes in section 4.2.1

Breast-feeding see notes in section 4.2.1

Side-effects see Trifluoperazine, section 4.2.1

Dose

- 2–4 mg daily in divided doses; max. 6 mg daily; CHILD 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily

Preparations

Section 4.2.1

Domperidone and metoclopramide

DOMPERIDONE

Indications nausea and vomiting, dyspepsia, gastro-oesophageal reflux

Cautions children; **interactions:** Appendix 1 (domperidone)

Contra-indications prolactinoma; if increased gastro-intestinal motility harmful

Hepatic impairment avoid

Renal impairment reduce dose

Pregnancy use only if potential benefit outweighs risk

Breast-feeding amount too small to be harmful

Side-effects *rarely* gastro-intestinal disturbances (including cramps) and hyperprolactinaemia; *very rarely* ventricular arrhythmias, agitation, drowsiness, nervousness, seizures, extrapyramidal effects, headache, and rashes; also reported QT-interval prolongation

Dose

- By mouth, ADULT and CHILD body-weight over 35 kg, 10–20 mg 3–4 times daily; max. 80 mg daily; CHILD body-weight up to 35 kg (nausea and vomiting only), 250–500 micrograms/kg 3–4 times daily; max. 2.4 mg/kg daily
- By rectum, ADULT and CHILD body-weight over 35 kg, 60 mg twice daily; CHILD 15–35 kg (nausea and vomiting only), 30 mg twice daily; CHILD body-weight under 15 kg, not recommended

[1] **Domperidone** (Non-proprietary) PoM

Tablets, 10 mg (as maleate), net price 30-tab pack = £1.12; 100-tab pack = £1.90

Suspension, domperidone 5 mg/5 mL, net price 200-mL pack = £12.00

1. Domperidone can be sold to the public for adults over 16 years (provided packs do not contain more than 200 mg) for the relief of postprandial symptoms of excessive fullness, nausea, epigastric bloating and belching occasionally accompanied by epigastric discomfort and heartburn, and for the relief of nausea and vomiting of less than 48 hours' duration (max. single dose 10 mg, max. daily dose 40 mg)

Motilium® (Sanofi-Aventis) PoM

Tablets, f/c, domperidone 10 mg (as maleate), net price 30-tab pack = £2.71; 100-tab pack = £9.04

Suppositories domperidone 30 mg, net price 10 = £3.06

METOCLOPRAMIDE HYDROCHLORIDE

Indications adults, nausea and vomiting, particularly in gastro-intestinal disorders (section 1.2) and treatment with cytotoxics or radiotherapy; migraine (section 4.7.4.1)

Patients under 20 years Use restricted to severe intractable vomiting of known cause, vomiting of radiotherapy and cytotoxics, aid to gastro-intestinal intubation, premedication; dose should be determined on the basis of body-weight

Cautions elderly, young adults (15–19 years old), and children; atopic allergy (including asthma); may mask underlying disorders such as cerebral irritation; acute porphyria (section 9.8.2); epilepsy; **interactions:** Appendix 1 (metoclopramide)

Contra-indications gastro-intestinal obstruction, perforation or haemorrhage; 3–4 days after gastro-intestinal surgery; phaeochromocytoma

Hepatic impairment reduce dose

Renal impairment avoid or use small dose in severe impairment; increased risk of extrapyramidal reactions

Pregnancy not known to be harmful

Breast-feeding small amount present in milk; avoid

Side-effects extrapyramidal effects (especially in children and young adults (15–19 years old)—see p. 249), hyperprolactinaemia, occasionally tardive dyskinesia on prolonged administration; also reported, anxiety, confusion, drowsiness, restlessness, diarrhoea, depression, neuroleptic malignant syndrome, rashes, pruritus, oedema; cardiac conduction abnormalities reported following intravenous administration; *rarely* methaemoglobinaemia (more severe in G6PD deficiency)

Dose

- By mouth *or* by intramuscular injection *or* by intravenous injection over 1–2 minutes, nausea and vomiting, 10 mg (5 mg in young adults 15–19 years, body-weight under 60 kg) 3 times daily; CHILD up to 1 year (body-weight up to 10 kg) 100 micrograms/kg (max. 1 mg) twice daily, 1–3 years (body-weight 10–14 kg) 1 mg 2–3 times daily, 3–5 years (body-weight 15–19 kg) 2 mg 2–3 times daily, 5–9 years (body-weight 20–29 kg) 2.5 mg 3 times daily, 9–15 years (body-weight 30 kg and over) 5 mg 3 times daily
  Note Daily dose of metoclopramide should not normally exceed 500 micrograms/kg, particularly for children and young adults (restricted use, see above)
  For diagnostic procedures, as a single dose 5–10 minutes before examination, 10–20 mg (10 mg in young adults 15–19 years); CHILD under 3 years 1 mg, 3–5 years 2 mg, 5–9 years 2.5 mg, 9–14 years 5 mg

Metoclopramide (Non-proprietary) PoM

Tablets, metoclopramide hydrochloride 10 mg, net price 28-tab pack = £1.01

Oral solution, metoclopramide hydrochloride 5 mg/5 mL, net price 150-mL pack = £6.51. Counselling, use of pipette

Injection, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 26p

Maxolon® (Amdipharm) PoM

Tablets, scored, metoclopramide hydrochloride 10 mg, net price 84-tab pack = £5.24

Injection, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 27p

High-dose (with cytotoxic chemotherapy only)

Maxolon High Dose® (Amdipharm) PoM

Injection, metoclopramide hydrochloride 5 mg/mL, net price 20-mL amp = £2.67.

For dilution and use as an intravenous infusion in nausea and vomiting associated with cytotoxic chemotherapy only

Dose by continuous intravenous infusion (preferred method), initially (before starting chemotherapy), 2–4 mg/kg over 15–20 minutes, then 3–5 mg/kg over 8–12 hours; max. in 24 hours, 10 mg/kg

By intermittent intravenous infusion, initially (before starting chemotherapy), up to 2 mg/kg over at least 15 minutes then up to 2 mg/kg over at least 15 minutes every 2 hours; max. in 24 hours, 10 mg/kg

Modified release

Maxolon SR® (Amdipharm) PoM

Capsules, m/r, clear, enclosing white granules, metoclopramide hydrochloride 15 mg, net price 56-cap pack = £7.01. Label: 25

Dose patients over 20 years, 1 capsule twice daily

Compound preparations (for migraine)

Section 4.7.4.1

5HT$_3$-receptor antagonists

GRANISETRON

Indications see under Dose

Cautions QT-interval prolongation (avoid concomitant use of drugs that prolong QT interval)

Pregnancy use only when compelling reasons—no information available

Breast-feeding avoid—no information available

Side-effects constipation, nausea, diarrhoea, vomiting, abdominal pain; headache, drowsiness, asthenia; fever; *rarely* hepatic dysfunction, chest pain, arrhythmia; *very rarely* anorexia, dizziness, insomnia, agitation, movement disorders, and rash

Dose

- Nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy, by mouth, 1–2 mg within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses during treatment; when intravenous infusion also used, max. combined total 9 mg in 24 hours; CHILD 20 micrograms/kg (max. 1 mg) within 1 hour before start of treatment, then 20 micrograms/kg (max. 1 mg) twice daily for up to 5 days during treatment

  By intravenous injection (diluted in 15 mL sodium chloride 0.9% and given over not less than 30 seconds) *or* by intravenous infusion (over 5 minutes), prevention, 3 mg before start of cytotoxic therapy (up to 2 additional 3-mg doses may be given within 24 hours); treatment, as for prevention (the two additional doses must not be given less than 10 minutes apart); max. 9 mg in 24 hours; CHILD, by intravenous infusion, (over 5 minutes), prevention, 40 micrograms/kg (max. 3 mg) before start of cytotoxic therapy; treatment, as for prevention—one additional dose of 40 micrograms/kg (max. 3 mg) may be given within 24 hours (not less than 10 minutes after initial dose)
- Postoperative nausea and vomiting, by intravenous injection (diluted to 5 mL and given over 30 seconds), prevention, 1 mg before induction of anaesthesia; treatment, 1 mg, given as for prevention; max. 2 mg in one day; CHILD not recommended

Granisetron (Non-proprietary) PoM

Tablets, granisetron (as hydrochloride) 1 mg, net price 10-tab pack = £51.20

Injection, granisetron (as hydrochloride) 1 mg/mL, for dilution before use, net price 1-mL amp = £1.20, 3-mL amp = £4.80

Kytril® (Roche) PoM

Tablets, f/c, granisetron (as hydrochloride) 1 mg, net price 10-tab pack = £52.39; 2 mg, 5-tab pack = £52.39

Injection, granisetron (as hydrochloride) 1 mg/mL, for dilution before use, net price 1-mL amp = £6.88, 3-mL amp = £20.63

ONDANSETRON

Indications see under Dose

Cautions QT-interval prolongation (avoid concomitant use of drugs that prolong QT interval); subacute intestinal obstruction; adenotonsillar surgery; **interactions:** Appendix 1 (ondansetron)

Hepatic impairment max. 8 mg daily in moderate or severe impairment

Pregnancy no information available; avoid unless potential benefit outweighs risk

Breast-feeding present in milk in *animal* studies—avoid

Side-effects constipation; headache; flushing; injection site-reactions; *less commonly* hiccups, hypotension, bradycardia, chest pain, arrhythmias, movement disorders, seizures; *on intravenous administration*, *rarely* dizziness, transient visual disturbances (*very rarely* transient blindness); suppositories may cause rectal irritation

Dose

- Moderately emetogenic chemotherapy or radiotherapy, ADULT over 18 years, by mouth, 8 mg 1–2 hours before treatment *or* by rectum, 16 mg 1–2 hours before treatment *or* by intramuscular injection *or* slow intravenous injection, 8 mg immediately before treatment

  then by mouth, 8 mg every 12 hours for up to 5 days *or* by rectum, 16 mg daily for up to 5 days
- Severely emetogenic chemotherapy, ADULT over 18 years, by intramuscular injection *or* slow intravenous injection, 8 mg immediately before treatment, where necessary followed by 2 further doses of 8 mg at intervals of 2–4 hours (*or* followed by 1 mg/hour by continuous intravenous infusion for up to 24 hours)

  then by mouth, 8 mg every 12 hours for up to 5 days *or* by rectum, 16 mg daily for up to 5 days;

  alternatively, by intravenous infusion over at least 15 minutes, 32 mg immediately before treatment *or* by rectum, 16 mg 1–2 hours before treatment

  then by mouth, 8 mg every 12 hours for up to 5 days *or* by rectum, 16 mg daily for up to 5 days
- Chemotherapy-induced nausea and vomiting, CHILD 6 months–18 years, by intravenous infusion over at least 15 minutes, 5 mg/m^2 (max. 8 mg) immediately before chemotherapy, then for body-surface area less than 0.6 m^2 2 mg by mouth every 12 hours for up to 5 days; for body-surface area 0.6 m^2 or greater 4 mg by mouth every 12 hours for up to 5 days; max. total daily dose 32 mg

  alternatively, by intravenous infusion over at least 15 minutes, 150 micrograms/kg (max. 8 mg) immediately before chemotherapy repeated at intervals of 4 hours for 2 further doses, then for body-weight 10 kg or less 2 mg by mouth every 12 hours for up to 5 days; for body-weight over 10 kg 4 mg by mouth every 12 hours for up to 5 days; max. total daily dose 32 mg
- Prevention of postoperative nausea and vomiting, by mouth, 16 mg 1 hour before anaesthesia *or* 8 mg 1 hour before anaesthesia followed by 8 mg at intervals of 8 hours for 2 further doses

  alternatively, by intramuscular *or* slow intravenous injection, 4 mg at induction of anaesthesia; CHILD 1 month–18 years, by slow intravenous injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg) before, during, or after induction of anaesthesia
- Treatment of postoperative nausea and vomiting, by intramuscular *or* slow intravenous injection, 4 mg;

CHILD 1 month–18 years, by slow intravenous injection over at least 30 seconds, 100 micrograms/kg (max. 4 mg)

Ondansetron (Non-proprietary) PoM

Tablets, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £66.85; 8 mg, 10-tab pack = £49.92
Brands include *Ondemet®*

Oral solution, ondansetron (as hydrochloride) 4 mg/5 mL, net price 50-mL pack = £38.19
Brands include *Demorem®*

Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £5.39, 4-mL amp = £10.79
Brands include *Ondemet®*

Zofran® (GSK) PoM

Tablets, yellow, f/c, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £107.91; 8 mg, 10-tab pack = £71.94

Oral lyophilisates (*Zofran Melt®*), ondansetron 4 mg, net price 10-tab pack = £35.97; 8 mg, 10-tab pack = £71.94. Counselling, administration
Excipients include aspartame (section 9.4.1)
Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed

Oral solution, sugar-free, strawberry-flavoured, ondansetron (as hydrochloride) 4 mg/5 mL, net price 50-mL pack = £35.97

Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £5.99; 4-mL amp = £11.99

Suppositories, ondansetron 16 mg, net price 1 = £14.39

PALONOSETRON

Indications prevention of nausea and vomiting induced by moderately and severely emetogenic chemotherapy

Cautions history of constipation; intestinal obstruction; concomitant use of drugs that prolong QT interval
Driving Dizziness or drowsiness may affect performance of skilled tasks (e.g. driving)

Pregnancy avoid—no information available

Breast-feeding avoid—no information available

Side-effects diarrhoea, constipation; headache, dizziness; *less commonly* dyspepsia, abdominal pain, dry mouth, flatulence, changes in blood pressure, tachycardia, bradycardia, arrhythmia, myocardial ischaemia, hiccups, drowsiness, asthenia, insomnia, anxiety, euphoria, paraesthesia, peripheral neuropathy, anorexia, motion sickness, influenza-like symptoms, urinary retention, glycosuria, hyperglycaemia, electrolyte disturbance, arthralgia, eye irritation, amblyopia, tinnitus, rash, pruritus

Dose

- By intravenous injection (over 30 seconds), 250 micrograms as a single dose 30 minutes before treatment; CHILD and ADOLESCENT under 18 years not recommended

Aloxi® (IS Pharmaceuticals) ▼ PoM

Injection, palonosetron (as hydrochloride) 50 micrograms/mL, net price 5-mL amp = £55.89

Neurokinin receptor antagonists

APREPITANT

Indications adjunct to dexamethasone and a $5HT_3$-receptor antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

Cautions **interactions:** Appendix 1 (aprepitant)

Hepatic impairment caution in moderate to severe impairment

Pregnancy avoid unless potential benefit outweighs risk—no information available

Breast-feeding avoid—present in milk in *animal* studies

Side-effects hiccups, dyspepsia, diarrhoea, constipation, anorexia; asthenia, headache, dizziness; *less commonly* weight changes, dry mouth, colitis, flatulence, stomatitis, abdominal pain, duodenal ulcer, taste disturbance, oedema, bradycardia, palpitations, cough, euphoria, anxiety, confusion, drowsiness, thirst, abnormal dreams, chills, hyperglycaemia, polyuria, anaemia, dysuria, haematuria, hyponatraemia, neutropenia, myalgia, conjunctivitis, pharyngitis, sneezing, tinnitus, sweating, pruritus, rash, acne, photosensitivity, and flushing; dyspnoea, insomnia, visual disturbances, dysarthria, urticaria, and Stevens-Johnson syndrome also reported

Dose

- ADULT over 18 years 125 mg 1 hour before chemotherapy, then 80 mg daily as a single dose for the next 2 days; consult product literature for dose of concomitant corticosteroid and $5HT_3$ antagonist

Emend® (MSD) PoM

Capsules, aprepitant 80 mg (white), net price 2-cap pack = £31.61; 125 mg (white/pink), 5-cap pack = £79.03; 3-day pack of one 125-mg capsule and two 80-mg capsules = £47.42

FOSAPREPITANT

Note Fosaprepitant is a prodrug of aprepitant

Indications adjunct to dexamethasone and a $5HT_3$ antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

Cautions **interactions:** Appendix 1 (aprepitant)

Hepatic impairment see Aprepitant

Pregnancy see Aprepitant

Breast-feeding see Aprepitant

Side-effects see Aprepitant

Dose

- By intravenous infusion, over 15 minutes, ADULT over 18 years, 115 mg 30 minutes before chemotherapy on day 1 of cycle (followed by aprepitant on days 2 and 3 of cycle); consult product literature for dose of concomitant corticosteroid and $5HT_3$ antagonist

Ivemend® (MSD) ▼ PoM

Injection, powder for reconstitution, fosaprepitant (as dimeglumine), net price 115-mg vial = £20.55
The *Scottish Medicines Consortium* (p. 4) has advised (September 2008) that fosaprepitant (*Ivemend®*) is accepted for restricted use for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy

Cannabinoid

NABILONE

Indications nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (under close observation, preferably in hospital setting)

Cautions history of psychiatric disorder; elderly; hypertension; heart disease; adverse effects on mental state can persist for 48–72 hours after stopping; **interactions:** Appendix 1 (nabilone)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Hepatic impairment avoid in severe impairment

Pregnancy avoid unless essential

Breast-feeding avoid—no information available

Side-effects drowsiness, vertigo, euphoria, dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache and nausea; also confusion, disorientation, hallucinations, psychosis, depression, decreased coordination, tremors, tachycardia, decreased appetite, and abdominal pain

Behavioural effects Patients should be made aware of possible changes of mood and other adverse behavioural effects

Dose

- Initially 1 mg twice daily, increased if necessary to 2 mg twice daily, throughout each cycle of cytotoxic therapy and, if necessary, for 48 hours after the last dose of each cycle; max. 6 mg daily given in 3 divided doses. The first dose should be taken the night before initiation of cytotoxic treatment and the second dose 1–3 hours before the first dose of cytotoxic drug; ADOLESCENT and CHILD under 18 years consult local treatment protocol [unlicensed use]

Nabilone (Meda) CD

Capsules, blue/white, nabilone 1 mg, net price 20-cap pack = £125.84. Label: 2, counselling, behavioural effects

Hyoscine

HYOSCINE HYDROBROMIDE
(Scopolamine Hydrobromide)

Indications motion sickness; hypersalivation associated with clozapine therapy; premedication (section 15.1.3); excessive respiratory secretions (see Prescribing in Palliative Care, p. 21)

Cautions section 1.2; also epilepsy

Contra-indications section 1.2

Hepatic impairment section 15.1.3

Renal impairment section 15.1.3

Pregnancy section 15.1.3

Breast-feeding section 15.1.3

Side-effects section 1.2

Dose

- Motion sickness, by mouth, ADULT and CHILD over 10 years, 150–300 micrograms up to 30 minutes before start of journey repeated every 6 hours if required; max. 900 micrograms daily; CHILD 3–4 years 75 micrograms up to 30 minutes before start of journey repeated after 6 hours if required, max. 150 micrograms daily; 4–10 years 75–150 micrograms up to 30 minutes before start of journey repeated every 6 hours if required; max. 450 micrograms daily
- Hypersalivation associated with clozapine therapy [unlicensed indication], by mouth, 300 micrograms up to 3 times daily; max. 900 micrograms daily; CHILD under 18 years, see *BNF for Children*

Joy Rides® (GSK Consumer Healthcare)

Tablets, chewable, raspberry-flavoured, hyoscine hydrobromide 150 micrograms, net price 12-tab pack = £1.49. Label: 2, 24

Kwells® (Bayer Consumer Care)

Tablets, chewable, scored, hyoscine hydrobromide 150 micrograms (*Kwells® Kids*) (white), net price 12-tab pack = £1.67; 300 micrograms (pink), 12-tab pack = £1.67. Label: 2

Patches

Scopoderm TTS® (Novartis Consumer Health) PoM

Patch, self-adhesive, pink, releasing hyoscine approx. 1 mg/72 hours when in contact with skin, net price 2 = £4.30. Label: 19, counselling, see below

Dose motion sickness prevention, apply 1 patch to hairless area of skin behind ear 5–6 hours before journey; replace if necessary after 72 hours, siting replacement patch behind other ear; CHILD under 10 years not recommended

Counselling Explain accompanying instructions to patient and in particular emphasise advice to wash hands after handling and to wash application site after removing, and to use one patch at a time

Parenteral preparations

Section 15.1.3

Other drugs for Ménière's disease

Betahistine has been promoted as a specific treatment for Ménière's disease.

BETAHISTINE DIHYDROCHLORIDE

Indications vertigo, tinnitus and hearing loss associated with Ménière's disease

Cautions asthma, history of peptic ulcer; **interactions:** Appendix 1 (betahistine)

Contra-indications phaeochromocytoma

Pregnancy avoid unless clearly necessary—no information available

Breast-feeding use only if potential benefit outweighs risk—no information available

Side-effects gastro-intestinal disturbances; headache, rashes and pruritus reported

Dose

- Initially 16 mg 3 times daily, preferably with food; maintenance 24–48 mg daily; CHILD not recommended

Betahistine Dihydrochloride (Non-proprietary) PoM

Tablets, betahistine dihydrochloride 8 mg, net price 84-tab pack = £2.15 120-tab pack = £1.76; 16 mg, 84-tab pack = £2.24. Label: 21

Serc® (Solvay) PoM

Tablets, betahistine dihydrochloride 8 mg (*Serc®-8*), net price 120-tab pack = £9.04; 16 mg (*Serc®-16*) (scored), 84-tab pack = £12.65. Label: 21

4.7 Analgesics

4.7.1 Non-opioid analgesics and compound analgesic preparations
4.7.2 Opioid analgesics
4.7.3 Neuropathic pain
4.7.4 Antimigraine drugs

The non-opioid drugs (section 4.7.1), paracetamol and aspirin (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics (section 4.7.2) are more suitable for moderate to severe pain, particularly of visceral origin.

Pain in palliative care For advice on pain relief in palliative care, see p. 20.

Pain in sickle-cell disease The pain of mild sickle-cell crises is managed with paracetamol, a NSAID (section 10.1.1), codeine, or dihydrocodeine. Severe crises may require the use of morphine or diamorphine; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used. Pethidine should be avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine necessitates frequent injections.

Dental and orofacial pain Analgesics should be used judiciously in dental care as a **temporary** measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpitis, apical infection, localised osteitis (dry socket) or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures, and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpitis, intra-osseous infection or abscess, reliance on analgesics alone is usually inappropriate.

Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by **benzydamine** mouthwash or spray (p. 694) until the cause of the mucosal disorder has been dealt with. However, where a patient is febrile, the antipyretic action of **paracetamol** (p. 259) or **ibuprofen** (p. 636) is often helpful.

The *choice* of an analgesic for dental purposes should be based on its suitability for the patient. Most dental pain is relieved effectively by non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs that are used for dental pain include **ibuprofen**, **diclofenac**, and **aspirin**; for further details see section 4.7.1 and section 10.1.1. **Paracetamol** has analgesic and antipyretic effects but no anti-inflammatory effect.

Opioid analgesics (section 4.7.2) such as **dihydrocodeine** act on the central nervous system and are traditionally used for *moderate to severe pain*. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant. Paracetamol, ibuprofen, or aspirin are adequate for most cases of dental pain and an opioid is rarely required.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen or aspirin is usually continued for about 24 to 72 hours.

Temporomandibular dysfunction can be related to anxiety in some patients who may clench or grind their teeth (bruxism) during the day or night. The muscle spasm (which appears to be the main source of pain) may be treated empirically with an overlay appliance which provides a free sliding occlusion and may also interfere with grinding. In addition, **diazepam** (section 4.1.2), which has muscle relaxant as well as anxiolytic properties, may be helpful but it should only be prescribed on a short-term basis during the acute phase. Analgesics such as aspirin (section 4.7.1) or ibuprofen (section 10.1.1) may also be required.

For the management of neuropathic pain, persistent idiopathic facial pain, and trigeminal neuralgia, see section 4.7.3.

Dysmenorrhoea Use of an oral contraceptive prevents the pain of dysmenorrhoea which is generally associated with ovulatory cycles. If treatment is necessary paracetamol or a NSAID (section 10.1.1) will generally provide adequate relief of pain. The vomiting and severe pain associated with dysmenorrhoea in women with endometriosis may call for an antiemetic (in addition to an analgesic). Antispasmodics (such as alverine citrate, section 1.2) have been advocated for dysmenorrhoea but the antispasmodic action does not generally provide significant relief.

4.7.1 Non-opioid analgesics and compound analgesic preparations

Aspirin is indicated for headache, transient musculoskeletal pain, dysmenorrhoea and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAID which may be better tolerated and more convenient for the patient. Aspirin is used increasingly for its antiplatelet properties (section 2.9). Aspirin tablets or dispersible aspirin tablets are adequate for most purposes as they act rapidly.

Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain).

Aspirin interacts significantly with a number of other drugs and its interaction with warfarin is a **special hazard**, see **interactions**: Appendix 1 (aspirin).

Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly. **Over-**

dosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not apparent for 4 to 6 days (see Emergency Treatment of Poisoning, p. 34).

Nefopam may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics. It causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.

Non-steroidal anti-inflammatory analgesics (NSAIDs, section 10.1.1) are particularly useful for the treatment of patients with chronic disease accompanied by pain and inflammation. Some of them are also used in the short-term treatment of mild to moderate pain including transient musculoskeletal pain but paracetamol is now often preferred, particularly in the elderly (see also p. 25). They are also suitable for the relief of pain in *dysmenorrhoea* and to treat pain caused by *secondary bone tumours*, many of which produce lysis of bone and release prostaglandins (see Prescribing in Palliative Care, p. 20). Selective inhibitors of cyclo-oxygenase-2 may be used in preference to non-selective NSAIDs for patients at high risk of developing serious gastro-intestinal side-effects. NSAIDs including ketorolac are also used for peri-operative analgesia (section 15.1.4.2).

A non-opioid analgesic administered by intrathecal infusion (**ziconotide** (*Prialt®*), available from Eisai) is licensed for the treatment of chronic severe pain; ziconotide can be used by a hospital specialist as an adjunct to opioid analgesics.

Dental and orofacial pain Most dental pain is relieved effectively by NSAIDs (section 10.1.1). **Aspirin** (below) is effective against mild to moderate dental pain; dispersible tablets provide a rapidly absorbed form of aspirin suitable for most purposes.

The analgesic effect of **paracetamol** in mild to moderate dental pain is probably less than that of aspirin, but it does not affect bleeding time or interact significantly with warfarin. Moreover, it is less irritant to the stomach. Paracetamol is a suitable analgesic for children; sugar-free versions can be requested by specifying 'sugar-free' on the prescription.

For further information on the management of dental and orofacial pain, see p. 257.

Compound analgesic preparations

Compound analgesic preparations that contain a simple analgesic (such as aspirin or paracetamol) with an opioid component reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol or aspirin with a *low dose* of an opioid analgesic (e.g. 8 mg of codeine phosphate per compound tablet) are commonly used, but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of **overdosage** (see p. 36) yet may not provide significant additional relief of pain.

A *full dose* of the opioid component (e.g. 60 mg codeine phosphate) in compound analgesic preparations effectively augments the analgesic activity but is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration). For details of the **side-effects** of opioid analgesics, see p. 262 (**important:** the elderly are particularly susceptible to opioid side-effects and should receive lower doses).

In general, when assessing pain, it is necessary to weigh up carefully whether there is a need for a non-opioid and an opioid analgesic to be taken simultaneously.

For information on the use of combination analgesic preparations in dental and orofacial pain, see p. 257.

Caffeine is a weak stimulant that is often included, in small doses, in analgesic preparations. It is claimed that the addition of caffeine may enhance the analgesic effect, but the alerting effect, mild habit-forming effect and possible provocation of headache may not always be desirable. Moreover, in excessive dosage or on withdrawal caffeine may itself induce headache.

Co-proxamol tablets (dextropropoxyphene in combination with paracetamol) are no longer licensed because of safety concerns, particularly toxicity in overdose. Co-proxamol tablets [unlicensed] may still be prescribed for patients who find it difficult to change, because alternatives are not effective or suitable.

ASPIRIN

(Acetylsalicylic Acid)

Indications mild to moderate pain, pyrexia; antiplatelet (section 2.9)

Cautions asthma, allergic disease, dehydration; preferably avoid during fever or viral infection in children (risk of Reye's syndrome, see below); elderly; G6PD-deficiency (section 9.1.5); concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (aspirin)

Contra-indications children under 16 years (Reye's syndrome, see below); previous or active peptic ulceration, haemophilia; not for treatment of gout

Hypersensitivity Aspirin and other NSAIDs are **contra-indicated** in patients with a history of hypersensitivity to aspirin or any other NSAID—*which includes those* in whom attacks of *asthma, angioedema, urticaria or rhinitis* have been precipitated by aspirin or any other NSAID

Reye's syndrome Owing to an association with Reye's syndrome, aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, e.g. for Kawasaki syndrome

Hepatic impairment avoid in severe impairment—increased risk of gastro-intestinal bleeding

Renal impairment use with caution; avoid in severe impairment; sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding

Pregnancy impaired platelet function with risk of haemorrhage, and delayed onset and increased duration of labour with increased blood loss, can occur if used during delivery; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); with high doses, closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of newborn; kernicterus in jaundiced neonates

Breast-feeding avoid—possible risk of Reye's syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low

Side-effects generally mild and infrequent but high incidence of gastro-intestinal irritation with slight asymptomatic blood loss, increased bleeding time,

bronchospasm and skin reactions in hypersensitive patients. Prolonged administration, see section 10.1.1.
Overdosage: see Emergency Treatment of Poisoning, p. 34

Dose

- By mouth, 300–900 mg every 4–6 hours when necessary; max. 4 g daily; CHILD under 16 years not recommended (see Reye's Syndrome, above)
- By rectum, 450–900 mg every 4 hours (max. 3.6 g daily); CHILD under 16 years not recommended (see Reye's Syndrome, above)

Aspirin (Non-proprietary)

Tablets PoM[1], aspirin 300 mg, net price 32-tab pack = 31p. Label: 21, 32

Tablets PoM[1], e/c, aspirin 300 mg, net price 100-tab pack = £5.29; 75 mg, see section 2.9. Label: 5, 25, 32

Dispersible tablets PoM[1], aspirin 300 mg, net price 100-tab pack = £2.88; 75 mg, see section 2.9. Label: 13, 21, 32

Note BP directs that when no strength is stated the 300-mg strength should be dispensed, and that when soluble aspirin tablets are prescribed, dispersible aspirin tablets shall be dispensed.

Dental prescribing on NHS Aspirin Dispersible Tablets 300 mg may be prescribed

Suppositories PoM, aspirin 150 mg, net price 10 = £13.13; 300 mg, 12 = £59.28. Label: 32

Brands include *Resprin®*

Caprin® (Pinewood)

Tablets PoM[1], e/c, f/c, pink, aspirin 300 mg, net price 100-tab pack = £4.89; 75 mg, see section 2.9. Label: 5, 25, 32

Nu-Seals® Aspirin (Alliance)

Tablets PoM[1], e/c, aspirin 300 mg, net price 100-tab pack = £4.15; 75 mg, see section 2.9. Label: 5, 25, 32

With codeine phosphate 8 mg

[1]**Co-codaprin** (Non-proprietary) PoM

Dispersible tablets, co-codaprin 8/400 (codeine phosphate 8 mg, aspirin 400 mg), net price 100-tab pack = £35.22. Label: 13, 21, 32

Dose 1–2 tablets in water every 4–6 hours; max. 8 tablets daily

When co-codaprin tablets or dispersible tablets are prescribed and no strength is stated, tablets or dispersible tablets, respectively, containing codeine phosphate 8 mg and aspirin 400 mg should be dispensed

With metoclopramide

For prescribing information on metoclopramide, see section 4.6

MigraMax® (Cephalon) PoM

Oral powder, aspirin (as lysine acetylsalicylate) 900 mg, metoclopramide hydrochloride 10 mg/sachet, net price 6-sachet pack = £6.60, 20-sachet pack = £21.99. Label: 13, 21, 32

Dose acute migraine, ADULT over 20 years 1 sachet in water at onset of attack, repeated after 2 hours if necessary (max. 3 sachets in 24 hours); YOUNG ADULT (under 20 years) and CHILD not recommended

Important Metoclopramide can cause **severe extrapyramidal effects**, particularly in children and young adults (for further details, see p. 249)

Excipients include aspartame (section 9.4.1)

1. Can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances; for details see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

PARACETAMOL
(Acetaminophen)

Indications mild to moderate pain, pyrexia

Cautions alcohol dependence; max. daily infusion dose 3 g in patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration; **interactions:** Appendix 1 (paracetamol)

Hepatic impairment dose-related toxicity—avoid large doses; see also Cautions

Renal impairment increase *infusion* dose interval to every 6 hours if eGFR less than 30 mL/minute/1.73 m^2; note also sodium content of effervescent tablets (see under relevant preparation entry)

Pregnancy not known to be harmful

Breast-feeding amount too small to be harmful

Side-effects side-effects rare, but rashes, blood disorders (including thrombocytopenia, leucopenia, neutropenia) reported; hypotension, flushing, and tachycardia also reported on infusion; **important:** liver damage (and less frequently renal damage) following **overdosage**, see Emergency Treatment of Poisoning, p. 34

Dose

- By mouth, 0.5–1 g every 4–6 hours to a max. of 4 g daily; CHILD 2 months 60 mg for post-immunisation pyrexia, repeated once after 6 hours if necessary; otherwise under 3 months, see *BNF for Children*; 3 months–1 year 60–120 mg, 1–6 years 120–250 mg, 6–12 years 250–500 mg; these doses may be repeated every 4–6 hours when necessary (max. of 4 doses in 24 hours)
- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily
- By rectum, ADULT and CHILD over 12 years 0.5–1 g every 4–6 hours to a max. of 4 g daily; CHILD under 3 months, see *BNF for Children*, 3 months–1 year 60–125 mg, 1–5 years 125–250 mg, 5–12 years 250–500 mg; these doses may be repeated every 4–6 hours as necessary (max. 4 doses in 24 hours)

Note For full Joint Committee on Vaccination and Immunisation recommendation on post-immunisation pyrexia, see section 14.1

Paracetamol (Non-proprietary)

Tablets (and caplets) PoM[1], paracetamol 500 mg, net price 16-tab pack = 17p, 32–tab pack = £1.00, 100-tab pack = £1.44. Label: 29, 30

Brands include *Panadol®* NHS

Dental prescribing on NHS Paracetamol Tablets may be prescribed

Capsules PoM[1], paracetamol 500 mg, net price 32-cap pack = £1.00, 100-cap pack = £3.13. Label: 29, 30

Brands include *Panadol Capsules®* NHS

Soluble tablets (= Dispersible tablets) PoM[2], paracetamol 500 mg, net price 60-tab pack = £4.39. Label: 13, 29, 30

Brands include *Panadol Soluble®* NHS (contains Na^+ 18.6 mmol/tablet), *Paracetamol Seltzer®* (contains Na^+ 16.9 mmol/tablet)

Dental prescribing on NHS Paracetamol Soluble Tablets 500 mg may be prescribed

2. Can be sold to the public in certain circumstances; for exemptions see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

Paediatric soluble tablets (= Paediatric dispersible tablets), paracetamol 120 mg, net price 16-tab pack = 89p. Label: 13, 30
Brands include *Disprol® Soluble Paracetamol* NHS

Oral suspension 120 mg/5 mL (= Paediatric Mixture), paracetamol 120 mg/5 mL, net price 100 mL = 72p, 150 mL = 84p, 200 mL = £1.05, 500 mL = £1.94. Label: 30
Note BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed; sugar-free versions can be ordered by specifying 'sugar-free' on the prescription
Brands include *Calpol® Paediatric*, *Calpol® Paediatric* sugar-free, *Disprol® Paediatric*, *Medinol® Paediatric* sugar-free, *Panadol®* sugar-free

Oral suspension 250 mg/5 mL (= Mixture), paracetamol 250 mg/5 mL, net price 100 mL = 82p, 200 mL = £1.10, 500 mL = £3.28. Label: 30
Brands include *Calpol® 6 Plus* NHS, *Medinol® Over 6* NHS
Dental prescribing on NHS Paracetamol Oral Suspension may be prescribed

Suppositories, paracetamol 60 mg, net price 10 = £9.96; 125 mg, 10 = £11.50; 250 mg, 10 = £23.00; 500 mg, 10 = £36.80; 1 g, 12 = £60.00. Label: 30
Brands include *Alvedon®*
Note Other strengths available from 'special-order' manufacturers or specialist importing companies, see p. 988

Panadol OA® (GSK) PoM
Tablets, f/c, paracetamol 1 g, net price 100-tab pack = £3.30. Label: 30
Dose ADULT and CHILD over 12 years, 1 tablet up to 4 times daily, not more often than every 4 hours

Perfalgan® (Bristol-Myers Squibb) ▼ PoM
Intravenous infusion, paracetamol 10 mg/mL, net price 50-mL vial = £1.39, 100-mL vial = £1.52

Co-codamol 8/500

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate **8 mg** and paracetamol **500 mg** should be dispensed.

[1]Co-codamol 8/500 (Non-proprietary) PoM
Tablets, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 30-tab pack = £1.25, 32-tab pack = 58p, 100-tab pack = £1.35. Label: 29, 30
Dose 1–2 tablets every 4–6 hours; max. 8 tablets daily; CHILD 6–12 years ½–1 tablet, max. 4 tablets daily

Effervescent *or* dispersible tablets, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 32-tab pack = £1.50, 100-tab pack = £4.32. Label: 13, 29, 30
Brands include *Paracodol®* NHS
Note The Drug Tariff allows tablets of co-codamol labelled 'dispersible' to be dispensed against an order for 'effervescent' and *vice versa*
Dose 1–2 tablets in water every 4–6 hours, max. 8 tablets daily; CHILD 6–12 years ½–1 tablet, max. 4 tablets daily

Capsules, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 10-cap pack = £1.10, 20-cap pack = £1.71. Label: 29, 30
Brands include *Paracodol®* NHS
Dose 1–2 capsules every 4 hours; max. 8 capsules daily

1. Can be sold to the public in certain circumstances; for exemptions see *Medicines, Ethics and Practice*, No. 34, London, Pharmaceutical Press, 2010 (and subsequent editions as available)

Co-codamol 15/500

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate **8 mg** and paracetamol **500 mg** should be dispensed (see preparations above).
See warnings and notes on p. 258 (**important:** special care in elderly—reduce dose)

Codipar® (Goldshield) PoM
Caplets (= tablets), co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg), net price 100-tab pack = £8.25. Label: 2, 29, 30
Dose 1–2 tablets every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Kapake® (Galen) PoM
Tablets, co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg), net price 100-tab pack = £8.25. Label: 2, 29, 30
Dose ADULT over 16 years 2 tablets every 4 hours; max. 8 tablets daily; CHILD 12–16 years 1 tablet every 4 hours; max. 4 tablets daily; CHILD under 12 years not recommended

Co-codamol 30/500

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate **8 mg** and on paracetamol **500 mg** should be dispensed (see preparations above).
See warnings and notes on p. 258 (**important:** special care in elderly—reduce dose)

Co-codamol 30/500 (Non-proprietary) PoM
Tablets (and caplets), co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £3.65. Label: 2, 29, 30
Dose 1–2 tablets every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Capsules, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £5.55. Label: 2, 29, 30
Brands include *Medocodene®*, *Zapain®*
Dose 1–2 capsules every 4 hours; max. 8 capsules daily; CHILD under 12 years not recommended

Effervescent tablets, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £7.67. Label: 2, 13, 29, 30
Brands include *Medocodene® Effervescent* (contains Na^+ 13.6 mmol/tablet)
Dose 1–2 tablets in water every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Kapake® (Galen) PoM
Tablets, scored, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 30-tab pack = £2.26 (hosp. only), 100-tab pack = £7.10. Label: 2, 29, 30
Dose 1–2 tablets every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Capsules, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £7.10. Label: 2, 29, 30
Dose 1–2 capsules every 4 hours; max. 8 capsules daily; CHILD under 12 years not recommended

Solpadol® (Sanofi-Aventis) PoM

Caplets (= tablets), co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £6.74. Label: 2, 29, 30

Dose 2 tablets every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Capsules, grey/purple, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £6.74. Label: 2, 29, 30

Dose 2 capsules every 4 hours; max. 8 capsules daily; CHILD under 12 years not recommended

Effervescent tablets, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 32-tab pack = £2.59, 100-tab pack = £8.09. Label: 2, 13, 29, 30

Electrolytes Na^+ 16.9 mmol/tablet

Dose 2 tablets in water every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Tylex® (UCB Pharma) PoM

Capsules, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £7.70. Label: 2, 29, 30

Dose 1–2 capsules every 4 hours; max. 8 capsules daily; CHILD under 12 years not recommended

Effervescent tablets, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £8.80. Label: 2, 13, 29, 30

Electrolytes Na^+ 14.2 mmol/tablet

Excipients include aspartame 25 mg/tablet (section 9.4.1)

Dose 1–2 tablets in water every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

With methionine (co-methiamol)

A mixture of methionine and paracetamol; methionine has no analgesic activity but may prevent paracetamol-induced liver toxicity if overdose taken

Paradote® (Penn)

Tablets, f/c, co-methiamol 100/500 (DL-methionine 100 mg, paracetamol 500 mg), net price 24-tab pack = £1.05, 96-tab pack = £2.77. Label: 29, 30

Dose 2 tablets every 4 hours; max. 8 tablets daily; CHILD under 12 years not recommended

With dihydrocodeine tartrate 10 mg

See notes on p. 258

When co-dydramol tablets are prescribed and no strength is stated, tablets containing dihydrocodeine tartrate 10 mg and paracetamol 500 mg should be dispensed

Co-dydramol (Non-proprietary) PoM

Tablets, scored, co-dydramol 10/500 (dihydrocodeine tartrate 10 mg, paracetamol 500 mg), net price 30-tab pack = £1.21. Label: 29, 30

Dose 1–2 tablets every 4–6 hours; max. 8 tablets daily; CHILD under 12 years not recommended

With dihydrocodeine tartrate 20 or 30 mg

See warnings and notes on p. 258 (**important:** special care in elderly—reduce dose)

When co-dydramol tablets are prescribed and no strength is stated, tablets containing dihydrocodeine tartrate 10 mg and paracetamol 500 mg should be dispensed

Remedeine® (Napp) PoM

Tablets, paracetamol 500 mg, dihydrocodeine tartrate 20 mg, net price 112-tab pack = £10.57. Label: 2, 29, 30

Dose 1–2 tablets every 4–6 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Forte tablets, paracetamol 500 mg, dihydrocodeine tartrate 30 mg, net price 56-tab pack = £6.53. Label: 2, 29, 30

Dose 1–2 tablets every 4–6 hours; max. 8 tablets daily; CHILD under 12 years not recommended

With isometheptene mucate

Isometheptene mucate (in combination with paracetamol) is licensed for the treatment of acute attacks of migraine; other more effective treatments are available.

[1] **Midrid®** (Manx) PoM

Capsules, red, isometheptene mucate 65 mg, paracetamol 325 mg, net price 30-cap pack = £5.50. Label: 30, counselling, dosage

Dose migraine, 2 capsules at onset of attack, followed by 1 capsule every hour if necessary; max. 5 capsules in 12 hours; CHILD not recommended

1. A pack containing 15 capsules may be sold to the public

With tramadol

For prescribing information on tramadol, see section 4.7.2

Tramacet® (Grünenthal) PoM

Tablets, f/c, yellow, tramadol hydrochloride 37.5 mg, paracetamol 325 mg, net price 60-tab pack = £9.68. Label: 2, 25, 29, 30

Dose 2 tablets not more often than every 6 hours; max. 8 tablets daily; CHILD under 12 years not recommended

Effervescent tablets, pink, tramadol hydrochloride 37.5 mg, paracetamol 325 mg, net price 60-tab pack = £9.68. Label: 2, 13, 29, 30

Electrolytes Na^+ 7.8 mmol/tablet

Dose 2 tablets not more often than every 6 hours; max. 8 tablets daily; CHILD under 12 years not recommended

With antiemetics

Migraleve® (McNeil)

Tablets, f/c, *pink tablets*, buclizine hydrochloride 6.25 mg, paracetamol 500 mg, codeine phosphate 8 mg; *yellow tablets*, paracetamol 500 mg, codeine phosphate 8 mg, net price 48-tab *Migraleve* PoM (32 pink + 16 yellow) = £4.81; 48 pink (*Migraleve Pink*) = £5.24; 48 yellow (*Migraleve Yellow*) = £4.70. Label: 2, (*Migraleve Pink*), 17, 30

Dose acute migraine, 2 pink tablets at onset of attack, followed by 2 yellow tablets every 4 hours if necessary; max. 2 pink and 6 yellow in 24 hours; CHILD under 10 years, only under close medical supervision; 10–14 years, half adult dose

Paramax® (Sanofi-Aventis) PoM

Tablets, scored, paracetamol 500 mg, metoclopramide hydrochloride 5 mg, net price 42-tab pack = £9.64. Label: 17, 30

Sachets, effervescent powder, sugar-free, the contents of 1 sachet = 1 tablet; to be dissolved in ¼ tumblerful of liquid before administration, net price 42-sachet pack = £12.52. Label: 13, 17, 30

Dose acute migraine, (tablets or sachets): 2 at onset of attack then every 4 hours when necessary to max. of 6 in 24 hours; YOUNG ADULT 12–19 years, 1 at onset of attack then 1 every 4 hours when necessary to max. of 3 in 24 hours (max. dose of metoclopramide 500 micrograms/kg daily)

Important Metoclopramide can cause **severe extrapyramidal effects**, particularly in children and young adults (for further details, see p. 249)

NEFOPAM HYDROCHLORIDE

Indications moderate pain

Cautions elderly, urinary retention; **interactions:** Appendix 1 (nefopam)

Contra-indications convulsive disorders; not indicated for myocardial infarction

Hepatic impairment caution

Renal impairment caution

Pregnancy no information available—avoid unless no safer treatment

Side-effects nausea, nervousness, urinary retention, dry mouth, lightheadedness; *less commonly* vomiting, blurred vision, drowsiness, sweating, insomnia, tachycardia, headache; confusion and hallucinations *also reported*; may colour urine (pink)

Dose

- By mouth, initially 60 mg (ELDERLY 30 mg) 3 times daily, adjusted according to response; usual range 30–90 mg 3 times daily; CHILD not recommended

Acupan® (Meda) PoM

Tablets, f/c, nefopam hydrochloride 30 mg, net price 90-tab pack = £10.53. Label: 2, 14

4.7.2 Opioid analgesics

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness, for guidelines see Prescribing in Palliative Care, p. 20. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the patient should be assessed at regular intervals.

Cautions Opioids should be used with caution in patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. A reduced dose is recommended in elderly or debilitated patients, in hypothyroidism, and in adrenocortical insufficiency. Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence. Avoid abrupt withdrawal after long-term treatment. Transdermal preparations (fentanyl or buprenorphine patches) are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. **Interactions**: Appendix 1 (opioid analgesics; **important:** special hazard with *pethidine and possibly other opioids* and MAOIs).

Palliative care In the control of pain in terminal illness, the cautions listed above should not necessarily be a deterrent to the use of opioid analgesics.

Contra-indications Opioid analgesics should be avoided in patients with acute respiratory depression and when there is a risk of paralytic ileus. They are also contra-indicated in conditions associated with raised intracranial pressure and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment). Comatose patients should not be treated with opioid analgesics.

Hepatic impairment Opioid analgesics may precipitate coma in patients with hepatic impairment; avoid use or reduce dose.

Renal impairment The effects of opioid analgesia are increased and prolonged and there is increased cerebral sensitivity when patients with renal impairment are treated with opioid analgesics; avoid use or reduce dose.

Pregnancy Respiratory depression and withdrawal symptoms can occur in the neonate if opioid analgesics are used during delivery; also gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.

Side-effects Opioid analgesics share many side-effects, although qualitative and quantitative differences exist. The most common side-effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth, and biliary spasm; larger doses produce muscle rigidity, hypotension, and respiratory depression (for reversal of opioid-induced respiratory depression, see section 15.1.7). Other common side-effects of opioid analgesics include bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion, drowsiness, sleep disturbances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus. **Overdosage**: see Emergency Treatment of Poisoning, p. 36.

Long-term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women. This can lead to amenorrhoea, reduced libido, infertility, depression, and erectile dysfunction. Long-term use of opioid analgesics has been associated with a state of abnormal pain sensitivity (hyperalgesia). Pain associated with hyperalgesia is usually qualitatively distinct from pain associated with disease progression or breakthrough pain, and is often more diffuse and less defined. Treatment of hyperalgesia involves reducing the dose of opioid medication or switching therapy; cases of suspected hyperalgesia should be referred to a specialist pain team.

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced. Driving at the start of therapy with opioid analgesics, and following dose changes, should be avoided.

Strong opioids **Morphine** remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of *severe pain in palliative care*. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations). For guidelines on dosage adjustment in palliative care, see p. 20.

A modified-release epidural preparation of morphine is available from Flynn Pharma Ltd (*Depodur®*).

Buprenorphine has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone.

Dipipanone used alone is less sedating than morphine but the only preparation available contains an antiemetic and is therefore not suitable for regular regimens in palliative care.

Diamorphine (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In *palliative care* the greater solubility of diamorphine allows effective doses to be injected in smaller volumes and this is important in the emaciated patient.

Alfentanil, **fentanyl** and **remifentanil** are used by injection for intra-operative analgesia (section 15.1.4.3); fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

Methadone is less sedating than morphine and acts for longer periods. In prolonged use, methadone should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone may be used instead of morphine in the occasional patient who experiences excitation (or exacerbation of pain) with morphine.

Oxycodone has an efficacy and side-effect profile similar to that of morphine. It is used primarily for control of *pain in palliative care*.

Papaveretum is rarely used; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pentazocine has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on other opioids. By injection it is more potent than dihydrocodeine or codeine, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour; however, other opioids, such as morphine or diamorphine, are often preferred for obstetric pain.

Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

Weak opioids **Codeine** is used for the relief of mild to moderate pain but is too constipating for long-term use.

Dihydrocodeine has an analgesic efficacy similar to that of codeine. The dose of dihydrocodeine by mouth is usually 30 mg every 4 hours; doubling the dose to 60 mg may provide some additional pain relief but this may be at the cost of more nausea and vomiting. A 40-mg tablet is also available.

Meptazinol is claimed to have a low incidence of respiratory depression. It has a reported length of action of 2 to 7 hours with onset within 15 minutes.

Dose The dose of opioids in the BNF may need to be **adjusted individually** according to the degree of analgesia and side-effects; patients' response to opioids varies widely.

Postoperative analgesia A combination of opioid and non-opioid analgesics (section 4.7.1 and section 15.1.4.2) is used to treat postoperative pain. The use of intra-operative opioids affects the prescribing of postoperative analgesics. A postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression (for the treatment of opioid-induced respiratory depression, see section 15.1.7).

Morphine is used most widely. **Tramadol** is not as effective in severe pain as other opioid analgesics. **Buprenorphine** may antagonise the analgesic effect of previously administered opioids and is generally not recommended. **Pethidine** is generally not recommended for postoperative pain because it is metabolised to norpethidine which may accumulate, particularly in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with morphine.

For details of patient-controlled analgesia (PCA) to relieve postoperative pain, consult hospital protocols. Formulations specifically designed for PCA are available (*Pharma-Ject® Morphine Sulphate*).

Dental and orofacial pain Opioid analgesics are **relatively ineffective** in dental pain. Like other opioids, **dihydrocodeine** often causes nausea and vomiting which limits its value in dental pain; if taken for more than a few doses it is also liable to cause constipation. Dihydrocodeine is not very effective in postoperative dental pain.

For the management of dental and orofacial pain, see p. 257.

Pain management and opioid dependence Although caution is necessary, patients who are dependent on opioids or have a history of drug dependence may be treated with opioid analgesics when there is a clinical need. Treatment with opioid analgesics in this patient group should normally be carried out with the advice of specialists. However, doctors do not require a special license to prescribe opioid analgesics to patients with opioid dependence for relief of pain due to organic disease or injury.

BUPRENORPHINE

Indications see under Dose and under Patches; opioid dependence (section 4.10.3)

Cautions see notes above; also impaired consciousness; effects only partially reversed by naloxone

Fever or external heat Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption)

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above and section 4.10.3

Breast-feeding avoid unless essential—may inhibit lactation; see also section 4.10.3

Side-effects see notes above; can induce mild withdrawal symptoms in patients dependent on opioids; also diarrhoea, abdominal pain, anorexia, dyspepsia; vasodilatation; dyspnoea; paraesthesia, asthenia, fatigue, agitation, anxiety; *less commonly* flatulence, taste disturbance, angina, hypertension, syncope,

hypoxia, wheezing, cough, restlessness, depersonalisation, dysarthria, impaired memory, hypoaesthesia, tremor, influenza-like symptoms, pyrexia, rhinitis, rigors, muscle cramp, myalgia, tinnitus, dry eye, and dry skin; *rarely* paralytic ileus, dysphagia, impaired concentration, and psychosis; *very rarely* retching, hyperventilation, hiccups, and muscle fasciculation

Dose

- Moderate to severe pain, by sublingual administration, 200–400 micrograms every 6–8 hours; CHILD over 6 years, 16–25 kg, 100 micrograms every 6–8 hours; 25–37.5 kg, 100–200 micrograms every 6–8 hours; 37.5–50 kg, 200–300 micrograms every 6–8 hours

  By intramuscular *or* slow intravenous injection, 300–600 micrograms every 6–8 hours; CHILD over 6 months 3–6 micrograms/kg every 6–8 hours (max. 9 micrograms/kg)
- Premedication, by sublingual administration, 400 micrograms

  By intramuscular injection, 300 micrograms
- Intra-operative analgesia, by slow intravenous injection, 300–450 micrograms

Temgesic® (Reckitt Benckiser) CD

Tablets (sublingual), buprenorphine (as hydrochloride), 200 micrograms, net price 50-tab pack = £5.13; 400 micrograms, 50-tab pack = £10.26. Label: 2, 26

Injection, buprenorphine (as hydrochloride) 300 micrograms/mL, net price 1-mL amp = 48p

Patches

BuTrans® (Napp) CD

Patches, self-adhesive, beige, buprenorphine, '5' patch (releasing 5 micrograms/hour for 7 days), net price 4 = £17.60; '10' patch (releasing 10 micrograms/hour for 7 days), 4 = £31.38; '20' patch (releasing 20 micrograms/hour for 7 days), 4 = £57.16. Label: 2

Dose moderate, non-malignant pain unresponsive to non-opioid analgesics, ADULT over 18 years, initially one '5 micrograms/hour' patch; apply to dry, non-irritated, non-hairy skin on upper torso, removing after 7 days and siting replacement patch on a different area (avoid same area for at least 3 weeks)

Dose adjustment When starting, analgesic effect should **not** be evaluated until the system has been worn for **72 hours** (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at 3-day intervals using a patch of the next strength or 2 patches of the same strength (applied at *same time* to avoid confusion). Max. 2 patches can be used at any one time

Long duration of action In view of the long duration of action, other opioids should not be administered within 24 hours of patch removal

Transtec® (Napp) CD

Patches, self-adhesive, skin-coloured, buprenorphine, '35' patch (releasing 35 micrograms/hour for 96 hours), net price 4 = £15.72; '52.5' patch (releasing 52.5 micrograms/hour for 96 hours), 4 = £23.58; '70' patch (releasing 70 micrograms/hour for 96 hours), 4 = £31.43. Label: 2

Dose moderate to severe chronic cancer pain and severe pain unresponsive to non-opioid analgesics, ADULT over 18 years, apply to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and siting replacement patch on a different area (avoid same area for at least 6 days). Patients who have not previously received strong opioid analgesic, initially, one '35 micrograms/hour' patch replaced after no longer than 96 hours; patients who have received strong opioid analgesic, initial dose based on previous 24-hour opioid requirement, consult product literature

Dose adjustment When starting, analgesic effect should **not** be evaluated until the system has been worn for **24 hours** (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength *or* using 2 patches of the same strength (applied at *same time* to avoid confusion). Max. 2 patches can be used at any one time. For breakthrough pain, consider 200–400 micrograms buprenorphine sublingually.
Important: it may take approx. 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed

Long duration of action In view of the long duration of action, patients who have severe side-effects should be monitored for up to 30 hours after removing patch

CODEINE PHOSPHATE

Indications mild to moderate pain; diarrhoea (section 1.4.2); cough suppression (section 3.9.1)

Cautions see notes above; also cardiac arrhythmias; acute abdomen; gallstones

Variation in metabolism The capacity to metabolise codeine can vary considerably and lead to either reduced therapeutic effect or marked increase in side-effects

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding amount usually too small to be harmful; however mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant

Side-effects see notes above; also abdominal pain, anorexia, seizures, malaise, hypothermia, and muscle fasciculation; pancreatitis also reported

Dose

- By mouth, 30–60 mg every 4 hours when necessary, to a max. of 240 mg daily; CHILD 1–12 years, 3 mg/kg daily in divided doses
- By intramuscular injection, 30–60 mg every 4 hours when necessary

Codeine Phosphate (Non-proprietary)

Tablets PoM, codeine phosphate 15 mg, net price 28-tab pack = £1.14; 30 mg, 28-tab pack = £1.22; 60 mg, 28-tab pack = £1.84. Label: 2

Syrup PoM, codeine phosphate 25 mg/5 mL, net price 100 mL = 93p. Label: 2

Injection CD, codeine phosphate 60 mg/mL, net price 1-mL amp = £2.44

Linctus

Section 3.9.1

DIAMORPHINE HYDROCHLORIDE

(Heroin Hydrochloride)

Indications see under Dose

Cautions see notes above; also severe diarrhoea; toxic psychosis, CNS depression; severe cor pulmonale

Contra-indications see notes above; also delayed gastric emptying; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

Side-effects see notes above; also anorexia, taste disturbance; syncope; asthenia, raised intracranial pressure; myocardial infarction also reported

Dose

- Acute pain, by subcutaneous *or* intramuscular injection, 5 mg repeated every 4 hours if necessary (up to 10 mg for heavier well-muscled patients); by slow intravenous injection, quarter to half corresponding intramuscular dose
- Myocardial infarction, by slow intravenous injection (1–2 mg/minute), 5 mg followed by a further 2.5–5 mg if necessary; elderly or frail patients, reduce dose by half
- Acute pulmonary oedema, by slow intravenous injection (1 mg/minute) 2.5–5 mg
- Chronic pain, by mouth *or* by subcutaneous *or* intramuscular injection, 5–10 mg regularly every 4 hours; dose may be increased according to needs; intramuscular dose should be approx. half corresponding oral dose, and approx. one third corresponding oral *morphine* dose—see also Prescribing in Palliative Care, p. 20; by subcutaneous infusion (using syringe driver), see Prescribing in Palliative Care, p. 23

Diamorphine (Non-proprietary) CD

Tablets, diamorphine hydrochloride 10 mg, net price 100-tab pack = £16.42. Label: 2

Injection, powder for reconstitution, diamorphine hydrochloride, net price 5-mg amp = £2.57, 10-mg amp = £3.59, 30-mg amp = £3.82, 100-mg amp = £9.34, 500-mg amp = £42.07

DIHYDROCODEINE TARTRATE

Indications moderate to severe pain

Cautions see notes above; also pancreatitis; severe cor pulmonale

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding use only if potential benefit outweighs risk

Side-effects see notes above; also paralytic ileus, abdominal pain, and paraesthesia

Dose

- By mouth, 30 mg every 4–6 hours when necessary (see also notes above); CHILD over 4 years 0.5–1 mg/kg every 4–6 hours
- By deep subcutaneous *or* intramuscular injection, up to 50 mg repeated every 4–6 hours if necessary; CHILD over 4 years 0.5–1 mg/kg every 4–6 hours

Dihydrocodeine (Non-proprietary)

Tablets PoM, dihydrocodeine tartrate 30 mg, net price 28-tab pack = £1.58. Label: 2

Dental prescribing on NHS Dihydrocodeine Tablets 30 mg may be prescribed

Oral solution PoM, dihydrocodeine tartrate 10 mg/5 mL, net price 150 mL = £3.50. Label: 2

Injection CD, dihydrocodeine tartrate 50 mg/mL, net price 1-mL amp = £3.17

DF118 Forte® (Martindale) PoM

Tablets, dihydrocodeine tartrate 40 mg, net price 100-tab pack = £11.51. Label: 2

Dose ADULT and CHILD over 12 years, severe pain, 40–80 mg 3 times daily; max. 240 mg daily

Modified release

DHC Continus® (Napp) PoM

Tablets, m/r, dihydrocodeine tartrate 60 mg, net price 56-tab pack = £5.18; 90 mg, 56-tab pack = £8.66; 120 mg, 56-tab pack = £10.89. Label: 2, 25

Dose ADULT and CHILD over 12 years, chronic severe pain, 60–120 mg every 12 hours

Note Dihydrocodeine is an ingredient of some compound analgesic preparations, section 4.7.1

DIPIPANONE HYDROCHLORIDE

Indications moderate to severe pain

Cautions see notes above; also diabetes mellitus; phaeochromocytoma

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding no information available

Side-effects see notes above; also psychosis, restlessness, raised intracranial pressure

Dose

- See preparation below

Diconal® (Amdipharm) CD

Tablets, pink, scored, dipipanone hydrochloride 10 mg, cyclizine hydrochloride 30 mg, net price 50-tab pack = £9.57. Label: 2

Dose *acute pain*, 1 tablet gradually increased to 3 tablets every 6 hours; CHILD not recommended

Caution **Not recommended** in palliative care, see Nausea and Vomiting, p. 22

FENTANYL

Indications severe chronic pain, breakthrough pain; parenteral indications (section 15.1.4.3)

Cautions see notes above; also diabetes mellitus, impaired consciousness, cerebral tumour; see also Transdermal Fentanyl, p. 267

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding monitor infant for opioid-induced side-effects

Side-effects see notes above; also abdominal pain, anorexia, dyspepsia, dysphagia, mouth ulceration, taste disturbance, stomatitis, dry mouth; vasodilatation; apnoea; anxiety; myoclonus; *less commonly* flatulence, diarrhoea, laryngospasm, dyspnoea, hypoventilation, depersonalisation, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, thirst and muscle weakness; *rarely* hiccups and arrhythmia; *very rarely* paralytic ileus, haemoptysis, psychosis, and seizures; shock, asystole, pyrexia, ataxia, and muscle fasciculation also reported; *with nasal spray* throat irritation, epistaxis, nasal ulcer, rhinorrhoea

Dose

- Chronic intractable pain, by transdermal route, apply to dry, non-irritated, non-irradiated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patch on a different area (avoid using the

same area for several days). ADULT over 16 years **not currently treated** with a strong opioid analgesic (but see Transdermal Fentanyl, p. 267), initial dose, one '12' or '25 micrograms/hour' patch replaced after 72 hours; ADULT and CHILD over 2 years **currently treated** with a strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (consult product literature)

Dose adjustment When starting, evaluation of the analgesic effect should **not** be made before the system has been worn for **24 hours** (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; if necessary dose should be adjusted at 48–72-hour intervals in steps of 12–25 micrograms/hour. More than one patch may be used at a time for doses greater than 100 micrograms/hour (but applied at the *same time* to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (**important:** it may take up to 25 hours for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually).

Long duration of action In view of the long duration of action, patients who have had severe side-effects should be monitored for up to 24 hours after patch removal

- Breakthrough pain, see under oral preparations

Conversion (from oral morphine to transdermal fentanyl) see Prescribing in Palliative Care, p. 21

Tablets

Abstral® (ProStrakan) ▼ CD

Tablets (sublingual), fentanyl (as citrate) 100 micrograms, net price 10-tab pack = £49.99, 30-tab pack = £149.70; 200 micrograms, 10-tab pack = £49.99, 30-tab pack = £149.70; 300 micrograms, 10-tab pack = £49.99, 30-tab pack = £149.70; 400 micrograms, 10-tab pack = £49.99, 30-tab pack = £149.70; 600 micrograms, 30-tab pack = £149.70; 800 micrograms, 30-tab pack = £149.70. Label: 2, 26

Dose breakthrough pain in patients receiving opioid therapy for chronic cancer pain, ADULT over 18 years, initially 100 micrograms repeated if necessary after 15–30 minutes; adjust dose according to response—consult product literature; no more than 2 dose units, 15–30 minutes apart, for each pain episode; max. 800 micrograms per episode of breakthrough pain

Note If more than 4 episodes of breakthrough pain each day, adjust background analgesia

The *Scottish Medicines Consortium* (p. 4) has advised (January 2009) that *Abstral®* sublingual tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable

Effentora® (Cephalon) ▼ CD

Tablets (buccal), fentanyl (as citrate) 100 micrograms, net price 4-tab pack = £19.96, 28-tab pack = £139.72; 200 micrograms, 4-tab pack = £19.96, 28-tab pack = £139.72; 400 micrograms, 4-tab pack = £19.96, 28-tab pack = £139.72; 600 micrograms, 4-tab pack = £19.96; 800 micrograms, 4-tab pack = £19.96, 28-tab pack = £139.72. Label: 2, counselling, administration

Electrolytes Na^+ 0.35 mmol/100 microgram tablet, Na^+ 0.70 mmol/tablet (all other strengths)

Dose breakthrough pain in patients receiving opioid therapy for chronic cancer pain, ADULT over 18 years, initially 100 micrograms repeated if necessary 30 minutes after first dose (no more than 2 dose units for each pain episode); adjust dose according to response—consult product literature; max. 800 micrograms per episode of breakthrough pain; leave at least 4 hours between treatment of episodes of breakthrough pain during titration

Counselling Place tablet between cheek and gum and leave to dissolve; if more than 1 tablet required, place second tablet on the other side of the mouth; tablet may alternatively be placed under the tongue (sublingually)

The *Scottish Medicines Consortium* (p. 4) has advised that *Effentora®* buccal tablets should be restricted for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable

Lozenges

Actiq® (Flynn) CD

Lozenge (buccal), with oromucosal applicator, fentanyl (as citrate) 200 micrograms, net price 3 = £17.52, 30 = £175.16; 400 micrograms, 3 = £17.52, 30 = £175.16; 600 micrograms, 3 = £17.52, 30 = £175.16; 800 micrograms, 3 = £17.52, 30 = £175.16; 1.2 mg, 3 = £17.52, 30 = £175.16; 1.6 mg, 3 = £17.52, 30 = £175.16. Label: 2

Dose breakthrough pain in patients receiving opioid therapy for chronic cancer pain, initially 200 micrograms (over 15 minutes) repeated if necessary 15 minutes after first dose (no more than 2 dose units for each pain episode); adjust dose according to response; max. 4 dose units daily

Note If more than 4 episodes of breakthrough pain each day, adjust background analgesia

Nasal spray

Instanyl® (Nycomed) ▼ CD

Nasal spray, fentanyl (as citrate) 50 micrograms/metered spray, net price 10-dose pack = £59.50, 20-dose pack = £119.00; 100 micrograms/metered spray, 10-dose pack = £59.50, 20-dose pack = £119.00; 200 micrograms/metered spray, 10-dose pack = £59.50, 20-dose pack = £119.00. Label: 2, counselling, administration

Dose breakthrough pain in patients receiving opioid therapy for chronic cancer pain, ADULT over 18 years, initially 50 micrograms into one nostril, repeated once if necessary after 10 minutes; adjust dose according to response; max. 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode

Note If more than 4 breakthrough pain episodes daily, adjust background analgesia

Counselling Patient should sit or stand during administration. Avoid concomitant use of other nasal preparations

The *Scottish Medicines Consortium* (p. 4) has advised that *Instanyl®* nasal spray should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable

PecFent® (Archimedes) ▼ CD

Nasal spray, fentanyl (as citrate) 100 micrograms/metered spray, net price 8-dose pack = £30.40, 32-dose pack = £121.60; 400 micrograms/metered spray, 8-dose pack = £30.40, 32-dose pack = £121.60. Label: 2, counselling, administration

Dose breakthrough pain in patients receiving opioid therapy for chronic cancer pain, ADULT over 18 years, initially 100 micrograms into one nostril; adjust dose according to response; max. 2 sprays for each pain episode and minimum 4 hours between treatment of each pain episode

Note If more than 4 breakthrough pain episodes daily, adjust background analgesia

Counselling Avoid concomitant use of other nasal preparations

Patches

Prescriptions Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write '*Fentanyl 25 patches*' to prescribe patches that release fentanyl 25 micrograms per hour. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. '*one patch to be applied every 72 hours*'. The total quantity of patches to be supplied should be written in words and figures.

Transdermal fentanyl

Fever or external heat Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption)

Respiratory depression Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients

Counselling Patients and carers should be informed about safe use, including correct administration and disposal, strict adherence to dosage instructions, and the symptoms and signs of opioid overdosage. Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or impaired speech, and patients and carers should seek prompt medical attention.

Fentanyl (Non-proprietary) CD

Patches, self-adhesive, fentanyl, '12' patch (releasing approx. 12 micrograms/hour for 72 hours), net price 5 = £17.76; '25' patch (releasing approx. 25 micrograms/hour for 72 hours), 5 = £25.38; '50' patch (releasing approx. 50 micrograms/hour for 72 hours), 5 = £47.40; '75' patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £66.08; '100' patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £81.45. Label: 2, counselling, administration

Brands include *Fentalis®*, *Matrifen®*, *Mezolar®*, *Osmanil®*, *Tilofyl®*, *Victanyl®*

Durogesic DTrans® (Janssen-Cilag) CD

Patches, self-adhesive, transparent, fentanyl, '12' patch (releasing approx. 12 micrograms/hour for 72 hours), net price 5 = £17.76; '25' patch (releasing approx. 25 micrograms/hour for 72 hours), 5 = £25.38; '50' patch (releasing approx. 50 micrograms/hour for 72 hours), 5 = £47.40; '75' patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £66.08; '100' patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £81.45. Label: 2, counselling, administration

HYDROMORPHONE HYDROCHLORIDE

Indications severe pain in cancer

Cautions see notes above; also pancreatitis; toxic psychosis

Contra-indications see notes above; also acute abdomen

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding avoid—no information available

Side-effects see notes above; also paralytic ileus, peripheral oedema, seizures, asthenia, dyskinesia, agitation, and tremor

Dose

- See under preparations below

Palladone® (Napp) CD

Capsules, hydromorphone hydrochloride 1.3 mg (orange/clear), net price 56-cap pack = £8.82; 2.6 mg (red/clear), 56-cap pack = £17.64. Label: 2, counselling, see below

Dose 1.3 mg every 4 hours, increased if necessary according to severity of pain; CHILD under 12 years not recommended

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Modified release

Palladone® SR (Napp) CD

Capsules, m/r, hydromorphone hydrochloride 2 mg (yellow/clear), net price 56-cap pack = £20.98; 4 mg (pale blue/clear), 56-cap pack = £28.75; 8 mg (pink/clear), 56-cap pack = £56.08; 16 mg (brown/clear), 56-cap pack = £106.53; 24 mg (dark blue/clear), 56-cap pack = £159.82. Label: 2, counselling, see below

Dose 4 mg every 12 hours, increased if necessary according to severity of pain; CHILD under 12 years not recommended

Counselling Swallow whole or open capsule and sprinkle contents on soft food

MEPTAZINOL

Indications moderate to severe pain, including post-operative and obstetric pain and renal colic; peri-operative analgesia, section 15.1.4.3

Cautions see notes above; effects only partially reversed by naloxone

Contra-indications see notes above; also myocardial infarction; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding use only if potential benefit outweighs risk

Side-effects see notes above; can induce withdrawal symptoms in patients dependent on opioids; also diarrhoea, abdominal pain, dyspepsia, and hypothermia

Dose

- By mouth, 200 mg every 3–6 hours as required; CHILD not recommended
- By intramuscular injection, 75–100 mg every 2–4 hours if necessary; obstetric analgesia, 100–150 mg according to patient's weight (2 mg/kg); CHILD not recommended
- By slow intravenous injection, 50–100 mg every 2–4 hours if necessary; CHILD not recommended

Meptid® (Almirall) PoM

Tablets, orange, f/c, meptazinol 200 mg, net price 112-tab pack = £22.11. Label: 2

Injection, meptazinol 100 mg (as hydrochloride)/mL, net price 1-mL amp = £1.92

METHADONE HYDROCHLORIDE

Indications severe pain, see notes above; cough in terminal disease (section 3.9.1); adjunct in treatment of opioid dependence (section 4.10.3)

Cautions see notes above; also history of cardiac conduction abnormalities, family history of sudden death (ECG monitoring recommended; see also QT Interval Prolongation, below)

QT interval prolongation Patients with the following risk factors for QT interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored

Contra-indications see notes above; also phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation

Side-effects see notes above; also QT interval prolongation, torsade de pointes, hypothermia, restlessness, raised intracranial pressure, dysmenorrhoea, dry eyes, and hyperprolactinaemia

Dose

- By mouth *or* by subcutaneous *or* intramuscular injection, 5–10 mg every 6–8 hours, adjusted according to response; on prolonged use not to be given more frequently than every 12 hours; CHILD not recommended

Methadone (Non-proprietary) CD

Tablets, methadone hydrochloride 5 mg, net price 50 = £2.84. Label: 2
Brands include *Physeptone®*

Injection ▼, methadone hydrochloride, 10 mg/mL, net price 1-mL amp = £1.00, 2-mL amp = £1.67, 3.5-mL amp = £2.11, 5-mL amp = £2.28
Brands include *Physeptone®*, *Synastone®*

Linctus

Section 3.9.1

Oral solution and oral concentrate

Section 4.10.3

MORPHINE SALTS

Indications see notes above and under Dose; acute diarrhoea (section 1.4.2); cough in terminal care (section 3.9.1)

Cautions see notes above; also pancreatitis, cardiac arrhythmias, severe cor pulmonale

Contra-indications see notes above; also delayed gastric emptying, acute abdomen; heart failure secondary to chronic lung disease; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

Side-effects see notes above; also paralytic ileus, abdominal pain, anorexia, dyspepsia, exacerbation of pancreatitis, taste disturbance; hypertension, hypothermia, syncope; bronchospasm, inhibition of cough reflex; restlessness, seizures, paraesthesia, asthenia, malaise, disorientation, excitation, agitation, delirium, raised intracranial pressure; amenorrhoea; myoclonus, muscle fasciculation, rhabdomyolysis, and nystagmus

Dose

The patient should be closely monitored for pain relief as well as for side-effects especially respiratory depression. See also notes above.

- Acute pain, by subcutaneous injection (not suitable for oedematous patients) *or* by intramuscular injection, initially 10 mg (ELDERLY or frail 5 mg) every 4 hours (or more frequently during titration), adjusted according to response; NEONATE initially 100 micrograms/kg every 6 hours, adjusted according to response; CHILD 1–6 months initially 100–200 micrograms/kg every 6 hours, adjusted according to response; CHILD 6 months–2 years initially 100–200 micrograms/kg every 4 hours, adjusted according to response; CHILD 2–12 years initially 200 micrograms/kg every 4 hours, adjusted according to response; CHILD 12–18 years initially 2.5–10 mg every 4 hours, adjusted according to response

  By slow intravenous injection, initially 5 mg (reduce dose in ELDERLY or frail) every 4 hours (or more frequently during titration), adjusted according to response; NEONATE initially 50 micrograms/kg every 6 hours, adjusted according to response; CHILD 1–6 months initially 100 micrograms/kg every 6 hours, adjusted according to response; CHILD 6 months–12 years initially 100 micrograms/kg every 4 hours, adjusted according to response
- Premedication, by subcutaneous *or* intramuscular injection, up to 10 mg 60–90 minutes before operation; CHILD, by intramuscular injection, 150 micrograms/kg
- Patient controlled analgesia (PCA), consult hospital protocols
- Myocardial infarction, by slow intravenous injection (1–2 mg/minute), 5–10 mg followed by a further 5–10 mg if necessary; ELDERLY or frail patients, reduce dose by half
- Acute pulmonary oedema, by slow intravenous injection (2 mg/minute) 5–10 mg; ELDERLY or frail patients, reduce dose by half
- Chronic pain, by mouth *or* by subcutaneous injection (not suitable for oedematous patients) *or* by intramuscular injection, initially 5–10 mg every 4 hours, adjusted according to response; see also Prescribing in Palliative Care, p. 20

  By rectum, initially 15–30 mg every 4 hours, adjusted according to response

Note The doses stated above refer equally to morphine hydrochloride and sulphate

Oral solutions

Note For advice on transfer from oral solutions of morphine to modified-release preparations of morphine, see Prescribing in Palliative Care, p. 20

Morphine Oral Solutions

PoM or CD

Oral solutions of morphine can be prescribed by writing the formula:
Morphine hydrochloride 5 mg
Chloroform water to 5 mL

Note The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 13 mg per 5 mL the solution becomes CD. For sample prescription see Controlled Drugs and Drug Dependence, p. 8. It is usual to adjust the strength so that the dose volume is 5 or 10 mL.

Oramorph® (Boehringer Ingelheim)

Oramorph® oral solution PoM, morphine sulphate 10 mg/5 mL, net price 100-mL pack = £1.78; 300-mL pack = £4.95; 500-mL pack = £7.47. Label: 2

Oramorph® concentrated oral solution CD, sugar-free, morphine sulphate 100 mg/5 mL, net price 30-mL pack = £4.98; 120-mL pack = £18.59 (both with calibrated dropper). Label: 2

Tablets

Sevredol® (Napp) CD

Tablets, f/c, scored, morphine sulphate 10 mg (blue), net price 56-tab pack = £5.28; 20 mg (pink), 56-tab pack = £10.55; 50 mg (pale green), 56-tab pack = £28.02. Label: 2

Modified-release 12-hourly oral preparations

Morphgesic® SR (Amdipharm) CD

Tablets, m/r, f/c, morphine sulphate 10 mg (buff), net price 60-tab pack = £3.85; 30 mg (violet), 60-tab pack

= £9.24; 60 mg (orange), 60-tab pack = £18.04; 100 mg (grey), 60-tab pack = £28.54. Label: 2, 25

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 20; dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify 'tablets' (i.e. Morphgesic SR tablets)

MST Continus® (Napp) CD

Tablets, m/r, f/c, morphine sulphate 5 mg (white), net price 60-tab pack = £3.29; 10 mg (brown), 60-tab pack = £5.16; 15 mg (green), 60-tab pack = £9.61; 30 mg (purple), 60-tab pack = £12.40; 60 mg (orange), 60-tab pack = £24.20; 100 mg (grey), 60-tab pack = £38.30; 200 mg (green), 60-tab pack = £76.62. Label: 2, 25

Suspension (= sachet of granules to mix with water), m/r, pink, morphine sulphate 20 mg/sachet, net price 30-sachet pack = £24.58; 30 mg/sachet, 30-sachet pack = £25.54; 60 mg/sachet, 30-sachet pack = £51.09; 100 mg/sachet, 30-sachet pack = £85.15; 200 mg/sachet pack, 30-sachet pack = £170.30. Label: 2, 13

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 20; dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify 'tablets' or 'suspension' (i.e. 'MST Continus tablets' or 'MST Continus suspension')

Zomorph® (Archimedes) CD

Capsules, m/r, morphine sulphate 10 mg (yellow/clear enclosing pale yellow pellets), net price 60-cap pack = £3.47; 30 mg (pink/clear enclosing pale yellow pellets), 60-cap pack = £8.30; 60 mg (orange/clear enclosing pale yellow pellets), 60-cap pack = £16.20; 100 mg (white/clear enclosing pale yellow pellets), 60-cap pack = £25.65; 200 mg (clear enclosing pale yellow pellets), 60-cap pack = £51.30. Label: 2, counselling, see below

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining doses, see Prescribing in Palliative Care, p. 20; dosage requirements should be reviewed if the brand is altered

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Note Prescriptions must also specify 'capsules' (i.e. 'Zomorph capsules')

Modified-release 24-hourly oral preparations

MXL® (Napp) CD

Capsules, m/r, morphine sulphate 30 mg (light blue), net price 28-cap pack = £10.91; 60 mg (brown), 28-cap pack = £14.95; 90 mg (pink), 28-cap pack = £22.04; 120 mg (green), 28-cap pack = £29.15; 150 mg (blue), 28-cap pack = £36.43; 200 mg (red-brown), 28-cap pack = £46.15. Label: 2, counselling, see below

Dose every 24 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 20; dosage requirements should be reviewed if the brand is altered

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Note Prescriptions must also specify 'capsules' (i.e. 'MXL capsules')

Suppositories

Morphine (Non-proprietary) CD

Suppositories, morphine hydrochloride or sulphate 10 mg, net price 12 = £11.21; 15 mg, 12 = £8.85; 20 mg, 12 = £33.22; 30 mg, 12 = £13.47. Label: 2

Note Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber

Injections

Morphine Sulphate (Non-proprietary) CD

Injection, morphine sulphate 10, 15, 20, and 30 mg/mL, net price 1- and 2-mL amp (all) = 72p–£1.40

Intravenous infusion, morphine sulphate 1 mg/mL, net price 50-mL vial = £5.00; 2 mg/mL, 50-mL vial = £5.89

Minijet® Morphine Sulphate (UCB Pharma) CD

Injection, morphine sulphate 1 mg/mL, net price 10-mL disposable syringe = £15.00

Injection with antiemetic

For prescribing information on cyclizine, see section 4.6.

Caution In myocardial infarction cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids, section 4.6. **Not recommended** in palliative care, see Nausea and Vomiting, p. 22

Cyclimorph® (Amdipharm) CD

Cyclimorph-10® Injection, morphine tartrate 10 mg, cyclizine tartrate 50 mg/mL, net price 1-mL amp = £1.75

Dose ADULT and CHILD over 12 years, moderate to severe pain (short-term use only) by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours; max. 3 doses in any 24-hour period

Cyclimorph-15® Injection, morphine tartrate 15 mg, cyclizine tartrate 50 mg/mL, net price 1-mL amp = £1.82

Dose ADULT and CHILD over 12 years, moderate to severe pain (short-term use only) by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours; max. 3 doses in any 24-hour period

OXYCODONE HYDROCHLORIDE

Indications moderate to severe pain in patients with cancer; postoperative pain; severe pain

Cautions see notes above; also toxic psychosis; pancreatitis

Contra-indications see notes above; also acute abdomen; delayed gastric emptying; chronic constipation; cor pulmonale; acute porphyria (section 9.8.2)

Hepatic impairment avoid in moderate to severe impairment; see also notes above

Renal impairment avoid if eGFR less than 10 mL/minute/1.73m^2; see also notes above

Pregnancy see notes above

Breast-feeding present in milk—avoid

Side-effects see notes above; also diarrhoea, abdominal pain, anorexia, dyspepsia; bronchospasm, dyspnoea, impaired cough reflex; asthenia, anxiety; chills; muscle fasciculation; *less commonly* paralytic ileus, cholestasis, gastritis, flatulence, dysphagia, taste disturbance, belching, hiccups, vasodilatation, supraventricular tachycardia, syncope, amnesia, hypoaesthesia, restlessness, seizures, pyrexia, amenorrhoea, hypotonia, paraesthesia, disorientation, malaise, agitation, speech disorder, tremor, thirst, and dry skin

Dose

- By mouth, initially 5 mg every 4–6 hours, increased if necessary according to severity of pain, usual max. 400 mg daily, but some patients may require higher doses; CHILD under 18 years, see *BNF for Children*
- By slow intravenous injection, 1–10 mg every 4 hours when necessary; CHILD under 18 years, not recommended

- By intravenous infusion, initially 2 mg/hour, adjusted according to response; CHILD under 18 years not recommended
- By subcutaneous injection, initially 5 mg every 4 hours when necessary; CHILD under 18 years, not recommended
- By subcutaneous infusion, initially 7.5 mg/24 hours adjusted according to response; CHILD under 18 years, not recommended
- Patient controlled analgesia (PCA), consult hospital protocols

Note 2 mg oral oxycodone is approximately equivalent to 1 mg parenteral oxycodone

Oxycodone (Non-proprietary) CD

Injection, oxycodone hydrochloride 10 mg/mL, net price 1-mL amp = £1.60, 2-mL amp = £3.20

OxyNorm® (Napp) CD

Capsules, oxycodone hydrochloride 5 mg (orange/beige), net price 56-cap pack = £11.36; 10 mg (white/beige), 56-cap pack = £22.73; 20 mg (pink/beige), 56-cap pack = £45.47. Label: 2

Liquid (= oral solution), sugar-free, oxycodone hydrochloride 5 mg/5 mL, net price 250 mL = £9.66. Label: 2

Concentrate (= concentrated oral solution), sugar-free, oxycodone hydrochloride 10 mg/mL, net price 120 mL = £46.39. Label: 2

Injection, oxycodone hydrochloride 10 mg/mL, net price 1-mL amp = £1.60, 2-mL amp = £3.20; 50 mg/mL, 1-mL amp = £14.02

Note The *Scottish Medicines Consortium* (p. 4) has advised (October 2004 and November 2010) that *OxyNorm®* injection is restricted for use within NHS Scotland for patients with cancer who have difficulty in tolerating morphine or diamorphine

Modified release

OxyContin® (Napp) CD

Tablets, f/c, m/r, oxycodone hydrochloride 5 mg (blue), net price 28-tab pack = £12.46; 10 mg (white), 56-tab pack = £24.91; 20 mg (pink), 56-tab pack = £49.82; 40 mg (yellow), 56-tab pack = £99.66; 80 mg (green), 56-tab pack = £199.33. Label: 2, 25

Dose initially, 10 mg every 12 hours, increased if necessary according to severity of pain, usual max. 200 mg every 12 hours, but some patients may require higher doses; CHILD under 18 years see *BNF for Children*

With naloxone

Targinact® (Napp) ▼ CD

Tablets 5 mg/2.5 mg, f/c, m/r, oxycodone hydrochloride 5 mg, naloxone hydrochloride 2.5 mg (blue), net price 28-tab pack = £17.56. Label: 2, 25

Tablets 10 mg/5 mg, f/c, m/r, oxycodone hydrochloride 10 mg, naloxone hydrochloride 5 mg (white), net price 56-tab pack = £35.11. Label: 2, 25

Tablets 20 mg/10 mg, f/c, m/r, oxycodone hydrochloride 20 mg, naloxone hydrochloride 10 mg (pink), net price 56-tab pack = £70.22. Label: 2, 25

Tablets 40 mg/20 mg, f/c, m/r, oxycodone hydrochloride 40 mg, naloxone hydrochloride 20 mg (yellow), net price 56-tab pack = £140.44. Label: 2, 25

Dose severe pain responsive only to opioid analgesics, ADULT over 18 years not currently treated with opioid analgesics, initially 10 mg/5 mg every 12 hours, increased according to response; patients already receiving opioid analgesics can start with a higher dose of *Targinact®*; max. *Targinact®* 40 mg/20 mg every 12 hours

Note Supplemental modified-release oxycodone (without naloxone) can be prescribed for patients who need higher doses—consult product literature

PAPAVERETUM

Important Do **not** confuse with papaverine (section 7.4.5)
A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride
To avoid confusion, the figures of 7.7 mg/ml or 15.4 mg/ml should be used for prescribing purposes

Indications premedication; enhancement of anaesthesia (but see section 15.1.4.3); postoperative analgesia; severe chronic pain

Cautions see notes above; supraventricular tachycardia

Contra-indications see notes above; heart failure secondary to chronic lung disease; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

Side-effects see notes above; also hypothermia

Dose

- By subcutaneous, intramuscular, *or* intravenous injection, 7.7–15.4 mg repeated every 4 hours if necessary (ELDERLY initially 7.7 mg); CHILD up to 1 month 115 micrograms/kg, 1–12 months 154 micrograms/kg, 1–5 years 1.93–3.85 mg, 6–12 years, 3.85–7.7 mg

Intravenous dose In general the intravenous dose should be 25–50% of the corresponding subcutaneous or intramuscular dose

Papaveretum (Non-proprietary) CD

Injection, papaveretum 15.4 mg/mL (providing the equivalent of 10 mg of anhydrous morphine/mL), net price 1-mL amp = £1.64

Note The name *Omnopon®* was formerly used for papaveretum preparations

With hyoscine

For prescribing information on hyoscine, see section 4.6.

Papaveretum and Hyoscine Injection (Non-proprietary) CD

Injection, papaveretum 15.4 mg (providing the equivalent of 10 mg of anhydrous morphine), hyoscine hydrobromide 400 micrograms/mL, net price 1-mL amp = £3.57

Dose premedication, by subcutaneous or intramuscular injection, 0.5–1 mL

PENTAZOCINE

Indications moderate to severe pain, but see notes above

Cautions see notes above; also pancreatitis, arterial or pulmonary hypertension, cardiac arrhythmias, myocardial infarction, phaeochromocytoma; effects only partially reversed by naloxone

Contra-indications see notes above; patients dependent on opioids (can precipitate withdrawal); heart

failure secondary to chronic lung disease; acute porphyria (section 9.8.2)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding small amount present in milk—caution

Side-effects see notes above; also abdominal pain, hypertension, syncope, seizures, paraesthesia, tremor, raised intracranial pressure, disorientation, hypothermia, chills, blood disorders, myalgia, and toxic epidermal necrolysis

Dose

- By mouth, pentazocine hydrochloride 50 mg every 3–4 hours preferably after food (range 25–100 mg); max. 600 mg daily; CHILD 6–12 years 25 mg
- By subcutaneous, intramuscular, or intravenous injection, moderate pain, pentazocine 30 mg, severe pain 45–60 mg every 3–4 hours when necessary; max. 360 mg daily; CHILD over 1 year, by subcutaneous *or* intramuscular injection, up to 1 mg/kg, by intravenous injection up to 500 micrograms/kg

Pentazocine (Non-proprietary) CD

Capsules, pentazocine hydrochloride 50 mg, net price 28-cap pack = £16.55. Label: 2, 21
Brands include *Fortral*® ⚠

Tablets, pentazocine hydrochloride 25 mg, net price 28-tab pack = £23.09. Label: 2, 21
Brands include *Fortral*® ⚠

Injection, pentazocine 30 mg (as lactate)/mL, net price 1-mL amp = £1.67; 2-mL amp = £3.21
Brands include *Fortral*® ⚠

PETHIDINE HYDROCHLORIDE

Indications moderate to severe pain, obstetric analgesia; peri-operative analgesia

Cautions see notes above; not suitable for severe continuing pain; accumulation of metabolites may result in neurotoxicity; cardiac arrhythmias, severe cor pulmonale

Contra-indications see notes above; phaeochromocytoma

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding present in milk but not known to be harmful

Side-effects see notes above; also restlessness, tremor, and hypothermia; convulsions reported in **overdosage**

Dose

- Acute pain, by mouth, 50–150 mg every 4 hours; CHILD 0.5–2 mg/kg

  By subcutaneous *or* intramuscular injection, 25–100 mg (ELDERLY or debilitated, initially 25 mg), repeated after 4 hours; CHILD, by intramuscular injection, 0.5–2 mg/kg

  By slow intravenous injection, 25–50 mg (ELDERLY or debilitated, initially 25 mg), repeated after 4 hours
- Obstetric analgesia, by subcutaneous *or* intramuscular injection, 50–100 mg, repeated 1–3 hours later if necessary; max. 400 mg in 24 hours
- Premedication, by intramuscular injection, 25–100 mg 1 hour before operation (ELDERLY or debilitated, 25 mg); CHILD 0.5–2 mg/kg
- Postoperative pain, by subcutaneous *or* intramuscular injection, 25–100 mg (ELDERLY or debilitated, initially 25 mg), every 2–3 hours if necessary; CHILD, by intramuscular injection, 0.5–2 mg/kg

  Note In the postoperative period, the patient should be closely monitored for pain relief as well as for side-effects especially respiratory depression

Pethidine (Non-proprietary) CD

Tablets, pethidine hydrochloride 50 mg, net price 50 = £6.68. Label: 2

Injection, pethidine hydrochloride 50 mg/mL, net price 1-mL amp = 48p, 2-mL amp = 51p; 10 mg/mL, 5-mL amp = £3.17, 10-mL amp = £2.18

With promethazine

For prescribing information on promethazine hydrochloride, see section 3.4.1.

Pamergan P100® (Martindale) CD

Injection, pethidine hydrochloride 50 mg, promethazine hydrochloride 25 mg/mL, net price 2-mL amp = £1.44

Dose by intramuscular injection, premedication, 2 mL 60–90 minutes before operation; CHILD 8–12 years 0.75 mL, 13–16 years 1 mL

Obstetric analgesia, 1–2 mL every 4 hours if necessary

Severe pain, 1–2 mL every 4–6 hours if necessary

Note Although usually given intramuscularly, may be given intravenously after dilution to at least 10 mL with water for injections

TRAMADOL HYDROCHLORIDE

Indications moderate to severe pain

Cautions see notes above; impaired consciousness; excessive bronchial secretions; not suitable as a substitute in opioid-dependent patients

General anaesthesia Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported)

Contra-indications see notes above; uncontrolled epilepsy

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy embryotoxic in animal studies—manufacturers advise avoid; see also notes above

Breast-feeding amount probably too small to be harmful, but manufacturer advises avoid

Side-effects see notes above; also diarrhoea; fatigue; *less commonly* retching, gastritis, and flatulence; *rarely* anorexia, syncope, hypertension, bronchospasm, dyspnoea, wheezing, seizures, paraesthesia, and muscle weakness; blood disorders also reported

Dose

- ADULT and CHILD over 12 years, by mouth, 50–100 mg not more often than every 4 hours; total of more than 400 mg daily not usually required
- ADULT and CHILD over 12 years, by intramuscular injection *or* by intravenous injection (over 2–3 minutes) *or* by intravenous infusion, 50–100 mg every 4–6 hours

  Postoperative pain, 100 mg initially then 50 mg every 10–20 minutes if necessary during first hour to total max. 250 mg (including initial dose) in first hour, *then* 50–100 mg every 4–6 hours; max. 600 mg daily

Tramadol Hydrochloride (Non-proprietary) PoM

Capsules, tramadol hydrochloride 50 mg, net price 30-cap pack = £1.22, 100-cap pack = £2.07. Label: 2
Brands include *Tramake*®

Injection, tramadol hydrochloride 50 mg/mL, net price 2-mL amp = 95p

Zamadol® (Meda) PoM

Capsules, tramadol hydrochloride 50 mg, net price 100-cap pack = £8.00. Label: 2

Orodispersible tablets (*Zamadol Melt®*), tramadol hydrochloride 50 mg, net price 60-tab pack = £7.12. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling *Zamadol Melt®* should be sucked and then swallowed. May also be dispersed in water

Injection, tramadol hydrochloride 50 mg/mL, net price 2-mL amp = £1.10

Zydol® (Grünenthal) PoM

Capsules, green/yellow, tramadol hydrochloride 50 mg, net price 30-cap pack = £2.29, 100-cap pack = £7.63. Label: 2

Soluble tablets, tramadol hydrochloride 50 mg, net price 20-tab pack = £2.79, 100-tab pack = £13.33. Label: 2, 13

Injection, tramadol hydrochloride 50 mg/mL, net price 2-mL amp = 80p

Modified-release 12-hourly preparations

Larapam® SR (Sandoz) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £17.55; 150 mg, 60-tab pack = £27.35; 200 mg, 60-tab pack = £36.50. Label: 2, 25

Dose ADULT and CHILD over 12 years, initially 100 mg twice daily increased if necessary; usual max. 200 mg twice daily

Mabron® (Morningside) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £18.26; 150 mg, 60-tab pack = £27.39; 200 mg, 60-tab pack = £36.52. Label: 2, 25

Dose ADULT and CHILD over 12 years, 100 mg twice daily increased if necessary; usual max. 200 mg twice daily

Marol® (Morningside) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £9.12; 150 mg, 60-tab pack = £13.68; 200 mg, 60-tab pack = £18.24. Label: 2, 25

Dose ADULT and CHILD over 12 years, 100 mg twice daily increased if necessary; usual max. 200 mg twice daily

Maxitram SR® (Chiesi) PoM

Capsules, m/r, tramadol hydrochloride 50 mg (white), net price 60-cap pack = £4.55; 100 mg (yellow), 60-cap pack = £12.14; 150 mg (yellow), 60-cap pack = £18.21; 200 mg (yellow), 60-cap pack = £24.28. Label: 2, 25

Dose ADULT and CHILD over 12 years, 100–200 mg twice daily; total of more than 400 mg daily not usually required

Tramquel® SR (Meda) PoM

Capsules, m/r, tramadol hydrochloride 50 mg (dark green), net price 60-cap pack = £7.20; 100 mg (white), 60-cap pack = £14.39; 150 mg (dark green), 60-cap pack = £21.59; 200 mg (yellow), 60-cap pack = £28.78. Label: 2, counselling, administration

Dose ADULT and CHILD over 12 years, 50–100 mg twice daily increased if necessary to 150–200 mg twice daily; total of more than 400 mg daily not usually required

Counselling Swallow whole or open capsule and swallow contents immediately without chewing

Zamadol® SR (Meda) PoM

Capsules, m/r, tramadol hydrochloride 50 mg (green), net price 60-cap pack = £7.20; 100 mg, 60-cap pack = £14.39; 150 mg (dark green), 60-cap pack = £21.59; 200 mg (yellow), 60-cap pack = £28.78. Label: 2, counselling, administration

Dose ADULT and CHILD over 12 years, 50–100 mg twice daily increased if necessary to 150–200 mg twice daily; total of more than 400 mg daily not usually required

Counselling Swallow whole or open capsule and swallow contents without chewing

Zeridame® SR (Actavis) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £17.21; 150 mg, 60-tab pack = £25.82; 200 mg, 60-tab pack = £34.43. Label: 2, 25

Dose ADULT and CHILD over 12 years, 100 mg twice daily increased if necessary to 150–200 mg twice daily; usual max. 400 mg daily

Zydol SR® (Grünenthal) PoM

Tablets, m/r, f/c, tramadol hydrochloride 100 mg, net price 60-tab pack = £18.26; 150 mg (beige), 60-tab pack = £27.39; 200 mg (orange), 60-tab pack = £36.52. Label: 2, 25

Dose ADULT and CHILD over 12 years, 100 mg twice daily increased if necessary to 150–200 mg twice daily; total of more than 400 mg daily not usually required

Modified-release 24-hourly preparations

Tradorec XL® (MSD) PoM

Tablets, m/r, tramadol hydrochloride 100 mg, net price 30-tab pack = £14.10; 200 mg, 30-tab pack = £14.98; 300 mg, 30-tab pack = £22.47. Label: 2, 25

Dose ADULT and CHILD over 12 years, initially 100 mg once daily, increased if necessary; usual max. 400 mg once daily

Zamadol® 24hr (Meda) PoM

Tablets, all f/c, all m/r, tramadol hydrochloride 150 mg, net price 28-tab pack = £10.70; 200 mg, 28-tab pack = £14.26; 300 mg, 28-tab pack = £21.39; 400 mg, 28-tab pack = £28.51. Label: 2, 25

Dose ADULT and CHILD over 12 years, 150 mg once daily increased if necessary; max. 400 mg once daily

Zydol XL® (Grünenthal) PoM

Tablets, m/r, f/c, tramadol hydrochloride 150 mg, net price 30-tab pack = £12.18; 200 mg, 30-tab pack = £17.98; 300 mg, 30-tab pack = £24.94; 400 mg, 30-tab pack = £32.47. Label: 2, 25

Dose ADULT and CHILD over 12 years, 150 mg once daily increased if necessary; usual max. 400 mg once daily

With paracetamol

Section 4.7.1

4.7.3 Neuropathic pain

Neuropathic pain, which occurs as a result of damage to neural tissue, includes *phantom limb pain*, *compression neuropathies*, *peripheral neuropathies* (e.g. due to diabetes (section 6.1.5), alcoholism, HIV infection, chemotherapy, idiopathic neuropathy), *trauma*, *central pain* (e.g. pain following stroke, spinal cord injury, and syringomyelia), and *postherpetic neuralgia* (peripheral nerve damage following acute herpes zoster infection (shingles)). The pain occurs in an area of sensory deficit and may be described as burning, shooting or scalding and is sometimes accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Trigeminal neuralgia is also caused by dysfunction of neural tissue, but its management (see below) is distinct from other forms of neuropathic pain.

Neuropathic pain is generally managed with a tricyclic antidepressant or with certain antiepileptic drugs. **Ami-**

triptyline (p. 235) [unlicensed indication] and **pregabalin** (p. 284) are effective treatments for neuropathic pain. Amitriptyline and pregabalin can be used in combination if the patient has an inadequate response to either drug at the maximum tolerated dose.

Nortriptyline [unlicensed indication] (p. 236) may be better tolerated than amitriptyline.

Gabapentin (p. 284) is also effective for the treatment of neuropathic pain.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for **tramadol** (p. 271), **morphine** (p. 268), and **oxycodone** (p. 269); however, treatment with morphine or oxycodone should be initiated only under specialist supervision. Tramadol can be prescribed when other treatments have been unsuccessful, while the patient is waiting for assessment by a specialist.

Patients with localised pain who are unable to take oral medicines may benefit from topical local anaesthetic preparations, such as lidocaine medicated plasters (section 15.2), while awaiting specialist review.

Capsaicin (p. 664) is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia. A self-adhesive patch containing capsaicin 8% is licensed for the treatment of peripheral neuropathic pain in non-diabetic patients.

A **corticosteroid** may help to relieve pressure in compression neuropathy and thereby reduce pain.

Neuromodulation by spinal cord stimulation may be of benefit in some patients. Many patients with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support.

The management of trigeminal neuralgia and chronic facial pain are outlined below; for the management of neuropathic pain in *palliative care*, see p. 21; for the management of diabetic neuropathy, see section 6.1.5.

Trigeminal neuralgia

Surgery may be the treatment of choice in many patients; a neurological assessment will identify those who stand to benefit. **Carbamazepine** (p. 281) taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. It is very effective for the severe pain associated with trigeminal neuralgia and (less commonly) glossopharyngeal neuralgia. Blood counts and electrolytes should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness. Some cases respond to **phenytoin** (p. 288); the drug may be given by intravenous infusion (possibly as fosphenytoin) in a crisis (specialist use only).

Chronic facial pain

Chronic oral and facial pain including persistent idiopathic facial pain (also termed 'atypical facial pain') and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs. Tricyclic antidepressants (section 4.3.1) may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners' List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Patients on long-term therapy need to be monitored both for progress and for side-effects.

4.7.4 Antimigraine drugs

4.7.4.1 Treatment of acute migraine
4.7.4.2 Prophylaxis of migraine
4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias

4.7.4.1 Treatment of acute migraine

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A **simple analgesic** such as aspirin, paracetamol (preferably in a soluble or dispersible form) or a NSAID is often effective; concomitant **antiemetic** treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as a **5HT$_1$-receptor agonist** ('triptan'). **Ergot alkaloids** are rarely required now; oral and rectal preparations are associated with many side-effects and they should be avoided in cerebrovascular or cardiovascular disease.

Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT$_1$ receptor agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

Analgesics

Most migraine headaches respond to analgesics such as **aspirin** (p. 258) or **paracetamol** (p. 259) but because peristalsis is often reduced during migraine attacks the medication may not be sufficiently well absorbed to be effective; dispersible or effervescent preparations are therefore preferred. Compound preparations containing analgesics and antiemetics are available (section 4.7.1).

The NSAID **tolfenamic acid** is licensed specifically for the treatment of an acute attack of migraine; **diclofenac potassium**, **flurbiprofen**, **ibuprofen**, and **naproxen sodium** (section 10.1.1) are also licensed for use in migraine.

TOLFENAMIC ACID

Indications treatment of acute migraine
Cautions see NSAIDs, section 10.1.1
Contra-indications see NSAIDs, section 10.1.1
Hepatic impairment section 10.1.1
Renal impairment section 10.1.1
Pregnancy section 10.1.1
Breast-feeding amount too small to be harmful
Side-effects see NSAIDs, section 10.1.1; also dysuria (most commonly in men), confusion, malaise, hallucination, paraesthesia, tremor, euphoria, fatigue, and visual disturbances reported

Dose

- ADULT over 18 years, 200 mg at onset repeated once after 1–2 hours if necessary

Clotam Rapid® (Galen) PoM
Tablets, tolfenamic acid 200 mg, net price 10-tab pack = £15.00. Label: 21

5HT$_1$-receptor agonists

A 5HT$_1$-receptor agonist is of considerable value in the treatment of an acute migraine attack. The 5HT$_1$-receptor agonists ('triptans') act on the 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as 5HT$_{1B/1D}$-receptor agonists. A 5HT$_1$-receptor agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics. 5HT$_1$-receptor agonists are not indicated for the treatment of hemiplegic, basilar, or opthalmoplegic migraine.

The 5HT$_1$-receptor agonists available for treating migraine are **almotriptan**, **eletriptan**, **frovatriptan**, **naratriptan**, **rizatriptan**, **sumatriptan**, and **zolmitriptan**. If a patient does not respond to one 5HT$_1$-receptor agonist, an alternative 5HT$_1$-receptor agonist should be tried. For patients who have prolonged attacks that frequently recur despite treatment with a 5HT$_1$-receptor agonist, combination therapy with a NSAID such as naproxen should be considered. Sumatriptan or zolmitriptan are also used to treat cluster headache (section 4.7.4.3).

Cautions 5HT$_1$-receptor agonists should be used with caution in the elderly [unlicensed], and in conditions which predispose to coronary artery disease (pre-existing cardiac disease, see Contra-indications below); **interactions**: Appendix 1 (5HT$_1$ agonists).

Contra-indications 5HT$_1$-receptor agonists are contra-indicated in ischaemic heart disease, previous myocardial infarction, coronary vasospasm (including Prinzmetal's angina), and uncontrolled or severe hypertension.

Pregnancy There is limited experience of using 5HT$_1$-receptor agonists during pregnancy; manufacturers advise that they should be avoided unless the potential benefit outweighs the risk.

Side-effects Side-effects of the 5HT$_1$-receptor agonists include sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis), flushing, dizziness, feeling of weakness; fatigue; nausea and vomiting also reported.

ALMOTRIPTAN

Indications treatment of acute migraine
Cautions see under 5HT$_1$-receptor agonists above; sensitivity to sulfonamides; **interactions:** Appendix 1 (5HT$_1$ agonists)
Contra-indications see under 5HT$_1$-receptor agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease
Hepatic impairment caution in mild to moderate impairment; avoid in severe impairment
Renal impairment max. 12.5 mg in 24 hours if eGFR less than 30 mL/minute/1.73 m^2
Pregnancy see notes above
Breast-feeding present in milk in *animal* studies—withhold breast-feeding for 24 hours
Side-effects see under 5HT$_1$-receptor agonists above; also transient increase in blood pressure, drowsiness; *less commonly* diarrhoea, dyspepsia, dry mouth, chest pain, palpitation, paraesthesia, headache, myalgia, bone pain, tinnitus; *very rarely* myocardial infarction, and tachycardia

Dose

- 12.5 mg as soon as possible after onset repeated after 2 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 25 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

Almogran® (Almirall) PoM
Tablets, f/c, almotriptan (as hydrogen malate) 12.5 mg, net price 3-tab pack = £9.07; 6-tab pack = £18.14; 9-tab pack = £27.20. Label: 3

ELETRIPTAN

Indications treatment of acute migraine
Cautions see under 5HT$_1$-receptor agonists above; **interactions**: Appendix 1 (5HT$_1$ agonists)
Contra-indications see under 5HT$_1$-receptor agonists above; previous cerebrovascular accident or transient ischaemic attack; arrhythmias; heart failure; peripheral vascular disease
Hepatic impairment avoid in severe impairment
Renal impairment reduce initial dose to 20 mg; max. 40 mg in 24 hours; avoid if eGFR less than 30 mL/minute/1.73 m^2
Pregnancy see notes above
Breast-feeding present in milk—avoid breast-feeding for 24 hours
Side-effects see under 5HT$_1$-receptor agonists above; also abdominal pain, dry mouth, dyspepsia; tachycardia, palpitation; drowsiness, headache; pharyngitis, rhinitis, chills; myasthenia, myalgia; sweating; *less commonly* diarrhoea, glossitis, thirst, anorexia, taste disturbance; dyspnoea, yawning, oedema, agitation, confusion, euphoria, depression, insomnia, depersonalisation, tremor, dysarthria, stupor, movement disorders, hypertonia, urinary frequency, arthralgia, photophobia, visual disturbances, tinnitus, rash, and pruritus; *rarely* constipation, oesophagitis, bradycardia, asthma, syncope, lymphadenopathy, and menorrhagia; ischaemic colitis and hypertension also reported

Dose

- ADULT over 18 years, 40 mg repeated after 2 hours if migraine recurs (patient not responding to initial dose should not take second dose for same attack); increase to 80 mg for subsequent attacks if 40-mg dose inadequate; max. 80 mg in 24 hours

Relpax® (Pfizer) ▼ PoM
Tablets, f/c, orange, eletriptan (as hydrobromide) 20 mg, net price 6-tab pack = £22.50; 40 mg, 6-tab pack = £22.50. Label: 3

FROVATRIPTAN

Indications treatment of acute migraine

Cautions see under $5HT_1$-receptor agonists above; **interactions:** Appendix 1 ($5HT_1$ agonists)

Contra-indications see under $5HT_1$-receptor agonists above; previous cerebrovascular attack or transient ischaemic attack; peripheral vascular disease

Hepatic impairment avoid in severe impairment

Pregnancy see notes above

Breast-feeding present in milk in *animal* studies—withhold breast-feeding for 24 hours

Side-effects see under $5HT_1$-receptor agonists above; also dry mouth, dyspepsia, abdominal pain, paraesthesia, drowsiness, headache, visual disturbances, sweating; *less commonly* diarrhoea, dysphagia, flatulence, tachycardia, palpitation, hypertension, rhinitis, pharyngitis, sinusitis, laryngitis, tremor, anxiety, asthenia, insomnia, confusion, nervousness, impaired concentration, agitation, depression, depersonalisation, taste disturbances, micturition disorders, thirst, dehydration, arthralgia, muscle stiffness, tinnitus, vertigo, pruritus; *rarely* constipation, gastro-oesophageal reflux, irritable bowel syndrome, hiccup, peptic ulcer, stomatitis, bradycardia, hyperventilation, amnesia, abnormal dreams, hypertonia, hypotonia, breast tenderness, hypocalcaemia, hypoglycaemia, bilirubinaemia, epistaxis, urticaria, pyrexia, and purpura

Dose

- 2.5 mg as soon as possible after onset repeated after 2 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 5 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

Migard® (Menarini) PoM

Tablets, f/c, frovatriptan (as succinate) 2.5 mg, net price 6-tab pack = £16.67. Label: 3

NARATRIPTAN

Indications treatment of acute migraine

Cautions see under $5HT_1$-receptor agonists above; sensitivity to sulfonamides; **interactions:** Appendix 1 ($5HT_1$ agonists)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications see under $5HT_1$-receptor agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease

Hepatic impairment max. 2.5 mg in 24 hours in moderate impairment; avoid if severe

Renal impairment max. 2.5 mg in 24 hours; avoid if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding withhold breast-feeding for 24 hours

Side-effects see under $5HT_1$-receptor agonists above; also *less commonly* bradycardia, tachycardia, palpitation, and visual disturbance; *rarely* ischaemic colitis, rash, and pruritus

Dose

- 2.5 mg, repeated after at least 4 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 5 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

Naramig® (GSK) PoM

Tablets, f/c, green, naratriptan (as hydrochloride) 2.5 mg, net price 6-tab pack = £24.55, 12-tab pack = £49.10. Label: 3

RIZATRIPTAN

Indications treatment of acute migraine

Cautions see under $5HT_1$-receptor agonists above; **interactions:** Appendix 1 ($5HT_1$ agonists)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications see under $5HT_1$-receptor agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease

Hepatic impairment reduce dose to 5 mg in mild to moderate impairment; avoid in severe impairment

Renal impairment reduce dose to 5 mg in mild to moderate impairment; avoid in severe impairment

Pregnancy see notes above

Breast-feeding present in milk in *animal* studies—withhold breast-feeding for 24 hours

Side-effects see under $5HT_1$-receptor agonists above; drowsiness, palpitation, tachycardia, dry mouth, diarrhoea, dyspepsia, thirst, pharyngeal discomfort, dyspnoea, headache, paraesthesia, decreased alertness, insomnia, tremor, ataxia, nervousness, vertigo, confusion, myalgia and muscle weakness, sweating, urticaria, pruritus, blurred vision; *rarely* syncope, hypertension, toxic epidermal necrolysis; seizures and taste disturbance reported

Dose

- 10 mg as soon as possible after onset repeated after 2 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 20 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

Maxalt® (MSD) PoM

Tablets, pink, rizatriptan (as benzoate) 5 mg, net price 6-tab pack = £26.74; 10 mg, 3-tab pack = £13.37, 6-tab pack = £26.74. Label: 3

Oral lyophilisates (*Maxalt® Melt Wafers*), rizatriptan (as benzoate) 10 mg, net price 3-wafer pack = £13.37, 6-wafer pack = £26.74. Label: 3, counselling, administration

Counselling *Maxalt® Melt* wafers should be placed on the tongue and allowed to dissolve

Excipients include aspartame equivalent to phenylalanine 2.1 mg (section 9.4.1)

SUMATRIPTAN

Indications treatment of acute migraine; cluster headache (subcutaneous injection only)

Cautions see under $5HT_1$-receptor agonists above; history of seizures; sensitivity to sulfonamides; **interactions:** Appendix 1 ($5HT_1$ agonists)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications see under $5HT_1$-receptor agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease; moderate and severe hypertension

Hepatic impairment reduce oral dose to 25–50 mg; avoid in severe impairment

Renal impairment use with caution

Pregnancy see notes above

Breast-feeding present in milk but amount probably too small to be harmful; withhold breast-feeding for 12 hours

Side-effects see under $5HT_1$-receptor agonists above; also dyspnoea, drowsiness, transient increase in blood pressure, myalgia; *also reported* diarrhoea, ischaemic colitis, hypotension, bradycardia or tachycardia, palpitation, arrhythmias, myocardial infarction, Raynaud's syndrome, anxiety, seizures, tremor, dystonia, nystagmus, arthralgia, visual disturbances, and sweating; epistaxis with nasal spray

Dose

- By mouth, 50 mg (some patients may require 100 mg); dose may be repeated after at least 2 hours if migraine recurs; max. 300 mg in 24 hours; CHILD under 18 years, see *BNF for Children*
- By subcutaneous injection using auto-injector, 6 mg; dose may be repeated once after at least 1 hour if headache recurs; max. 12 mg in 24 hours; CHILD 10–18 years see *BNF for Children*
  Important **Not** for intravenous injection which may cause coronary vasospasm and angina
- Intranasally, 10–20 mg into one nostril; dose may be repeated once after at least 2 hours if migraine recurs; max. 40 mg in 24 hours; CHILD 12–18 years [unlicensed dose], 10–20 mg into one nostril; dose may be repeated once after at least 2 hours if migraine recurs; max. 40 mg in 24 hours

Note Patient not responding to initial dose should not take second dose for same attack

[1] **Sumatriptan** (Non-proprietary) PoM

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £1.71, 12-tab pack = £2.49; 100 mg, 6-tab pack = £2.43. Label: 3, 10, patient information leaflet

1. Sumatriptan 50 mg tablets can be sold to the public to treat previously diagnosed migraine; max. daily dose 100 mg

Imigran® (GSK) PoM

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £26.54; 100 mg, 6-tab pack = £42.90. Label: 3, 10, patient information leaflet

Injection, sumatriptan (as succinate) 12 mg/mL (= 6 mg/0.5-mL syringe), net price, treatment pack (2 × 0.5-mL prefilled syringes and auto-injector) = £42.47; refill pack 2 × 0.5-mL prefilled cartridges = £40.41. Label: 3, 10, patient information leaflet

Nasal spray, sumatriptan 10 mg/0.1-mL actuation, net price 2 unit-dose spray device = £11.80; 20 mg/0.1-mL actuation, 2 unit-dose spray device = £11.80, 6 unit-dose spray device = £35.39. Label: 3, 10, patient information leaflet

Imigran® Radis (GSK) PoM

Tablets, f/c, sumatriptan (as succinate) 50 mg (pink), net price 6-tab pack = £23.90; 100 mg (white), 6-tab pack = £42.90. Label: 3, 10, patient information leaflet

ZOLMITRIPTAN

Indications treatment of acute migraine; cluster headache (nasal route only) [unlicensed use]

Cautions see under $5HT_1$-receptor agonists above; should not be taken within 12 hours of any other $5HT_1$-receptor agonist; **interactions:** Appendix 1 ($5HT_1$ agonists)

Contra-indications see under $5HT_1$-receptor agonists above; Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways; previous cerebrovascular accident or transient ischaemic attack

Hepatic impairment max. 5 mg in 24 hours in moderate or severe impairment

Pregnancy see notes above

Breast-feeding use with caution—present in milk in *animal* studies

Side-effects see under $5HT_1$-receptor agonists above; also abdominal pain, dry mouth; palpitation; drowsiness, paraesthesia, headache; myalgia, muscle weakness; *less commonly* tachycardia, transient increase in blood pressure, polyuria; *rarely* urticaria; *very rarely* gastro-intestinal and splenic infarction, ischaemic colitis, angina, myocardial infarction; *with nasal spray*, taste disturbance, and epistaxis

Dose

- By mouth, migraine, ADULT over 18 years, 2.5 mg repeated after not less than 2 hours if migraine persists or recurs (increase to 5 mg for subsequent attacks in patients not achieving satisfactory relief with 2.5-mg dose); max. 10 mg in 24 hours; CHILD 12–18 years see *BNF for Children*
- Intranasally, cluster headache [unlicensed] or migraine, ADULT over 18 years, 5 mg (1 spray) into one nostril as soon as possible after onset, repeated after not less than 2 hours if headache persists or recurs; max. 10 mg in 24 hours; CHILD 12–18 years see *BNF for Children*

Zomig® (AstraZeneca) PoM

Tablets, f/c, yellow, zolmitriptan 2.5 mg, net price 6-tab pack = £18.00, 12-tab pack = £36.00

Orodispersible tablets (*Zomig Rapimelt®*), zolmitriptan 2.5 mg, net price 6-tab pack = £17.90; 5 mg, 6-tab pack = £22.80 Counselling, administration

Counselling *Zomig Rapimelt®* should be placed on the tongue, allowed to disperse and swallowed

Excipients include aspartame equivalent to phenylalanine 2.81 mg/tablet (section 9.4.1)

Nasal spray, zolmitriptan 5 mg/0.1-mL unit-dose spray device, net price 6 unit-dose sprays = £36.50

Ergot alkaloids

The value of **ergotamine** for migraine is limited by difficulties in absorption and by its side-effects, particularly nausea, vomiting, abdominal pain, and *muscular cramps*; it is best avoided. The recommended doses of ergotamine preparations should **not** be exceeded and treatment should **not** be repeated at intervals of less than 4 days.

To avoid habituation the frequency of administration of ergotamine should be limited to **no more than** twice a month. It should **never** be prescribed prophylactically but in the management of cluster headache a low dose (e.g. ergotamine 1 mg at night for 6 nights in 7) is occasionally given for 1 to 2 weeks [unlicensed indication].

ERGOTAMINE TARTRATE

Indications treatment of acute migraine and migraine variants unresponsive to analgesics

Cautions risk of peripheral vasospasm (see below); elderly; dependence (see Ergot Alkaloids above); cardiac disease; anaemia; **interactions:** Appendix 1 (ergot alkaloids)

Peripheral vasospasm Warn patient to stop treatment immediately if numbness or tingling of extremities develops and to contact doctor.

Contra-indications peripheral vascular disease, coronary heart disease, obliterative vascular disease and Raynaud's syndrome, temporal arteritis, sepsis, severe or inadequately controlled hypertension, hyperthyroidism, acute porphyria (section 9.8.2)

Hepatic impairment avoid in severe impairment—risk of toxicity increased

Renal impairment avoid; risk of renal vasoconstriction

Pregnancy avoid; oxytocic effect on the uterus

Breast-feeding avoid; ergotism may occur in infant; repeated doses may inhibit lactation

Side-effects abdominal pain, nausea, vomiting; dizziness; *less commonly* diarrhoea, pain and weakness in extremities, cyanosis, peripheral vasoconstriction, paraesthesia, and hypoaesthesia; *rarely* intestinal ischaemia, arrhythmias, increased blood pressure, bradycardia, tachycardia, dyspnoea, ergotism (including absence of pulse and numbness in extremities), myalgia, rash, and urticaria; *very rarely* myocardial ischaemia, myocardial infarction, heart-valve fibrosis, and gangrene; constipation, dry mouth, cerebral ischaemia, thrombosis, drowsiness, sleep disturbances, tremor, seizures, extrapyramidal effects, anxiety, depression, confusion, hallucinations, renal artery spasm, urinary retention, blood disorders, blurred vision, and arthralgia also reported; *with suppositories* rectal and anal ulcers on prolonged use

Dose

- See under preparations below

Cafergot® (Alliance) PoM

Tablets, s/c, ergotamine tartrate 1 mg, caffeine 100 mg, net price 30-tab pack = £5.02. Label: 18, counselling, dosage

Dose ADULT and CHILD over 12 years, 1–2 tablets at onset; max. 4 tablets in 24 hours; not to be repeated at intervals of less than 4 days; max. 8 tablets in one week (but see also notes above)

Suppositories, ergotamine tartrate 2 mg, caffeine 100 mg, net price 30 = £10.13. Label: 18, counselling, dosage

Dose ADULT and CHILD over 12 years, 1 suppository at onset; max. 2 in 24 hours; max. 4 suppositories in one week (but see also notes above)

Migril® (Wockhardt) PoM

Tablets, scored, ergotamine tartrate 2 mg, cyclizine hydrochloride 50 mg, caffeine hydrate 100 mg, net price 100 = £51.00. Label: 2, 18, counselling, dosage

Dose 1 tablet at onset, followed after 30 minutes by ½–1 tablet, repeated every 30 minutes if necessary; max. 3 tablets in 24 hours, 4 tablets per attack, 6 tablets in one week (but see also notes above); CHILD not recommended

Antiemetics

Antiemetics (section 4.6), such as **metoclopramide** or **domperidone**, or phenothiazine and antihistamine antiemetics, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem. Metoclopramide and domperidone have the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms. Oral analgesic preparations containing metoclopramide are a convenient alternative (**important:** for warnings relating to extrapyramidal effects of metoclopramide particularly in children and young adults, see p. 249).

4.7.4.2 Prophylaxis of migraine

Where migraine attacks are frequent, possible provoking factors such as stress, irregular life-style (e.g. lack of sleep), or chemical triggers (e.g. alcohol and nitrates) should be sought; combined oral contraceptives may also provoke migraine, see section 7.3.1 for advice.

Preventive treatment for migraine should be considered for patients who:

- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine attacks.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migrainous infarction.

The **beta-blockers** propranolol, atenolol, metoprolol, nadolol, and timolol (section 2.4) are all effective. Propranolol is the most commonly used.

Tricyclic antidepressants (section 4.3.1) [unlicensed indication], **topiramate** (section 4.8.1), **sodium valproate** (section 4.8.1) [unlicensed indication], **valproic acid** (section 4.2.3) [unlicensed indication], and **gabapentin** (section 4.8.1) [unlicensed indication] are also effective for preventing migraine.

Pizotifen is an antihistamine and a serotonin-receptor antagonist, structurally related to the tricyclic antidepressants. It is of limited value and may cause weight gain.

Botulinum toxin type A is licensed for the prophylaxis of headaches in adults with chronic migraine, defined as headache on at least 15 days per month, of which at least 8 of those days are with migraine.

Clonidine (*Dixarit®*) is **not** recommended; it can aggravate depression and cause insomnia. Methysergide, a semi-synthetic ergot alkaloid, has dangerous side-effects (retroperitoneal fibrosis and fibrosis of the heart valves and pleura); **important**: it should only be administered under hospital supervision.

PIZOTIFEN

Indications prevention of vascular headache including classical migraine, common migraine, and cluster headache

Cautions urinary retention; susceptibility to angle-closure glaucoma; history of epilepsy; **interactions:** Appendix 1 (pizotifen)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Renal impairment use with caution

Pregnancy avoid unless potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful, but manufacturer advises avoid

Side-effects dry mouth, nausea; dizziness, drowsiness, increased appetite, weight gain; *less commonly* constipation; *rarely* anxiety, aggression, insomnia, paraesthesia, hallucination, depression, arthralgia, myalgia; *very rarely* seizures

Dose

- Initially 500 micrograms at night increased gradually to usual dose of 1.5 mg at night *or* in 3 divided doses; may be further increased up to max. daily dose 4.5 mg (but rarely necessary), max. single dose 3 mg; CHILD

over 5 years, up to 1.5 mg daily in divided doses; max. single dose at night 1 mg

Pizotifen (Non-proprietary) PoM
Tablets, pizotifen (as hydrogen malate), 500 micrograms, net price 28-tab pack = £1.28; 1.5 mg, 28-tab pack = £2.17. Label: 2

Sanomigran® (Novartis) PoM
Tablets, both ivory-yellow, s/c, pizotifen (as hydrogen malate), 500 micrograms, net price 60-tab pack = £2.06; 1.5 mg, 28-tab pack = £3.42. Label: 2

Elixir, pizotifen (as hydrogen malate) 250 micrograms/5 mL, net price 300 mL = £3.61. Label: 2

CLONIDINE HYDROCHLORIDE

Indications prevention of recurrent migraine (but see notes above), vascular headache, menopausal flushing; hypertension (section 2.5.2)

Cautions depressive illness; heart failure; Raynaud's syndrome; concurrent antihypertensive therapy; cerebrovascular disease; polyneuropathy; constipation; **interactions:** Appendix 1 (clonidine)

Contra-indications severe bradyarrhythmia

Renal impairment use with caution in severe impairment—reduce initial dose and increase gradually

Pregnancy avoid unless potential benefit outweighs risk

Breast-feeding avoid

Side-effects constipation, dry mouth, nausea, vomiting; postural hypotension; depression, sleep disorder, dizziness, headache, drowsiness; erectile dysfunction; *less commonly* Raynaud's syndrome, paraesthesia, hallucination, rash, and pruritus; *rarely* AV block, gynaecomastia, and alopecia

Dose

- 50 micrograms twice daily, increased after 2 weeks to 75 micrograms twice daily if necessary; CHILD not recommended

Clonidine (Non-proprietary) PoM
Tablets, clonidine hydrochloride 25 micrograms, net price 112-tab pack = £13.84

Dixarit® (Boehringer Ingelheim) PoM
Tablets, blue, s/c, clonidine hydrochloride 25 micrograms, net price 112-tab pack = £6.75

Catapres® PoM
Section 2.5.2 (hypertension)

METHYSERGIDE

Indications prevention of severe recurrent migraine, cluster headache and other vascular headaches in patients who are refractory to other treatment and whose lives are seriously disrupted (**important:** hospital supervision only, see notes above); diarrhoea associated with carcinoid syndrome

Cautions history of peptic ulceration; avoid abrupt withdrawal of treatment; after 6 months withdraw (gradually over 2 to 3 weeks) for reassessment for at least 1 month (see also notes above); **interactions:** Appendix 1 (ergot alkaloids)

Contra-indications pulmonary and cardiovascular disease, severe hypertension, collagen disease, cellulitis, urinary-tract disorders, cachectic or septic conditions

Hepatic impairment avoid

Renal impairment avoid

Pregnancy avoid

Breast-feeding avoid

Side-effects nausea, vomiting, heartburn, abdominal discomfort, drowsiness, and dizziness occur frequently in initial treatment; mental and behavioural disturbances, insomnia, oedema, weight gain, rashes, loss of scalp hair, cramps, arterial spasm (including coronary artery spasm with angina and possible myocardial infarction), paraesthesias of extremities, postural hypotension, and tachycardia also occur; retroperitoneal and other abnormal fibrotic reactions may occur on prolonged administration, requiring immediate withdrawal of treatment

Dose

- Initially 1 mg at bedtime, increased gradually over about 2 weeks to 1–2 mg 3 times daily with food (see notes above); CHILD not recommended
- Diarrhoea associated with carcinoid syndrome, usual range, 12–20 mg daily (hospital supervision); CHILD not recommended

Deseril® (Alliance) PoM
Tablets, s/c, methysergide (as maleate) 1 mg, net price 60-tab pack = £12.94. Label: 2, 21

4.7.4.3 Cluster headache and the trigeminal autonomic cephalalgias

Cluster headache rarely responds to standard analgesics. **Sumatriptan** (p. 275) given by subcutaneous injection is the drug of choice for the *treatment* of cluster headache. If an injection is unsuitable, sumatriptan nasal spray or **zolmitriptan** nasal spray [both unlicensed use] may be used. Alternatively, 100% **oxygen** at a rate of 10–15 litres/minute for 10–20 minutes is useful in aborting an attack.

Prophylaxis of cluster headache is considered if the attacks are frequent, last over 3 weeks, or if they cannot be treated effectively. **Verapamil** (p. 133) or **lithium** [both unlicensed use] are used for prophylaxis.

Prednisolone (section 6.3.2) can be used for short-term prophylaxis of episodic cluster headache [unlicensed use] either as monotherapy, or in combination with verapamil during verapamil titration. The dose of prednisolone for monotherapy or adjunctive therapy is 60–100 mg once daily for 2–5 days followed by a dose reduction of 10 mg every 2–3 days until prednisolone is discontinued.

Ergotamine, used on an intermittent basis is an alternative for patients with short bouts, but it should **not** be used for prolonged periods. **Methysergide** is effective but must be used with extreme caution (section 4.7.4.2) and only if other drugs cannot be used or if they are not effective.

The other trigeminal autonomic cephalalgias, paroxysmal hemicrania (sensitive to indometacin), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, are seen rarely and are best managed by a specialist.

4.8 Antiepileptic drugs

4.8.1 Control of the epilepsies
4.8.2 Drugs used in status epilepticus
4.8.3 Febrile convulsions

4.8.1 Control of the epilepsies

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the seizure type, concomitant medication, co-morbidity, age, and sex should be taken into account. For women of childbearing age, see Pregnancy, p. 280.

The dosage frequency is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage adherence with the prescribed regimen. Most antiepileptics, when used in the usual dosage, can be given twice daily. Lamotrigine, phenobarbital, and phenytoin, which have long half-lives, can be given once daily at bedtime. However, with large doses, some antiepileptics may need to be given more frequently to avoid adverse effects associated with high peak plasma-drug concentration. Young children metabolise some antiepileptics more rapidly than adults and therefore may require more frequent doses and a higher dose in proportion to their body-weight.

Management When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried; the diagnosis should be checked before starting an alternative drug if the first drug showed lack of efficacy. The change from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions (see below). If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy.

Interactions Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by *hepatic enzyme induction* or *hepatic enzyme inhibition*; *displacement from protein binding sites* is not usually a problem. These interactions are highly variable and unpredictable.

For interactions of antiepileptic drugs, see **Appendix 1**; for advice on hormonal contraception and enzyme-inducing drugs, see section 7.3.1 and section 7.3.2

Significant interactions that occur **between antiepileptics** and that may affect dosing requirements are as follows:

Note Check under each drug for possible interactions when two or more antiepileptic drugs are used

Carbamazepine
often lowers plasma concentration of clobazam, clonazepam, lamotrigine, phenytoin (but may also raise phenytoin concentration), tiagabine, topiramate, valproate, zonisamide, and an active metabolite of oxcarbazepine

sometimes lowers plasma concentration of eslicarbazepine, ethosuximide, primidone (but tendency for corresponding increase in phenobarbital level), and rufinamide

Eslicarbazepine
often raises plasma concentration of phenytoin

sometimes lowers plasma concentration of carbamazepine

Ethosuximide
sometimes raises plasma concentration of phenytoin

Lamotrigine
sometimes raises plasma concentration of an active metabolite of carbamazepine (but evidence is conflicting)

Oxcarbazepine
sometimes lowers plasma concentration of carbamazepine (but may raise concentration of an active metabolite of carbamazepine)

sometimes raises plasma concentration of phenytoin

often raises plasma concentration of phenobarbital

Phenobarbital *or* **primidone**
often lowers plasma concentration of carbamazepine, clonazepam, lamotrigine, phenytoin (but may also raise phenytoin concentration), tiagabine, valproate, and zonisamide

sometimes lowers plasma concentration of ethosuximide and rufinamide

Phenytoin
often lowers plasma concentration of clonazepam, carbamazepine, eslicarbazepine, lamotrigine, tiagabine, topiramate, valproate, zonisamide, and an active metabolite of oxcarbazepine

often raises plasma concentration of phenobarbital

sometimes lowers plasma concentration of ethosuximide, primidone (by increasing conversion to phenobarbital), and rufinamide

Rufinamide
sometimes lowers plasma concentration of carbamazepine

sometimes raises plasma concentration of phenytoin and phenobarbital

Topiramate
sometimes raises plasma concentration of phenytoin

Valproate
sometimes lowers plasma concentration of an active metabolite of oxcarbazepine

often raises plasma concentration of lamotrigine, primidone, phenobarbital, phenytoin (but may also lower), and an active metabolite of carbamazepine

sometimes raises plasma concentration of ethosuximide, primidone (and tendency for significant increase in phenobarbital level), and rufinamide

Vigabatrin
often lowers plasma concentration of phenytoin

sometimes lowers plasma concentration of phenobarbital and primidone

Withdrawal Antiepileptic drugs should be withdrawn under specialist supervision. Avoid abrupt withdrawal, particularly of barbiturates and benzodiazepines, because this may precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.

The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is often difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal.

In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

Driving Patients with epilepsy may drive a motor vehicle (but not a large goods or passenger carrying vehicle) provided that they have been seizure-free for one year or, if subject to attacks only while asleep, have established a 3-year period of asleep attacks without awake attacks. Those affected by drowsiness should not drive or operate machinery.

Guidance issued by the Drivers Medical Unit of the Driver and Vehicle Licensing Agency (DVLA) recommends that patients should be advised not to drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months afterwards (see also Drugs and Driving under General Guidance, p. 3).

Patients who have had a first or single epileptic seizure must not drive for 6 months (5 years in the case of large goods or passenger carrying vehicles) after the event; driving may then be resumed, provided the patient has been assessed by a specialist as fit to drive because no abnormality was detected on investigation.

Pregnancy Women of child-bearing potential should discuss the impact of both epilepsy and the treatment of epilepsy on the outcome of pregnancy with a specialist.

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and if the patient takes two or more antiepileptic drugs). Valproate is associated with the highest risk of major and minor congenital malformations, and with developmental delay. Valproate should not be prescribed unless there is no safer alternative and only after a careful discussion of the risks; doses greater than 1 g daily are associated with an increased risk of teratogenicity. There is also an increased risk of teratogenicity with phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. There is not enough evidence to establish the risk of teratogenicity with other antiepileptic drugs.

Women of child-bearing potential who take antiepileptic drugs should be given contraceptive advice. Some antiepileptic drugs can reduce the efficacy of hormonal contraceptives, and the efficacy of some antiepileptics may be affected by hormonal contraceptives (see section 7.3.1 and interactions of antiepileptics, Appendix 1).

Women who want to become pregnant should be referred to a specialist for advice in advance of conception. For some women, the severity of seizure or the seizure type may not pose a serious threat, and drug withdrawal may be considered; therapy may be resumed after the first trimester. If treatment with antiepileptic drugs must continue throughout pregnancy, then monotherapy is preferable at the lowest effective dose.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen; the risk of harm to the mother and fetus from convulsive seizures outweighs the risk of continued therapy. The likelihood of a woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus.

To reduce the risk of neural tube defects, folate supplementation (section 9.1.2) is advised before conception and throughout the first trimester.

The concentration of antiepileptic drugs in the plasma can change during pregnancy, particularly in the later stages. Doses of phenytoin (see p. 288), carbamazepine, and lamotrigine should be adjusted on the basis of plasma-drug concentration monitoring; the dose of other antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis. Plasma-drug concentration monitoring during pregnancy is also useful to check compliance. Additionally, in patients taking topiramate or levetiracetam, it is recommended that fetal growth should be monitored.

Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Status epilepticus should be treated according to the standard protocol, see section 4.8.2.

Routine injection of vitamin K (section 9.6.6) at birth minimises the risk of neonatal haemorrhage associated with antiepileptics.

Withdrawal effects in the newborn may occur with some antiepileptic drugs, in particular benzodiazepines and phenobarbital.

Epilepsy and Pregnancy Register
All pregnant women with epilepsy, whether taking medication or not, should be encouraged to notify the UK Epilepsy and Pregnancy Register (Tel: 0800 389 1248).

Breast-feeding Breast-feeding is acceptable with all antiepileptic drugs taken in normal doses, with the possible exception of the barbiturates and some of the newer antiepileptics (see under individual drugs).

Focal seizures with or without secondary generalisation

Carbamazepine, **lamotrigine**, **oxcarbazepine**, and **sodium valproate** are the drugs of choice for focal seizures; second-line drugs include clobazam, gabapentin, levetiracetam, pregabalin, tiagabine, topiramate, and zonisamide.

Generalised seizures

Tonic-clonic seizures The drugs of choice for tonic-clonic seizures are **carbamazepine**, **lamotrigine**, and **sodium valproate**. Clobazam, levetiracetam, oxcarbazepine, and topiramate are second-line drugs.

Absence seizures **Ethosuximide** and **sodium valproate** are the drugs of choice in typical absence seizures; alternatives include clonazepam and lamotrigine. Sodium valproate is also highly effective in treating the generalised tonic-clonic seizures which can co-exist with absence seizures in idiopathic primary generalised epilepsy.

Myoclonic seizures Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. **Sodium valproate** is the drug of choice; **clonazepam** and **levetiracetam** can also be used. Alternatives include lamotrigine and topiramate, but lamotrigine may occasionally exacerbate myoclonic seizures. For reference to the adjunctive use of piracetam, see section 4.9.3.

Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that co-exist with myoclonic seizures in idiopathic generalised epilepsy.

Atypical absence, atonic, and tonic seizures Atypical absence, atonic, and tonic seizures are usually seen in childhood, in specific epilepsy syndromes, or associated with cerebral damage or mental retardation. They may respond poorly to the traditional drugs. **Sodium valproate**, **lamotrigine**, and **clonazepam** can be tried. Second-line drugs that are occasionally helpful include clobazam, ethosuximide, levetiracetam, and topiramate.

Epilepsy syndromes

Some drugs are licensed for use in particular epilepsy syndromes, such as lamotrigine and rufinamide in Lennox-Gastaut syndrome. The epilepsy syndromes are specific types of epilepsy that are characterised according to a number of features including seizure type, age of onset, and EEG characteristics.

For more information on epilepsy syndromes in children, see *BNF for Children*, section 4.8.1. Prescribing information for stiripentol (*Diacomit*®) in severe myoclonic epilepsy of infancy (Dravet syndrome) can also be found in *BNF for Children*.

Carbamazepine and related antiepileptics

Carbamazepine is a drug of choice for simple and complex focal seizures and for tonic-clonic seizures secondary to a focal discharge. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly with increments of 100–200 mg every two weeks. Some side-effects (such as headache, ataxia, drowsiness, nausea, vomiting, blurring of vision, dizziness, unsteadiness, and allergic skin reactions) are dose-related, and may be dose-limiting. These side-effects are more common at the start of treatment and in the elderly. They may be reduced by altering the timing of medication; use of modified-release tablets also significantly lessens the incidence of dose-related side-effects.

Oxcarbazepine is licensed as monotherapy or adjunctive therapy for the treatment of focal seizures with or without secondary generalised tonic-clonic seizures.

Eslicarbazepine is licensed for adjunctive treatment in adults with focal seizures with or without secondary generalisation.

The *Scottish Medicines Consortium* (p. 4) has advised (October 2010) that eslicarbazepine (*Zebinix*®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with focal seizures with or without secondary generalisation. It is restricted for use in refractory epilepsy.

CARBAMAZEPINE

Indications focal and secondary generalised tonic-clonic seizures, primary generalised tonic-clonic seizures; trigeminal neuralgia; prophylaxis of bipolar disorder unresponsive to lithium; adjunct in acute alcohol withdrawal [unlicensed] (section 4.10.1); diabetic neuropathy [unlicensed] (section 6.1.5)

Cautions cardiac disease (see also Contra-indications); skin reactions (see also Blood, Hepatic, or Skin Disorders, below and under Side-effects); test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele); history of haematological reactions to other drugs; manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value uncertain); may exacerbate absence and myoclonic seizures; consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; susceptibility to angle-closure glaucoma; cross-sensitivity reported with oxcarbazepine and with phenytoin; avoid abrupt withdrawal; **interactions:** see p. 279 and Appendix 1 (carbamazepine)

Blood, hepatic, or skin disorders Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative).

Contra-indications AV conduction abnormalities (unless paced); history of bone marrow depression, acute porphyria (section 9.8.2); hypersensitivity to tricyclic antidepressants

Hepatic impairment metabolism impaired in advanced liver disease; see also Blood, Hepatic, or Skin Disorders, above

Renal impairment use with caution

Pregnancy see Pregnancy, p. 280

Breast-feeding amount probably too small to be harmful but monitor infant for possible adverse reactions; see also Breast-feeding, p. 280

Side-effects see notes above; dry mouth, nausea, vomiting; oedema; ataxia, dizziness, drowsiness, fatigue, headache; hyponatraemia (leading in rare cases to water intoxication); blood disorders (including eosinophilia, leucopenia, thrombocytopenia, haemolytic anaemia, and aplastic anaemia); dermatitis, and urticaria; *less commonly* diarrhoea, constipation, involuntary movements (including nystagmus), visual disturbances; *rarely* abdominal pain, anorexia, hepatitis, jaundice, vanishing bile duct syndrome, cardiac conduction disorders, hypertension, hypotension, peripheral neuropathy, dysarthria, aggression, agitation, confusion, depression, hallucinations, restlessness, paraesthesia, lymph node enlargement, muscle weakness, systemic lupus erythematosus, and delayed multi-organ hypersensitivity disorder; *very*

rarely pancreatitis, stomatitis, hepatic failure, taste disturbance, exacerbation of coronary artery disease, AV block with syncope, circulatory collapse, hypercholesterolaemia, thrombophlebitis, thromboembolism, pulmonary hypersensitivity (with dyspnoea, pneumonitis, or pneumonia), psychosis, neuroleptic malignant syndrome, osteomalacia (see Cautions), osteoporosis, galactorrhoea, gynaecomastia, impaired male fertility, interstitial nephritis, renal failure, sexual dysfunction, urinary frequency, urinary retention, arthralgia, muscle pain, muscle spasm, conjunctivitis, angle-closure glaucoma, hearing disorders, acne, alterations in skin pigmentation, alopecia, hirsutism, sweating, photosensitivity, purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, and aseptic meningitis; suicidal ideation

Dose

Note Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation

- By mouth, epilepsy, initially, 100–200 mg 1–2 times daily, increased slowly (see notes above) to usual dose of 0.8–1.2 g daily in divided doses; in some cases 1.6–2 g daily in divided doses may be needed; ELDERLY reduce initial dose; CHILD daily in divided doses, up to 1 year 100–200 mg, 1–5 years 200–400 mg, 5–10 years 400–600 mg, 10–15 years 0.6–1 g

  Trigeminal neuralgia, initially 100 mg 1–2 times daily (but some patients may require higher initial dose), increased gradually according to response; usual dose 200 mg 3–4 times daily, up to 1.6 g daily in some patients

  Diabetic neuropathy [unlicensed indication], initially 100 mg 1–2 times daily, increased gradually according to response; usual dose 200 mg 3–4 times daily, up to 1.6 g daily in some patients

  Prophylaxis of bipolar disorder unresponsive to lithium (see also section 4.2.3), initially 400 mg daily in divided doses increased until symptoms controlled; usual range 400–600 mg daily; max. 1.6 g daily

  Treatment of alcohol withdrawal [unlicensed indication], initially 800 mg daily in divided doses, reduced gradually over 5 days to 200 mg daily; usual treatment duration 7–10 days

- By rectum, epilepsy, for short-term use (max. 7 days) when oral therapy temporarily not possible; 125-mg suppository approx. equivalent to 100-mg tablet, but final adjustment should always depend on clinical response (plasma concentration monitoring recommended); max. 1 g daily in 4 divided doses

Note Plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre)

Carbamazepine (Non-proprietary) PoM

Tablets, carbamazepine 100 mg, net price 28 = £5.69; 200 mg, 28 = £4.99; 400 mg, 28 = £6.59. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Brands include *Epimaz*®

Dental prescribing on NHS Carbamazepine Tablets may be prescribed

Tegretol® (Novartis) PoM

Tablets, scored, carbamazepine 100 mg, net price 84-tab pack = £2.07; 200 mg, 84-tab pack = £3.83; 400 mg, 56-tab pack = £5.02. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Chewtabs, orange, carbamazepine 100 mg, net price 56-tab pack = £3.16; 200 mg, 56-tab pack = £5.88. Label: 3, 8, 21, 24, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Liquid, sugar-free, carbamazepine 100 mg/5 mL. Net price 300-mL pack = £6.12. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Suppositories, carbamazepine 125 mg, net price 5 = £8.03; 250 mg, 5 = £10.71. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Modified release

Carbagen® SR (Generics) PoM

Tablets, m/r, f/c, scored, carbamazepine 200 mg, net price 56-tab pack = £5.20; 400 mg, 56-tab pack = £10.24. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Dose epilepsy, ADULT and CHILD over 5 years, as above; trigeminal neuralgia, as above; bipolar disorder, as above; total daily dose given in 1–2 divided doses

Tegretol® Retard (Novartis) PoM

Tablets, m/r, scored, carbamazepine 200 mg (beige-orange), net price 56-tab pack = £5.20; 400 mg (brown-orange), 56-tab pack = £10.24. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Dose epilepsy, ADULT and CHILD over 5 years, as above; trigeminal neuralgia, as above; bipolar disorder, as above; total daily dose given in 2 divided doses

ESLICARBAZEPINE ACETATE

Indications see notes above

Cautions avoid abrupt withdrawal; hyponatraemia (monitor plasma-sodium concentration in patients at risk and discontinue treatment if hyponatraemia occurs); PR-interval prolongation (avoid concomitant administration of drugs that prolong PR interval); elderly; **interactions:** see p. 279 and Appendix 1 (eslicarbazepine)

Contra-indications second- or third-degree AV block

Hepatic impairment avoid in severe impairment—no information available

Renal impairment reduce initial dose to 400 mg every other day for 2 weeks then 400 mg once daily if eGFR 30–60 mL/minute/1.73 m^2, adjusted according to response; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies; see also Breast-feeding, p. 280

Side-effects gastro-intestinal disturbances; dizziness, drowsiness, headache, impaired coordination, tremor, visual disturbances, fatigue; rash; *less commonly* dry mouth, dehydration, gingival hyperplasia, stomatitis; palpitation, bradycardia, hypertension, hypotension, epistaxis, appetite changes, weight changes, agitation, hyperactivity, confusion, mood changes, psychosis, impaired memory, insomnia, dysaesthesia, dystonia, parosmia, movement disorders, convulsions, peripheral neuropathy, nystagmus, dysarthria, taste disturbance, liver disorders, hypothyroidism, anaemia, hyponatraemia (see Cautions), electrolyte imbalance, tinnitus, alopecia, sweating, nail disorder, myalgia, nocturia, menstruation changes, malaise, chills, per-

ipheral oedema; *very rarely* pancreatitis, thrombocytopenia, and leucopenia; PR-interval prolongation also reported; suicidal ideation

Dose

- ADULT over 18 years, initially 400 mg once daily, increased after 1–2 weeks to 800 mg once daily; max. 1.2 g

Zebinix® (Eisai) ▼ PoM

Tablets, scored, eslicarbazepine acetate 800 mg, net price 30-tab pack = £154.20. Label: 8, counselling, driving (see notes above)

OXCARBAZEPINE

Indications see notes above

Cautions hypersensitivity to carbamazepine; avoid abrupt withdrawal; hyponatraemia (monitor plasma-sodium concentration in patients at risk), heart failure (monitor body-weight), cardiac conduction disorders; avoid in acute porphyria (section 9.8.2); **interactions:** see p. 279 and Appendix 1 (oxcarbazepine)

Blood, hepatic, or skin disorders Patients or their carers should be told how to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as lethargy, confusion, muscular twitching, fever, sore throat, rash, blistering, mouth ulcers, bruising, or bleeding develop

Hepatic impairment caution in severe impairment—no information available

Renal impairment halve initial dose if eGFR less than 30 mL/minute/1.73 m^2; increase according to response at intervals of at least 1 week

Pregnancy see Pregnancy , p. 280

Breast-feeding present in milk—manufacturer advises avoid; see also Breast-feeding, p. 280

Side-effects nausea, vomiting, constipation, diarrhoea, abdominal pain; dizziness, headache, drowsiness, agitation, amnesia, asthenia, ataxia, confusion, impaired concentration, depression, tremor; hyponatraemia; acne, alopecia, rash, nystagmus, visual disorders including diplopia; *less commonly* urticaria, leucopenia; *very rarely* hepatitis, pancreatitis, arrhythmias, blood disorders, systemic lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis; hypertension and hypothyroidism also reported; suicidal ideation

Dose

- Initially 300 mg twice daily increased according to response in steps of up to 600 mg daily at weekly intervals; usual dose range 0.6–2.4 g daily in divided doses; CHILD 6–18 years, 8–10 mg/kg daily in 2 divided doses increased according to response in steps of up to 10 mg/kg daily at weekly intervals (in adjunctive therapy, maintenance dose approx. 30 mg/kg daily); max. 46 mg/kg daily in divided doses

  Note In adjunctive therapy, the dose of concomitant anti-epileptics may need to be reduced when using high doses of oxcarbazepine

Oxcarbazepine (Non-proprietary) PoM

Tablets, oxcarbazepine 150 mg, net price 50-tab pack = £11.02; 300 mg, 50-tab pack = £22.38; 600 mg, 50-tab pack = £44.72. Label: 3, 8, counselling, blood, hepatic, or skin disorders (see above), driving (see notes above)

Trileptal® (Novartis) PoM

Tablets, f/c, scored, oxcarbazepine 150 mg (green), net price 50-tab pack = £8.50; 300 mg (yellow), 50-tab pack = £17.00; 600 mg (pink), 50-tab pack = £34.00. Label: 3, 8, counselling, blood, hepatic or skin disorders (see above), driving (see notes above)

Oral suspension, sugar-free, oxcarbazepine 300 mg/5 mL, net price 250 mL (with oral syringe) = £34.00. Label: 3, 8, counselling, blood, hepatic or skin disorders (see above), driving (see notes above)

Excipients include propylene glycol (see Excipients, p. 2)

Ethosuximide

Ethosuximide is used for typical absence seizures; it may also be used for atypical absence seizures. Ethosuximide is rarely used for myoclonic or tonic seizures.

ETHOSUXIMIDE

Indications see notes above

Cautions avoid abrupt withdrawal avoid in acute porphyria (section 9.8.2); **interactions:** see p. 279 and Appendix 1 (ethosuximide)

Blood disorders Patients or their carers should be told how to recognise signs of blood disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk; hyperexcitability and sedation reported; see also Breast-feeding, p. 280

Side-effects gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, abdominal pain, anorexia, weight loss); *less frequently* headache, fatigue, drowsiness, dizziness, hiccup, ataxia, euphoria, irritability, aggression, impaired concentration; *rarely* tongue swelling, sleep disturbances, night terrors, depression, psychosis, photophobia, dyskinesia, increased libido, vaginal bleeding, myopia, gingival hypertrophy, and rash; *also reported* hyperactivity, increase in seizure frequency, blood disorders such as leucopenia, agranulocytosis, pancytopenia, and aplastic anaemia (blood counts required if features of infection), systemic lupus erythematosus, and Stevens-Johnson syndrome; suicidal ideation

Dose

- ADULT and CHILD over 6 years, initially 500 mg daily in 2 divided doses, increased by 250 mg every 4–7 days to usual dose of 1–1.5 g daily in 2 divided doses; occasionally up to 2 g daily may be needed;
  CHILD 1 month–6 years, initially 10 mg/kg (max. 250 mg) daily in 2 divided doses, increased gradually over 2–3 weeks to usual dose of 20–40 mg/kg (max. 1 g) daily in 2 divided doses; total daily dose may be given in 3 divided doses

Ethosuximide (Non-proprietary) PoM

Capsules, ethosuximide 250 mg, net price 56-cap pack = £38.23. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Emeside® (Chemidex) PoM

Syrup, black currant, ethosuximide 250 mg/5 mL, net price 200-mL pack = £6.60. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Zarontin® (Pfizer) PoM

Syrup, yellow, ethosuximide 250 mg/5 mL, net price 200-mL pack = £4.22. Label: 8, counselling, blood disorders (see above), driving (see notes above)

Gabapentin and pregabalin

Gabapentin and **pregabalin** are used for the treatment of focal seizures with or without secondary generalisation. They are also licensed for the treatment of neuropathic pain (p. 272). Pregabalin is licensed for the treatment of generalised anxiety disorder (p. 233). Gabapentin is an effective treatment for migraine prophylaxis [unlicensed] (p. 277).

The *Scottish Medicines Consortium* (p. 4) has advised (July 2007) that pregabalin (*Lyrica®*) is not recommended for the treatment of central neuropathic pain.

The *Scottish Medicines Consortium* (p. 4) has advised (April 2009) that pregabalin (*Lyrica®*) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in adults who have not achieved adequate pain relief with, or have not tolerated, first- or second-line treatments; discontinue treatment if sufficient benefit is not achieved within 8 weeks of reaching the maximum tolerated dose.

GABAPENTIN

Indications monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation; peripheral neuropathic pain (section 4.7.3); migraine prophylaxis (section 4.7.4.2)

Cautions avoid abrupt withdrawal (may cause anxiety, insomnia, nausea, pain, and sweating—taper off over at least 1 week); elderly; diabetes mellitus; false positive readings with some urinary protein tests; history of psychotic illness; **interactions:** Appendix 1 (gabapentin)

Renal impairment reduce dose to 600–1800 mg daily in 3 divided doses if eGFR 50–80 mL/minute/1.73 m^2; reduce dose to 300–900 mg daily in 3 divided doses if eGFR 30–50 mL/minute/1.73 m^2; reduce dose to 300 mg on alternate days (up to max. 600 mg daily) in 3 divided doses if eGFR 15–30 mL/minute/1.73 m^2; reduce dose to 300 mg on alternate days (up to max. 300 mg daily) in 3 divided doses if eGFR less than 15 mL/minute/1.73 m^2—consult product literature

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk—manufacturer advises use only if potential benefit outweighs risk; see also Breast-feeding, p. 280

Side-effects diarrhoea, dry mouth, dyspepsia, nausea, vomiting, constipation, abdominal pain, flatulence, appetite changes, gingivitis, weight gain; hypertension, vasodilation, oedema; dyspnoea, cough, rhinitis; confusion, depression, hostility, sleep disturbances, headache, dizziness, anxiety, amnesia, ataxia, dysarthria, nystagmus, tremor, asthenia, paraesthesia, hyperkinesia; influenza-like symptoms; impotence, urinary incontinence; leucopenia; myalgia, arthralgia; diplopia, amblyopia; rash, purpura, pruritus, acne; *rarely* pancreatitis, hepatitis, jaundice, palpitation, hallucinations, movement disorders, thrombocytopenia, blood-glucose fluctuations in patients with diabetes, tinnitus, acute renal failure, Stevens-Johnson syndrome, and alopecia; suicidal ideation; psychosis *also reported*

Dose

- Epilepsy, 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 *or* initially 300 mg 3 times daily on day 1; then increased according to response in steps of 300 mg (in 3 divided doses) every 2–3 days; usual dose 0.9–3.6 g daily in 3 divided doses; CHILD 6–12 years (adjunctive therapy only) initially 10–15 mg/kg (max. 300 mg) once daily, then increased according to response over 3 days to usual dose 25–35 mg/kg daily in 3 divided doses; max. 50 mg/kg daily in 3 divided doses; CHILD 2–6 years see *BNF for Children*
- Neuropathic pain, ADULT over 18 years, 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times daily on day 3 *or* initially 300 mg 3 times daily on day 1, then increased according to response in steps of 300 mg (in 3 divided doses) every 2–3 days up to max. 3.6 g daily
- Migraine prophylaxis [unlicensed], initially 300 mg daily, increased according to response up to 2.4 g daily in divided doses

Gabapentin (Non-proprietary) PoM

Capsules, gabapentin 100 mg, net price 100-cap pack = £3.57; 300 mg, 100-cap pack = £8.83; 400 mg, 100-cap pack = £5.53. Label: 3, 5, 8, counselling, driving (see notes above)

Tablets, gabapentin 600 mg, net price 100-tab pack = £24.85; 800 mg, 100-tab pack = £36.42. Label: 3, 5, 8, counselling, driving (see notes above)

Neurontin® (Pfizer) PoM

Capsules, gabapentin 100 mg (white), net price 100-cap pack = £18.29; 300 mg (yellow), 100-cap pack = £42.40; 400 mg (orange), 100-cap pack = £49.06. Label: 3, 5, 8, counselling, driving (see notes above)

Tablets, f/c, gabapentin 600 mg, net price 100-tab pack = £84.80; 800 mg, 100-tab pack = £98.13. Label: 3, 5, 8, counselling, driving (see notes above)

PREGABALIN

Indications peripheral and central neuropathic pain (section 4.7.3); adjunctive therapy for focal seizures with or without secondary generalisation; generalised anxiety disorder (section 4.3)

Cautions avoid abrupt withdrawal (taper over at least 1 week); severe congestive heart failure; conditions that may precipitate encephalopathy

Renal impairment initially 75 mg daily and max. 300 mg daily if eGFR 30–60 mL/minute/1.73 m^2; initially 25–50 mg daily and max. 150 mg daily in 1–2 divided doses if eGFR 15–30 mL/minute/1.73 m^2; initially 25 mg once daily and max. 75 mg once daily if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid; see also Breast-feeding, p. 280

Side-effects dry mouth, constipation, vomiting, flatulence, oedema, dizziness, drowsiness, irritability, impaired attention, disturbances in muscle control and movement, speech disorder, impaired memory, paraesthesia, euphoria, confusion, malaise, appetite changes, insomnia, weight gain, sexual dysfunction, visual disturbances (including blurred vision, diplopia, visual field defects); *less commonly* abdominal distension, hypersalivation, gastro-oesophageal reflux disease, thirst, taste disturbance, flushing, hypotension, hypertension, tachycardia, syncope, first-degree AV block, dyspnoea, nasal dryness, stupor, depersonalisation, depression, abnormal dreams, hallucinations, agitation, cognitive impairment, panic

attacks, chills, hypoglycaemia, thrombocytopenia, urinary incontinence, dysuria, myalgia, arthralgia, dry eye, lacrimation, hyperacusis, nasopharyngitis, sweating, rash; *rarely* ascites, dysphagia, pancreatitis, weight loss, cold extremities, arrhythmia, bradycardia, cough, epistaxis, rhinitis, parosmia, hyperglycaemia, renal failure, oliguria, menstrual disturbances, breast pain, breast discharge, breast hypertrophy, neutropenia, hypokalaemia, leucopenia, rhabdomyolysis, urticaria; *also reported* diarrhoea, nausea, congestive heart failure, QT-interval prolongation, aggression, headache, convulsions, encephalopathy, urinary retention, keratitis, Stevens-Johnson syndrome, pruritus; suicidal ideation

Dose

- Neuropathic pain, ADULT over 18 years, initially 150 mg daily in 2–3 divided doses, increased if necessary after 3–7 days to 300 mg daily in 2–3 divided doses, increased further if necessary after 7 days to max. 600 mg daily in 2–3 divided doses
- Epilepsy, ADULT over 18 years, initially 25 mg twice daily, increased at 7-day intervals in steps of 50 mg daily to 300 mg daily in 2–3 divided doses, increased further if necessary after 7 days to max. 600 mg daily in 2–3 divided doses
- Generalised anxiety disorder, ADULT over 18 years, initially 150 mg daily in 2–3 divided doses, increased if necessary at 7-day intervals in steps of 150 mg daily; max. 600 mg daily in 2–3 divided doses

Note Pregabalin doses in BNF may differ from those in product literature

Lyrica® (Pfizer) PoM

Capsules, pregabalin 25 mg (white), net price 56-cap pack = £64.40, 84-cap pack = £96.60; 50 mg (white), 84-cap pack = £96.60; 75 mg (white/orange), 56-cap pack = £64.40; 100 mg (orange), 84-cap pack = £96.60; 150 mg (white), 56-cap pack = £64.40; 200 mg (orange), 84-cap pack = £96.60; 225 mg (white/orange), 56-cap pack = £64.40; 300 mg (white/orange), 56-cap pack = £64.40. Label: 3, 8, counselling, driving (see notes above)

Lacosamide

Lacosamide is licensed for adjunctive treatment of focal seizures with or without secondary generalisation.

The *Scottish Medicines Consortium* (p. 4) has advised (January 2009) that lacosamide (*Vimpat®*) is accepted for restricted use within NHS Scotland as adjunctive treatment for focal seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.

LACOSAMIDE

Indications see notes above

Cautions risk of PR-interval prolongation (including conduction problems, severe cardiac disease, and concomitant use of drugs that prolong PR interval), elderly; **interactions:** Appendix 1 (lacosamide)

Contra-indications second- or third-degree AV block

Hepatic impairment caution in severe impairment—no information available

Renal impairment titrate dose with caution; max. 250 mg daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies; see also Breast-feeding, p. 280

Side-effects nausea, vomiting, constipation, flatulence, dizziness, headache, impaired coordination, cognitive disorder, drowsiness, tremor, depression, fatigue, abnormal gait, blurred vision, nystagmus, pruritus; *also reported* dyspepsia, dry mouth, first-degree AV block, bradycardia, PR-interval prolongation, confusion, hypoesthesia, dysarthria, irritability, muscle spasm, tinnitus, rash; suicidal ideation

Dose

- By intravenous infusion over 15–60 minutes (for up to 5 days) or by mouth, ADULT and CHILD over 16 years, initially 50 mg twice daily, increased weekly by 50 mg twice daily; max. 200 mg twice daily

Vimpat® (UCB Pharma) ▼ PoM

Tablets, f/c, lacosamide 50 mg (pink), net price 14-tab pack = £10.81; 100 mg (yellow), 14-tab pack = £21.62, 56-tab pack = £86.50; 150 mg (pink), 14-tab pack = £32.44, 56-tab pack £129.74; 200 mg (blue), 56-tab pack = £144.16. Label: 8, counselling, driving (see notes above)

Syrup, lacosamide 15 mg/mL, net price 200 mL = £38.61. Label: 8, counselling, driving (see notes above)
Electrolytes Na^+ 0.4 mmol/5 mL
Excipients include aspartame (section 9.4.1)

Intravenous infusion, lacosamide 10 mg/mL, net price 200-mg vial = £29.70
Electrolytes Na^+ 2.6 mmol/vial

Lamotrigine

Lamotrigine is an antiepileptic for focal seizures and primary and secondary generalised tonic-clonic seizures. It is also licensed for typical absence seizures in children (but efficacy may not be maintained in all children). Lamotrigine may cause serious rashes especially in children; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration, whereas the enzyme-inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. When the potential for interaction is not known, treatment should be initiated with lower doses, such as those used with valproate.

LAMOTRIGINE

Indications monotherapy and adjunctive treatment of focal seizures and generalised seizures including tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome; monotherapy of typical absence seizures in children; prevention of depressive episodes associated with bipolar disorder

Cautions closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome develop; avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs; myoclonic seizures (may be exacerbated); Parkinson's disease (may be exacerbated); **interactions:** see p. 279 and Appendix 1 (lamotrigine)

Blood disorders Be alert for symptoms and signs suggestive of bone-marrow failure such as anaemia, bruising, or

infection. Aplastic anaemia, bone-marrow depression and pancytopenia have been associated rarely with lamotrigine

Hepatic impairment halve dose in moderate impairment; quarter dose in severe impairment

Renal impairment caution in renal failure; metabolite may accumulate; consider reducing maintenance dose in significant impairment

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk but limited data suggest no harmful effects on infants; see also Breast-feeding, p. 280

Side-effects nausea, vomiting, diarrhoea, dry mouth, aggression, agitation, headache, drowsiness, dizziness, tremor, insomnia, ataxia, back pain, arthralgia, nystagmus, diplopia, blurred vision, rash (see Skin Reactions, below); *rarely* conjunctivitis; *very rarely* hepatic failure, aseptic meningitis, movement disorders, unsteadiness, increase in seizure frequency, exacerbation of Parkinson's disease, confusion, hallucination, blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia—see Blood Disorders, above), hypersensitivity syndrome (possibly including rash, fever, facial oedema, lymphadenopathy, hepatic dysfunction, blood disorders, disseminated intravascular coagulation, and multiorgan dysfunction), lupus erythematosus-like reactions; *also reported* suicidal ideation

Skin reactions Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have developed especially in children; most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome (see Side-effects, above) and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

Counselling Warn patients to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop

Dose

Important Do not confuse the different combinations or indications; see also notes above

Note Dose titration should be repeated if restarting after an interval of more than 5 days

- Monotherapy of seizures, ADULT and CHILD over 12 years, initially 25 mg once daily for 14 days, increased to 50 mg once daily for further 14 days, then increased by max. 100 mg every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses (up to 500 mg daily has been required)
- Monotherapy of typical absence seizures, CHILD 2–12 years see *BNF for Children*
- Adjunctive therapy of seizures *with valproate*, ADULT and CHILD over 12 years, initially 25 mg on alternate days for 14 days then 25 mg once daily for further 14 days, thereafter increased by max. 50 mg every 7–14 days; usual maintenance, 100–200 mg daily in 1–2 divided doses; CHILD 2–12 years initially 150 micrograms/kg once daily for 14 days (those weighing under 13 kg may receive 2 mg on alternate days for first 14 days) then 300 micrograms/kg once daily for further 14 days, thereafter increased by max. 300 micrograms/kg every 7–14 days; usual maintenance 1–5 mg/kg daily in 1–2 divided doses (max. single dose 100 mg)
- Adjunctive therapy of seizures (with enzyme inducing drugs) *without valproate*, ADULT and CHILD over 12 years, initially 50 mg once daily for 14 days then 50 mg twice daily for further 14 days, thereafter increased by max. 100 mg every 7–14 days; usual maintenance 200–400 mg daily in 2 divided doses (up to 700 mg daily has been required); CHILD 2–12 years initially 600 micrograms/kg daily in 2 divided doses for 14 days then 1.2 mg/kg daily in 2 divided doses for further 14 days, thereafter increased by max. 1.2 mg/kg every 7–14 days; usual maintenance 5–15 mg/kg daily in 2 divided doses (max. single dose 200 mg)
- Adjunctive therapy of seizures (without enzyme inducing drugs) *without valproate*, ADULT and CHILD over 12 years, initially 25 mg once daily for 14 days, increased to 50 mg once daily for further 14 days, then increased by max. 100 mg every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses; CHILD 2–12 years initially 300 micrograms/kg daily in 1–2 divided doses for 14 days then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, thereafter increased by max. 600 micrograms/kg every 7–14 days; usual maintenance 1–10 mg/kg daily in 1–2 divided doses; max. 200 mg daily
- Monotherapy *or* adjunctive therapy of bipolar disorder (without enzyme inducing drugs) *without valproate*, ADULT over 18 years, initially 25 mg once daily for 14 days, then 50 mg daily in 1–2 divided doses for further 14 days, then 100 mg daily in 1–2 divided doses for further 7 days; usual maintenance 200 mg daily in 1–2 divided doses; max. 400 mg daily
- Adjunctive therapy of bipolar disorder *with valproate*, ADULT over 18 years, initially 25 mg on alternate days for 14 days, then 25 mg once daily for further 14 days, then 50 mg daily in 1–2 divided doses for further 7 days; usual maintenance 100 mg daily in 1–2 divided doses; max. 200 mg daily
- Adjunctive therapy of bipolar disorder (with enzyme inducing drugs) *without valproate*, ADULT over 18 years, initially 50 mg once daily for 14 days, then 50 mg twice daily for further 14 days, then 100 mg twice daily for further 7 days, then 150 mg twice daily for further 7 days; usual maintenance 200 mg twice daily

Note Patients stabilised on lamotrigine for bipolar disorder may require dose adjustments if other drugs are added to or withdrawn from their treatment regimens—consult product literature

Lamotrigine (Non-proprietary) ▼ PoM

Tablets, lamotrigine 25 mg, net price 56-tab pack = £2.25; 50 mg, 56-tab pack = £3.07; 100 mg, 56-tab pack = £4.53; 200 mg, 30-tab pack = £27.53, 56-tab pack = £7.51. Label: 8, counselling, driving (see notes above), skin reactions (see above)

Dispersible tablets, lamotrigine 5 mg, net price 28-tab pack = £2.27; 25 mg, 56-tab pack = £2.91; 100 mg, 56-tab pack = £5.86. Label: 8, 13, counselling, driving (see notes above), skin reactions (see above)

Lamictal® (GSK) ▼ PoM

Tablets, yellow, lamotrigine 25 mg, net price 56-tab pack = £19.61; 50 mg, 56-tab pack = £33.35; 100 mg, 56-tab pack = £57.53; 200 mg, 56-tab pack = £97.79. Label: 8, counselling, driving (see notes above), skin reactions (above)

Dispersible tablets, chewable, lamotrigine 2 mg, net price 30-tab pack = £10.45; 5 mg, 28-tab pack = £7.82; 25 mg, 56-tab pack = £19.61; 100 mg, 56-tab pack = £57.53. Label: 8, 13, counselling, , driving (see notes above), skin reactions (above)

Levetiracetam

Levetiracetam is licensed for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, and for adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic-clonic seizures.

LEVETIRACETAM

Indications see notes above

Cautions avoid abrupt withdrawal; **interactions:** Appendix 1 (levetiracetam)

Hepatic impairment halve dose in severe hepatic impairment if eGFR less than 60 mL/minute/1.73 m^2

Renal impairment max. 2 g daily if eGFR 50–80 mL/minute/1.73 m^2; max. 1.5 g daily if eGFR 30–50 mL/minute/1.73 m^2; max. 1 g daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk—manufacturer advises avoid; see also Breast-feeding, p. 280

Side-effects anorexia, weight changes, abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, cough, drowsiness, amnesia, ataxia, convulsion, dizziness, headache, tremor, hyperkinesia, malaise, impaired attention, aggression, agitation, depression, insomnia, anxiety, irritability, personality disorder, thrombocytopenia, myalgia, diplopia, blurred vision, rash; *also reported* pancreatitis, hepatic failure, paraesthesia, confusion, psychosis, suicidal ideation, leucopenia, neutropenia, pancytopenia, alopecia, toxic epidermal necrolysis, Stevens-Johnson syndrome

Dose

- Monotherapy of focal seizures with or without secondary generalisation, by mouth *or* by intravenous infusion, ADULT and CHILD over 16 years, initially 250 mg once daily increased after 1–2 weeks to 250 mg twice daily; thereafter, increased according to response in steps of 250 mg twice daily every 2 weeks; max. 1.5 g twice daily
- Adjunctive therapy of focal seizures with or without secondary generalisation, by mouth, ADULT and CHILD over 12 years, body-weight over 50 kg, initially 250 mg twice daily, adjusted in steps of 500 mg twice daily every 2–4 weeks; max. 1.5 g twice daily; CHILD over 6 months, body-weight under 50 kg, initially 10 mg/kg once daily, adjusted in steps not exceeding 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily; CHILD 1–6 months, initially 7 mg/kg once daily, adjusted in steps not exceeding 7 mg/kg twice daily every 2 weeks; max. 21 mg/kg twice daily

  By intravenous infusion, ADULT and CHILD over 12 years, body-weight over 50 kg, initially 250 mg twice daily, adjusted in steps of 500 mg twice daily every 2–4 weeks; max. 1.5 g twice daily; CHILD over 4 years, body-weight under 50 kg, initially 10 mg/kg once daily, adjusted in steps not exceeding 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily
- Adjunctive therapy of myoclonic seizures and tonic-clonic seizures, by mouth *or* by intravenous infusion, ADULT and CHILD over 12 years, body-weight over 50 kg, initially 250 mg twice daily, adjusted in steps of 500 mg twice daily every 2–4 weeks; max. 1.5 g twice daily; CHILD 12–18 years, body-weight under 50 kg, initially 10 mg/kg once daily, adjusted in steps not exceeding 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily
- If switching from oral to intravenous therapy (because oral route temporarily unavailable), by intravenous infusion, same as established oral dose

Note Levetiracetam doses in BNF may differ from those in product literature

Keppra® (UCB Pharma) PoM

Tablets, f/c, levetiracetam 250 mg (blue), net price 60-tab pack = £29.70; 500 mg (yellow), 60-tab pack = £52.30; 750 mg (orange) 60-tab pack = £89.10; 1 g (white), 60-tab pack = £101.10. Label: 8

Oral solution, sugar-free, levetiracetam 100 mg/mL, net price 150 mL (with 1 mL or 3 mL syringe) = £42.60, 300 mL = £71.00. Label: 8

Concentrate for intravenous infusion, levetiracetam 100 mg/mL, net price 5-mL vial = £13.50

Electrolytes Na^+ 0.83 mmol/vial

Note For dilution before use

Phenobarbital and other barbiturates

Phenobarbital is effective for tonic-clonic and focal seizures but may be sedative in adults and cause behavioural disturbances and hyperkinesia in children. It may be tried for atypical absence, atonic, and tonic seizures. Rebound seizures may be a problem on withdrawal. For therapeutic purposes phenobarbital and phenobarbital sodium should be considered equivalent in effect. Plasma-phenobarbital concentration for optimum response is 15–40 mg/litre (60–180 micromol/litre); however, monitoring the plasma concentration is less useful than with other drugs because tolerance occurs.

Primidone is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. A low initial dose of primidone is essential, and the drug should be introduced over several weeks.

PHENOBARBITAL
(Phenobarbitone)

Indications all forms of epilepsy except typical absence seizures; status epilepticus (section 4.8.2)

Cautions see notes above; elderly; debilitated; children; respiratory depression (avoid if severe); avoid abrupt withdrawal (dependence with prolonged use); history of drug or alcohol abuse; consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; avoid in acute porphyria (section 9.8.2); **interactions:** see p. 279 and Appendix 1 (barbiturates)

Hepatic impairment may precipitate coma; avoid in severe impairment

Renal impairment use with caution

Pregnancy see Pregnancy, p. 280

Breast-feeding avoid if possible; drowsiness may occur; see also Breast-feeding, p. 280

Side-effects hepatitis, cholestasis; hypotension; respiratory depression; behavioural disturbances, nystagmus, irritability, drowsiness, lethargy, depression, ataxia, paradoxical excitement, hallucinations, impaired memory and cognition, hyperactivity particularly in the elderly and in children; osteomalacia (see Cautions); megaloblastic anaemia (may be treated with folic acid), agranulocytosis, thrombocytopenia; allergic skin reactions; *very rarely* Stevens-John-

son syndrome and toxic epidermal necrolysis; suicidal ideation; **overdosage:** see Emergency Treatment of Poisoning, p. 33

Dose

- By mouth, 60–180 mg at night; CHILD 5–8 mg/kg daily

Phenobarbital (Non-proprietary) CD

Tablets, phenobarbital 15 mg, net price 28-tab pack = 95p; 30 mg, 28-tab pack = 96p; 60 mg, 28-tab pack = 71p. Label: 2, 8, counselling, driving (see notes above)

Elixir, phenobarbital 15 mg/5 mL in a suitable flavoured vehicle, containing alcohol 38%, net price 100 mL = 78p. Label: 2, 8, counselling, driving (see notes above)

Note Some hospitals supply **alcohol-free** formulations of varying phenobarbital strengths

Injection

Section 4.8.2

PRIMIDONE

Indications all forms of epilepsy except absence seizures; essential tremor (section 4.9.3)

Cautions see under Phenobarbital; **interactions:** see p. 279 and Appendix 1 (primidone)

Hepatic impairment reduce dose; may precipitate coma

Renal impairment see Phenobarbital

Pregnancy see Phenobarbital

Breast-feeding see Phenobarbital

Side-effects see Phenobarbital; also nausea, visual disturbances; *less commonly* vomiting, headache, dizziness; *rarely* psychosis, lupus erythematosus, arthralgia; *also reported* Dupuytren's contracture

Dose

- Epilepsy, ADULT and CHILD over 9 years, initially 125 mg daily at bedtime, increased by 125 mg every 3 days to 500 mg daily in 2 divided doses, then increased according to response by 250 mg every 3 days to usual maintenance 0.75–1.5 g daily in 2 divided doses; CHILD under 9 years, initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, CHILD under 2 years, 250–500 mg daily in 2 divided doses; 2–5 years, 500–750 mg daily in 2 divided doses; 5–9 years 0.75–1 g daily in 2 divided doses
- Essential tremor, initially 50 mg daily increased gradually over 2–3 weeks according to response; max. 750 mg daily

Note Monitor plasma concentrations of derived phenobarbital; optimum range as for phenobarbital.

Mysoline® (Acorus) PoM

Tablets, scored, primidone 50 mg, net price 100–tab pack = £12.60; 250 mg, 100-tab pack = £12.60. Label: 2, 8, counselling, driving (see notes above)

Phenytoin

Phenytoin is effective for tonic-clonic and focal seizures. It has a narrow therapeutic index and the relationship between dose and plasma concentration is non-linear; small dosage increases in some patients may produce large increases in plasma concentration with acute toxic side-effects. Similarly, a few missed doses or a small change in drug absorption may result in a marked change in plasma concentration. Monitoring of plasma concentration improves dosage adjustment. Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia.

Phenytoin may cause coarsening of the facial appearance, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

When only parenteral administration is possible, **fosphenytoin** (section 4.8.2), a pro-drug of phenytoin, may be convenient to give. Whereas phenytoin can be given intravenously only, fosphenytoin may also be given by intramuscular injection.

PHENYTOIN

Indications all forms of epilepsy except absence seizures; status epilepticus (section 4.8.2); trigeminal neuralgia if carbamazepine inappropriate (see also section 4.7.3)

Cautions cross-sensitivity reported with carbamazepine; avoid abrupt withdrawal; HLA-B*1502 allele in individuals of Han Chinese or Thai origin—avoid unless essential (increased risk of Stevens-Johnson syndrome); manufacturer recommends blood counts (but evidence of practical value uncertain); consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; enteral feeding (interrupt feeding for 2 hours before and after dose; more frequent monitoring may be necessary); avoid in acute porphyria (section 9.8.2); **interactions:** see p. 279 and Appendix 1 (phenytoin)

Blood or skin disorders Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative)

Hepatic impairment reduce dose to avoid toxicity

Pregnancy changes in plasma-protein binding make interpretation of plasma-phenytoin concentrations difficult—monitor unbound fraction; see also Pregnancy, p. 280

Breast-feeding small amount present in milk, but not known to be harmful; see also Breast-feeding, p. 280

Side-effects nausea, vomiting, constipation, drowsiness, insomnia, transient nervousness, tremor, paraesthesia, dizziness, headache, anorexia; gingival hypertrophy and tenderness (maintain good oral hygiene); rash (discontinue; if mild re-introduce cautiously but discontinue immediately if recurrence), acne, hirsutism, coarsening of facial appearance; *rarely* hepatotoxicity, peripheral neuropathy, dyskinesia, lymphadenopathy, osteomalacia (see Cautions); blood disorders (including megaloblastic anaemia, leucopenia, thrombocytopenia, and aplastic anaemia), polyarteritis nodosa, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis; *also reported* polyarthropathy, pneumonitis, and interstitial nephritis; suicidal ideation

Dose

- By mouth, initially 3–4 mg/kg daily *or* 150–300 mg daily (as a single dose *or* in 2 divided doses) increased gradually as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily (exceptionally, higher doses may be used); CHILD initially 5 mg/kg daily in 2 divided doses, usual dose range 4–8 mg/kg daily (max. 300 mg daily)

Note Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre)

Counselling Take preferably with or after food

Phenytoin (Non-proprietary) PoM

Tablets, coated, phenytoin sodium 100 mg, net price 28-tab pack = £30.00. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients

Epanutin® (Pfizer) PoM

Capsules, phenytoin sodium 25 mg (white/purple), net price 28-cap pack = 66p; 50 mg (white/pink), 28-cap pack = 67p; 100 mg (white/orange), 84-cap pack = £2.83; 300 mg (white/green), 28-cap pack = £2.83. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Chewable tablets (*Infatabs®*), yellow, scored, phenytoin 50 mg, net price 112 = £7.38. Label: 8, 24, counselling, blood or skin disorder symptoms (see above), driving (see notes above)

Note Contain phenytoin 50 mg (as against phenytoin sodium) therefore care is needed on changing to capsules or tablets containing phenytoin sodium

Suspension, red, phenytoin 30 mg/5 mL, net price 500 mL = £4.27. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note Suspension of phenytoin 90 mg in 15 mL may be considered to be approximately equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg, but nevertheless care is needed in making changes

Rufinamide

Rufinamide is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome.

The *Scottish Medicines Consortium* (p. 4) has advised (October 2008) that rufinamide (*Inovelon®*) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.

RUFINAMIDE

Indications see notes above

Cautions closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome develop; avoid abrupt withdrawal; **interactions:** see p. 279 and Appendix 1 (rufinamide)

Hepatic impairment caution and careful dose titration in mild to moderate impairment; avoid in severe impairment

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises avoid—no information available; see also Breast-feeding, p. 280

Side-effects nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain, weight loss, anorexia; rhinitis, epistaxis; dizziness, headache, drowsiness, insomnia, anxiety, fatigue, increase in seizure frequency, impaired coordination, hyperactivity, tremor, gait disturbances; influenza-like symptoms; oligomenorrhoea; back pain; nystagmus, diplopia, blurred vision; rash and acne; hypersensitivity syndrome (possibly including rash, fever, lymphadenopathy, hepatic dysfunction, haematuria, and multi-organ dysfunction) also reported

Hypersensitivity syndrome Serious hypersensitivity syndrome (see Side-effects) has developed, especially in children and upon initiation of therapy; consider withdrawal if rash or signs or symptoms of hypersensitivity syndrome develop

Counselling Warn patients to seek immediate medical attention if signs or symptoms of hypersensitivity develop

Dose

- ADULT and CHILD over 4 years body-weight over 30 kg, initially 200 mg twice daily increased according to response in steps of 200 mg twice daily at intervals of not less than 2 days; body-weight 30–50 kg max. 900 mg twice daily; body-weight 50–70 kg max. 1.2 g twice daily; body-weight over 70 kg max. 1.6 g twice daily; CHILD over 4 years body-weight less than 30 kg, initially 100 mg twice daily increased according to response in steps of 100 mg twice daily at intervals of not less than 2 days; max. 500 mg twice daily (max. 300 mg twice daily if adjunctive therapy *with valproate*)

Inovelon® (Eisai) ▼ PoM

Tablets, pink, f/c, scored, rufinamide 100 mg, net price10-tab pack = £5.15; 200 mg, 60-tab pack = £61.77; 400 mg, 60-tab pack = £102.96. Label: 21, counselling, driving (see notes above), hypersensitivity syndrome (see above)

Tiagabine

Tiagabine is used as adjunctive treatment for focal seizures with or without secondary generalisation that are not satisfactorily controlled by other antiepileptics.

TIAGABINE

Indications see notes above

Cautions avoid in acute porphyria (section 9.8.2); avoid abrupt withdrawal; **interactions:** Appendix 1 (tiagabine)

Driving May impair performance of skilled tasks (e.g. driving)

Hepatic impairment maintenance dose 5–10 mg 1–2 times daily initially in mild to moderate impairment; avoid in severe impairment

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises use only if potential benefit outweighs risk; see also Breast-feeding, p. 280

Side-effects diarrhoea; dizziness, tiredness, nervousness, tremor, impaired concentration, emotional lability, speech impairment; *rarely* confusion, depression, drowsiness, psychosis, non-convulsive status epilepticus, bruising, and visual disturbances; suicidal ideation; leucopenia also reported

Dose

- Adjunctive therapy, ADULT and CHILD over 12 years, with *enzyme-inducing* drugs, 5 mg twice daily for 1 week, then increased at weekly intervals in steps of 5–10 mg daily; usual maintenance dose 30–45 mg daily (doses above 30 mg given in 3 divided doses); in patients receiving *non-enzyme-inducing* drugs, initial maintenance dose 15–30 mg daily

Gabitril® (Cephalon) PoM

Tablets, f/c, tiagabine (as hydrochloride) 5 mg, net price 100-tab pack = £40.89; 10 mg, 100-tab pack = £81.77; 15 mg, 100-tab pack = £122.66. Label: 21

Topiramate

Topiramate can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or focal seizures with or without secondary generalisation. It can be used as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome. Topiramate is also licensed for prophylaxis of migraine (section 4.7.4.2).

TOPIRAMATE

Indications see notes above

Cautions avoid abrupt withdrawal; risk of metabolic acidosis; risk of nephrolithiasis—ensure adequate hydration (especially in strenuous activity or warm environment); avoid in acute porphyria (section 9.8.2); **interactions:** see p. 279 and Appendix 1 (topiramate)

Important Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. If raised intra-ocular pressure occurs:

- seek specialist ophthalmological advice;
- use appropriate measures to reduce intra-ocular pressure;
- stop topiramate as rapidly as feasible

Hepatic impairment use with caution in moderate to severe impairment—clearance may be reduced

Renal impairment use with caution if eGFR less than 60 mL/minute/1.73 m^2—reduced clearance and longer time to steady-state plasma concentration

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises avoid—present in milk; see also Breast-feeding, p. 280

Side-effects nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, dry mouth, taste disturbance, gastritis, appetite changes, dyspnoea, impaired attention, cognitive impairment, movement disorders, seizures, tremor, malaise, impaired coordination, speech disorder, drowsiness, dizziness, sleep disturbance, anxiety, confusion, paraesthesia, aggression, mood changes, depression, agitation, irritability, nephrolithiasis, urinary disorders, anaemia, arthralgia, muscle spasm, myalgia, muscular weakness, visual disturbances, nystagmus, tinnitus, epistaxis, alopecia, rash, pruritus; *less commonly* pancreatitis, flatulence, abdominal distension, gingival bleeding, salivation, halitosis, thirst, glossodynia, bradycardia, palpitation, hypotension, postural hypotension, flushing, altered sense of smell, peripheral neuropathy, suicidal ideation, psychosis, panic attack, influenza-like symptoms, sexual dysfunction, urinary calculus, haematuria, blood disorders (including leucopenia, neutropenia, and thrombocytopenia), hypokalaemia, metabolic acidosis, dry eye, photophobia, blepharospasm, increased lacrimation, mydriasis, hearing loss, reduced sweating, skin discoloration; *rarely* Raynaud's syndrome, periorbital oedema, unilateral blindness, Stevens-Johnson syndrome, abnormal skin odour, calcinosis; *very rarely* angle-closure glaucoma; *also reported* maculopathy, toxic epidermal necrolysis

Dose

- Monotherapy, initially 25 mg at night for 1 week *then* increased in steps of 25–50 mg taken in 2 divided doses at intervals of 1–2 weeks; usual dose 100–200 mg daily in 2 divided doses, adjusted according to response; max. 500 mg daily (doses of 1 g daily have been used in refractory epilepsy); CHILD 6–18 years, initially 0.5–1 mg/kg (max. 25 mg) at night for 1 week *then* increased in steps of 0.5–1 mg/kg taken in 2 divided doses at intervals of 1–2 weeks; initial target dose 100 mg daily in 2 divided doses; max. 15 mg/kg (max. 500 mg) daily
- Adjunctive therapy, initially 25–50 mg at night for 1 week *then* increased in steps of 25–50 mg taken in 2 divided doses at intervals of 1–2 weeks; usual dose 200–400 mg daily in 2 divided doses; max. 400 mg daily; CHILD 2–18 years, initially 1–3 mg/kg (max. 25 mg) at night for 1 week *then* increased in steps of 1–3 mg/kg (max. 50 mg) taken in 2 divided doses at intervals of 1–2 weeks; usual dose 5–9 mg/kg daily in 2 divided doses; max. 15 mg/kg (max. 400 mg) daily
- Migraine prophylaxis, ADULT, initially 25 mg daily at night for 1 week *then* increased in steps of 25 mg at intervals of 1 week; usual dose 50–100 mg daily in 2 divided doses; max. 200 mg daily

Topiramate (Non-proprietary) ▼ PoM

Tablets, topiramate 25 mg, net price 60-tab pack = £6.17; 50 mg, 60-tab pack = £10.74; 100 mg, 60-tab pack = £12.52; 200 mg, 60-tab pack = £17.21. Label: 3, 8, counselling, driving (see notes above)

Capsules, topiramate 15 mg, net price 60-cap pack = £16.61; 25 mg, 60-cap pack = £24.91; 50 mg, 60-cap pack = £40.93. Label: 3, 8, counselling, driving (see notes above)

Topamax® (Janssen-Cilag) ▼ PoM

Tablets, f/c, topiramate 25 mg, net price 60-tab pack = £19.29; 50 mg (light yellow), 60-tab pack = £31.69; 100 mg (yellow), 60-tab pack = £56.76; 200 mg (salmon), 60-tab pack = £110.23. Label: 3, 8, counselling, driving (see notes above)

Capsules (*Sprinkle®*), topiramate 15 mg, net price 60-cap pack = £14.79; 25 mg, 60-cap pack = £22.18; 50 mg, 60-cap pack = £36.45. Label: 3, 8, counselling, administration, driving (see notes above)

Counselling Swallow whole or sprinkle contents of capsule on soft food and swallow immediately without chewing

Valproate

Sodium valproate is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised epilepsy, generalised absences and myoclonic seizures, and can be tried in atypical absence, atonic, and tonic seizures. Sodium valproate has widespread metabolic effects and monitoring is essential (see Cautions below).

Valproic acid (as semisodium valproate) (section 4.2.3) is licensed for acute mania associated with bipolar disorder.

SODIUM VALPROATE

Indications all forms of epilepsy; migraine prophylaxis [unlicensed] (section 4.7.4.2)

Cautions monitor liver function before therapy and during first 6 months especially in patients most at risk (see also below); measure full blood count and ensure no undue potential for bleeding before starting and before surgery; systemic lupus erythematosus; false-positive urine tests for ketones; avoid abrupt withdrawal; consider vitamin D supplementation in patients that are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium; **interactions:** see p. 279 and Appendix 1 (valproate)

Liver toxicity Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities).

Blood or hepatic disorders Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop

Pancreatitis Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea, or vomiting develop; discontinue if pancreatitis is diagnosed

Contra-indications family history of severe hepatic dysfunction; acute porphyria (section 9.8.2)

Hepatic impairment avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months); avoid in active liver disease; see also under Cautions

Renal impairment reduce dose; adjust dosage according to free serum-valproic acid concentration

Pregnancy see Pregnancy, p. 280; neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported

Breast-feeding amount too small to be harmful; see also Breast-feeding, p. 280

Side-effects nausea, gastric irritation, diarrhoea; weight gain; hyperammonaemia, thrombocytopenia; transient hair loss (regrowth may be curly); *less frequently* increased alertness, aggression, hyperactivity, behavioural disturbances, ataxia, tremor, and vasculitis; *rarely* hepatic dysfunction (see under Cautions; withdraw treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control), lethargy, drowsiness, confusion, stupor, hallucinations, blood disorders (including anaemia, leucopenia, pancytopenia), hearing loss, and rash; *very rarely* pancreatitis (see under Cautions), peripheral oedema, increase in bleeding time, extrapyramidal symptoms, dementia, encephalopathy, coma, gynaecomastia, Fanconi's syndrome, hirsutism, acne, enuresis, hyponatraemia, toxic epidermal necrolysis, and Stevens-Johnson syndrome; suicidal ideation; reduced bone mineral density (see Cautions); *also reported* menstrual disturbances

Dose

- Epilepsy, by mouth, initially 600 mg daily in 1–2 divided doses, increased by 200 mg daily every 3 days; usual maintenance dose 1–2 g daily (20–30 mg/kg daily), max. 2.5 g daily; CHILD body-weight up to 20 kg, initially 20 mg/kg daily in 1–2 divided doses, increased according to response (dose above 40 mg/kg daily monitor clinical chemistry and haematological parameters); CHILD under 12 years body-weight over 20 kg, initially 400 mg daily in 1–2 divided doses increased according to response; usual maintenance dose 20–30 mg/kg daily, max. 35 mg/kg daily

  Initiation of valproate treatment, by intravenous injection (over 3–5 minutes), up to 10 mg/kg (usually 400–800 mg) followed by intravenous infusion up to max. 2.5 g daily; CHILD under 12 years, usually 20–30 mg/kg daily, increased according to response (dose above 40 mg/kg daily monitor clinical chemistry and haematological parameters)

  Continuation of valproate treatment by intravenous injection (over 3–5 minutes) in 2 divided doses *or* by intravenous infusion, same as established oral dose
- Migraine prophylaxis [unlicensed], by mouth, initially 200 mg twice daily, increased if necessary to 1.2–1.5 g daily in divided doses

Oral

Sodium Valproate (Non-proprietary) PoM

Tablets (crushable), scored, sodium valproate 100 mg, net price 100-tab pack = £5.60. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Tablets, e/c, sodium valproate 200 mg, net price 100-tab pack = £4.83; 500 mg, 100-tab pack = £10.09. Label: 5, 8, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Brands include *Orlept®*

Oral solution, sodium valproate 200 mg/5 mL, net price 300 mL = £5.42. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Brands include *Orlept®* (sugar-free)

Epilim® (Sanofi-Aventis) PoM

Tablets (crushable), scored, sodium valproate 100 mg, net price 100 = £5.60. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Tablets, e/c, lilac, sodium valproate 200 mg, net price 100 = £7.70; 500 mg, 100 = £19.25. Label: 5, 8, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Liquid, red, sugar-free, sodium valproate 200 mg/5 mL, net price 300-mL pack = £9.33. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Syrup, red, sodium valproate 200 mg/5 mL, net price 300-mL pack = £7.78. Label: 8, 21, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)

Note May be diluted, preferably in Syrup BP; use within 14 days

Modified release

Epilim Chrono® (Sanofi-Aventis) PoM

Tablets, m/r, lilac, sodium valproate 200 mg (as sodium valproate and valproic acid), net price 100-tab pack = £11.65; 300 mg, 100-tab pack = £17.47; 500 mg, 100-tab pack = £29.10. Label: 8, 21, 25,

counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)
Dose ADULT and CHILD over 20 kg, as above, total daily dose given in 1–2 divided doses

Epilim Chronosphere® (Sanofi-Aventis) PoM
Granules, m/r, sodium valproate 50 mg (as sodium valproate and valproic acid), net price 30-sachet pack = £30.00; 100 mg, 30-sachet pack = £30.00; 250 mg, 30-sachet pack = £30.00; 500 mg, 30-sachet pack = £30.00; 750 mg, 30-sachet pack = £30.00; 1000 mg, 30-sachet pack = £30.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)
Dose ADULT and CHILD, as above to the nearest whole 50-mg sachet; total daily dose given in 1–2 divided doses
Counselling Granules may be mixed with soft food or drink that is cold or at room temperature, and swallowed immediately without chewing

Episenta® (Beacon) PoM
Capsules, enclosing m/r granules, sodium valproate 150 mg, net price 100-cap pack = £7.00; 300 mg, 100-cap pack = £13.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)
Dose ADULT and CHILD, as above, total daily dose given in 1–2 divided doses
Counselling Contents of capsule may be mixed with cold food or drink and swallowed immediately without chewing
Granules, m/r, sodium valproate 500 mg, net price 100-sachet pack = £21.00; 1 g, 100-sachet pack = £41.00. Label: 8, 21, 25, counselling, administration, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)
Dose ADULT and CHILD, as above, total daily dose given in 1–2 divided doses
Counselling Granules may be mixed with cold food or drink and swallowed immediately without chewing

Parenteral

Epilim® Intravenous (Sanofi-Aventis) PoM
Injection, powder for reconstitution, sodium valproate, net price 400-mg vial (with 4-mL amp water for injections) = £11.58

Episenta® (Beacon) PoM
Injection, sodium valproate 100 mg/mL, net price 3-mL amp = £7.00

Valproic acid

Convulex® (Pharmacia) PoM
Capsules, e/c, valproic acid 150 mg, net price 100-cap pack = £3.68; 300 mg, 100-cap pack = £7.35; 500 mg, 100-cap pack = £12.25. Label: 8, 21, 25, counselling, pancreatitis, blood, or hepatic disorder symptoms (see above), driving (see notes above)
Dose epilepsy, ADULT and CHILD over 12 years, initially 600 mg daily in 2–4 divided doses, increased by 300 mg every 3 days to max. 2.5 g daily, usual maintenance dose 1–2 g daily (20–30 mg/kg daily); CHILD body-weight up to 20 kg, initially 20 mg/kg daily in 2–4 divided doses, increased according to response (dose above 40 mg/kg daily monitor clinical chemistry and haematological parameters); CHILD body-weight over 20 kg, initially 300 mg daily in 2–4 divided doses increased according to response (usual range 20–30 mg/kg daily); max. 35 mg/kg daily
Equivalence to sodium valproate *Convulex®* has a 1:1 dose relationship with products containing sodium valproate, but nevertheless care is needed if switching

Depakote® (Sanofi-Aventis) PoM
Section 4.2.3 (bipolar disorder)

Vigabatrin

Vigabatrin can be prescribed in combination with other antiepileptic treatment for focal epilepsy with or without secondary generalisation. It should not be prescribed unless all other appropriate drug combinations are ineffective or have not been tolerated, and it should be initiated and supervised by an appropriate specialist. Vigabatrin can be prescribed as monotherapy in the management of infantile spasms in West's syndrome.

About one-third of patients treated with vigabatrin have suffered visual field defects; counselling and **careful monitoring** for this side-effect are required (see also Visual Field Defects under Cautions below). Vigabatrin has prominent behavioural side-effects in some patients.

VIGABATRIN

Indications see notes above

Cautions elderly; closely monitor neurological function; avoid sudden withdrawal (taper off over 2–4 weeks); history of psychosis, depression or behavioural problems; absence seizures (may be exacerbated); **interactions:** see p. 279 and Appendix 1 (vigabatrin)
Visual field defects Vigabatrin is associated with visual field defects. The onset of symptoms varies from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation, and further deterioration after discontinuation cannot be excluded. Product literature advises visual field testing before treatment and at 6-month intervals. Patients should be warned to report any new visual symptoms that develop and those with symptoms should be referred for an urgent ophthalmological opinion. Gradual withdrawal of vigabatrin should be considered.

Contra-indications visual field defects

Renal impairment consider reduced dose or increased dose interval if eGFR less than 60 mL/minute/1.73 m^2

Pregnancy see Pregnancy, p. 280

Breast-feeding present in milk—manufacturer advises avoid; see also Breast-feeding, p. 280

Side-effects nausea, abdominal pain; oedema; drowsiness (*rarely* encephalopathic symptoms including marked sedation, stupor, and confusion with non-specific slow wave EEG—reduce dose or withdraw), fatigue, excitation (in children), agitation, dizziness, headache, nervousness, depression, aggression, irritability, paranoia, impaired concentration, impaired memory, tremor, paraesthesia, speech disorder, weight gain; visual field defects (see under Cautions), blurred vision, nystagmus, diplopia; *less commonly* ataxia, psychosis, mania, and rash; occasional increase in seizure frequency (especially if myoclonic); *rarely* suicidal ideation and retinal disorders (including peripheral retinal neuropathy); *very rarely* hepatitis, optic neuritis, and optic atrophy; *also reported* movement disorders in infantile spasms

Dose

- With current antiepileptic therapy, initially 1 g daily in single or 2 divided doses then increased according to response in steps of 500 mg at weekly intervals; usual range 2–3 g daily (max. 3 g daily); CHILD initially 40 mg/kg daily in single or 2 divided doses then adjusted according to body-weight 10–15 kg, 0.5–1 g daily; body-weight 15–30 kg, 1–1.5 g daily; body-weight 30–50 kg, 1.5–3 g daily; body-weight over 50 kg, 2–3 g daily

- Infantile spasms (West's syndrome), *monotherapy*, 50 mg/kg daily, adjusted according to response over 7 days; up to 150 mg/kg daily used with good tolerability

Sabril® (Sanofi-Aventis) PoM

Tablets, f/c, scored, vigabatrin 500 mg, net price 100-tab pack = £30.84. Label: 3, 8, counselling, driving (see notes above)

Powder, sugar-free, vigabatrin 500 mg/sachet. Net price 50-sachet pack = £17.08. Label: 3, 8, 13, counselling, driving (see notes above)

Note The contents of a sachet should be dissolved in water or a soft drink immediately before taking

Zonisamide

Zonisamide can be used as adjunctive treatment for refractory focal seizures with or without secondary generalisation.

ZONISAMIDE

Indications see notes above

Cautions elderly; ensure adequate hydration (especially if predisposition to nephrolithiasis or in strenuous activity or warm environment); concomitant use of drugs that increase risk of hyperthermia or nephrolithiasis; metabolic acidosis (consider dose reduction or discontinuation); avoid abrupt withdrawal; **interactions:** see p. 279 and Appendix 1 (zonisamide)

Contra-indications hypersensitivity to sulfonamides

Hepatic impairment initially increase dose at 2-week intervals if mild or moderate impairment; avoid in severe impairment

Renal impairment initially increase dose at 2-week intervals; discontinue if renal function deteriorates

Pregnancy see Pregnancy, p. 280

Breast-feeding manufacturer advises avoid for 4 weeks after administration; see also Breast-feeding, p. 280

Side-effects nausea, diarrhoea, abdominal pain, constipation, dyspepsia, anorexia, weight loss; drowsiness, dizziness, confusion, agitation, irritability, depression, psychosis, ataxia, speech disorder, impaired memory and attention, fatigue, nystagmus, paraesthesia, tremor, pyrexia, insomnia; diplopia; ecchymosis; rash (consider withdrawal); *less commonly* vomiting, cholelithiasis, cholecystitis, aggression, suicidal ideation, seizures, pneumonia, urinary tract infection, urinary calculus, and hypokalaemia; *very rarely* hepatitis, pancreatitis, aspiration, dyspnoea, hallucinations, amnesia, coma, myasthenic syndrome, neuroleptic malignant syndrome, heat stroke, hydronephrosis, renal failure, metabolic acidosis, renal tubular acidosis, blood disorders, rhabdomyolysis, impaired sweating, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

- ADULT over 18 years, initially 50 mg daily in 2 divided doses, increased after 7 days to 100 mg daily in 2 divided doses; then increase if necessary by 100 mg every 7 days; usual maintenance 300–500 mg daily in 1–2 divided doses

Zonegran® (Eisai) ▼ PoM

Capsules, zonisamide 25 mg (white), net price 14-cap pack = £8.82; 50 mg (white/grey), 56-cap pack = £47.04; 100 mg (white/red), 56-cap pack = £62.72. Label: 3

Benzodiazepines

Clobazam may be used as adjunctive therapy in the treatment of epilepsy. **Clonazepam** is occasionally used in tonic-clonic or focal seizures, but its sedative side-effects may be prominent.

The effectiveness of clobazam and clonazepam may decrease significantly after weeks or months of continuous therapy.

CLOBAZAM

Indications adjunct in epilepsy; anxiety (short-term use)

Cautions see Diazepam, section 4.1.2

Contra-indications see Diazepam, section 4.1.2

Hepatic impairment see Benzodiazepines, section 4.1.2

Renal impairment see Benzodiazepines, section 4.1.2

Pregnancy see Benzodiazepines, section 4.1.2

Breast-feeding see Benzodiazepines, section 4.1.2

Side-effects see Diazepam, section 4.1.2

Dose

- Epilepsy, 20–30 mg daily; max. 60 mg daily; CHILD over 3 years, not more than half adult dose
- Anxiety, 20–30 mg daily in divided doses or as a single dose at bedtime, increased in severe anxiety (in hospital patients) to a max. of 60 mg daily in divided doses; ELDERLY (or debilitated) 10–20 mg daily

[1] **Clobazam** (Non-proprietary) PoM NHS

Tablets, clobazam 10 mg. Net price 30-tab pack = £4.68. Label: 2 or 19, 8, counselling, driving (see notes above)

Brands include *Frisium®* NHS

1. NHS except for epilepsy and endorsed 'SLS'

CLONAZEPAM

Indications all forms of epilepsy; myoclonus; status epilepticus (section 4.8.2)

Cautions see notes above; elderly and debilitated, respiratory disease, spinal or cerebellar ataxia; history of alcohol or drug abuse, depression or suicidal ideation; avoid sudden withdrawal; myasthenia gravis (avoid if unstable); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome; marked neuromuscular respiratory weakness including unstable myasthenia gravis

Hepatic impairment see Benzodiazepines, section 4.1.2

Renal impairment see Benzodiazepines, section 4.1.2

Pregnancy see Benzodiazepines, section 4.1.2

Breast-feeding see Benzodiazepines, section 4.1.2

Side-effects drowsiness, fatigue, dizziness, muscle hypotonia, co-ordination disturbances; also poor concentration, restlessness, confusion, amnesia, dependence, and withdrawal; salivary or bronchial hypersecretion in infants and small children; *rarely* gastro-intestinal symptoms, respiratory depression, headache, paradoxical effects including aggression and anxiety, sexual dysfunction, urinary incontinence, urticaria, pruritus, reversible hair loss, skin pigmentation changes; dysarthria, and visual disturbances on long-term treatment; blood disorders reported; suicidal ideation; **overdosage:** see Emergency Treatment of Poisoning, p. 37

Dose

- 1 mg (ELDERLY 500 micrograms) initially at night for 4 nights, increased according to response over 2–4 weeks to usual maintenance dose of 4–8 mg usually at night (may be given in 3–4 divided doses if necessary); CHILD up to 1 year, initially 250 micrograms increased as above to usual maintenance dose of 0.5–1 mg, 1–5 years, initially 250 micrograms increased as above to 1–3 mg, 5–12 years, initially 500 micrograms increased as above to 3–6 mg
  Note Clonazepam doses in BNF may differ from those in product literature

Rivotril® (Roche) PoM

Tablets, both scored, clonazepam 500 micrograms (beige), net price 100-tab pack = £3.69; 2 mg (white), 100-tab pack = £4.93. Label: 2, 8, counselling, driving (see notes above)

Injection, section 4.8.2

Other drugs

Acetazolamide (section 11.6), a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation. It can also be used with other antiepileptics for refractory tonic-clonic, absence, and focal seizures. It is occasionally helpful in atypical absence, atonic, and tonic seizures.

Piracetam (section 4.9.3) is used as adjunctive treatment for cortical myoclonus.

4.8.2 Drugs used in status epilepticus

Convulsive status epilepticus Immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral **thiamine** should be considered if alcohol abuse is suspected; **pyridoxine** (section 9.6.2) should be given if the status epilepticus is caused by pyridoxine deficiency.

Convulsive status epilepticus should be treated urgently with intravenous **lorazepam**, repeated once after 10 minutes if seizures recur or fail to respond. Intravenous diazepam is effective but it carries a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. **Clonazepam** can also be used as an alternative.

Where facilities for resuscitation are not immediately available, **diazepam** can be administered as a rectal solution or **midazolam** [unlicensed use] can be given into the buccal cavity.

> **Important**
> If, after initial treatment with benzodiazepines, seizures recur or fail to respond 20 minutes after onset, phenytoin sodium, fosphenytoin, or phenobarbital sodium should be used; contact intensive care unit if seizures continue at 30 minutes after onset.
> If these measures fail to control seizures 40 minutes after onset, anaesthesia with thiopental (section 15.1.1), midazolam (section 15.1.4), or in adults, a non-barbiturate anaesthetic such as propofol [unlicensed indication] (section 15.1.1), should be instituted with full intensive care support.

Phenytoin sodium may be given by slow intravenous injection, followed by the maintenance dosage if appropriate; monitor ECG and blood pressure and reduce rate of administration if bradycardia or hypotension occurs. Intramuscular use of phenytoin is not recommended (absorption is slow and erratic).

Alternatively, **fosphenytoin**, a pro-drug of phenytoin, can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin. Intravenous administration requires ECG monitoring. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin should be expressed in terms of phenytoin sodium.

Paraldehyde also remains a valuable drug. Given rectally it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

For advice on the management of epileptic seizures in dental practice, see p. 27.

Non-convulsive status epilepticus The urgency to treat non-convulsive status epilepticus depends upon the severity of the patient's condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

CLONAZEPAM

Indications status epilepticus; other forms of epilepsy, and myoclonus (section 4.8.1)

Cautions see Clonazepam, section 4.8.1; facilities for reversing respiratory depression with mechanical ventilation must be at hand (but see also notes above)
Intravenous infusion Intravenous infusion of clonazepam is potentially hazardous (especially if prolonged), calling for close and constant observation and best carried out in specialist centres with intensive care facilities. Prolonged infusion may lead to accumulation and delay recovery

Contra-indications see Clonazepam, section 4.8.1; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Hepatic impairment see Benzodiazepines, section 4.1.2

Renal impairment see Benzodiazepines, section 4.1.2

Pregnancy see Benzodiazepines, section 4.1.2, and Pregnancy, p. 280

Breast-feeding see Benzodiazepines, section 4.1.2

Side-effects see Clonazepam, section 4.8.1; hypotension and apnoea

Dose

- By intravenous injection into a large vein (over at least 2 minutes) *or* by intravenous infusion, 1 mg, repeated if necessary; CHILD all ages, 500 micrograms

Rivotril® (Roche) PoM

Injection, clonazepam 1 mg/mL in solvent, for dilution with 1 mL water for injections immediately before injection or as described in Appendix 6. Net price 1-mL amp (with 1 mL water for injections) = 60p

Excipients include benzyl alcohol (avoid in neonates unless there is no safer alternative available, see Excipients, p. 2), ethanol, propylene glycol

Oral preparations

Section 4.8.1

DIAZEPAM

Indications status epilepticus; febrile convulsions (section 4.8.3); convulsions due to poisoning (see p. 33); other indications (section 4.1.2, section 10.2.2, and section 15.1.4.1)

Cautions see Diazepam, section 4.1.2; when given intravenously facilities for reversing respiratory depression with mechanical ventilation must be at hand (but see also notes above)

Contra-indications see Diazepam, section 4.1.2

Hepatic impairment see Benzodiazepines, section 4.1.2

Renal impairment see Benzodiazepines, section 4.1.2

Pregnancy see Benzodiazepines, section 4.1.2, and Pregnancy, p. 280

Breast-feeding see Benzodiazepines, section 4.1.2

Side-effects see Diazepam, section 4.1.2; hypotension and apnoea

Dose

- Status epilepticus (but see notes above), febrile convulsions, and convulsions due to poisoning, by intravenous injection, 10 mg at a rate of 1 mL (5 mg) per minute, repeated once after 10 minutes if necessary; CHILD under 12 years, 300–400 micrograms/kg (max. 10 mg) [unlicensed dose], repeated once after 10 minutes if necessary

  By rectum as rectal solution, ADULT and CHILD over 12 years, 10–20 mg, repeated once after 10–15 minutes if necessary; ELDERLY 10 mg; NEONATE [unlicensed] 1.25–2.5 mg; CHILD 1 month–1 year [unlicensed] 5 mg; 1–2 years 5 mg; 2–12 years 5–10 mg

Diazepam (Non-proprietary) PoM

Injection (solution), diazepam 5 mg/mL. See Appendix 6. Net price 2-mL amp = 45p

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2), ethanol, propylene glycol

Injection (emulsion), diazepam 5 mg/mL (0.5%). See Appendix 6. Net price 2-mL amp = 91p

Brands include *Diazemuls®*

Rectal tubes (= rectal solution), diazepam 2 mg/mL, net price 1.25-mL (2.5-mg) tube = 90p, 2.5-mL (5-mg) tube = £1.41; 4 mg/mL, 2.5-mL (10-mg) tube = £1.88

Brands include *Diazepam Rectubes®*, *Stesolid®*

Oral preparations

Section 4.1.2

FOSPHENYTOIN SODIUM

Note Fosphenytoin is a pro-drug of phenytoin

Indications status epilepticus; seizures associated with neurosurgery or head injury; when phenytoin by mouth not possible

Cautions see Phenytoin Sodium; resuscitation facilities must be available; **interactions:** see p. 279 and Appendix 1 (phenytoin)

Contra-indications see Phenytoin Sodium

Hepatic impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Renal impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Pregnancy see Phenytoin, section 4.8.1, and Pregnancy, p. 280

Breast-feeding see Phenytoin, section 4.8.1

Side-effects see Phenytoin Sodium; also dry mouth, taste disturbance, vasodilatation, asthenia, euphoria, incoordination; chills; visual disturbances; tinnitus; pruritus, ecchymosis; *less commonly* dysarthria, hypoaesthesia, increased or decreased reflexes, stupor, muscle weakness, pain, and hypoacusis; *also reported* extrapyraidal disorder, twitching, confusion, hyperglycaemia

Important Intravenous infusion of fosphenytoin has been associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia and heart block have also been reported. The following are recommended:

- monitor heart rate, blood pressure, and respiratory function for duration of infusion;
- observe patient for at least 30 minutes after infusion;
- if hypotension occurs, reduce infusion rate or discontinue;
- reduce dose or infusion rate in elderly, and in renal or hepatic impairment.

Dose

Note Prescriptions for fosphenytoin sodium should state the dose in terms of phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg ≡ phenytoin sodium 1 mg

- Status epilepticus, by intravenous infusion (at a rate of 100–150 mg(PE)/minute), initially 20 mg(PE)/kg then by intravenous infusion (at a rate of 50–100 mg(PE)/minute), 4–5 mg(PE)/kg daily in 1–2 divided doses, dose adjusted according to response and trough plasma-phenytoin concentration

  CHILD 5 years and over, by intravenous infusion (at a rate of 2–3 mg(PE)/kg/minute), initially 20 mg(PE)/kg then by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute), 4–5 mg(PE)/kg daily in 1–4 divided doses, dose adjusted according to response and trough plasma-phenytoin concentration
- Prophylaxis or treatment of seizures associated with neurosurgery or head injury, by intramuscular injection *or* by intravenous infusion (at a rate of 50–100 mg(PE)/minute), initially 10–15 mg(PE)/kg then by intramuscular injection *or* by intravenous infusion (at a rate of 50–100 mg(PE)/minute), 4–5 mg(PE)/kg daily (in 1–2 divided doses), dose adjusted according to response and trough plasma-phenytoin concentration

  CHILD 5 years and over, by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute), initially 10–15 mg(PE)/kg then 4–5 mg(PE)/kg daily in 1–4

divided doses, dose adjusted according to response and trough plasma-phenytoin concentration

- Temporary substitution for oral phenytoin, by intramuscular injection *or* by intravenous infusion (at a rate of 50–100 mg(PE)/minute), same dose and dosing frequency as oral phenytoin therapy; CHILD 5 years and over, by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute, max. 100 mg(PE)/minute), same dose and dosing frequency as oral phenytoin therapy

Note ELDERLY consider 10–25% reduction in dose or infusion rate

Note Fosphenytoin sodium doses in BNF may differ from those in product literature

Pro-Epanutin® (Pfizer) PoM

Injection, fosphenytoin sodium 75 mg/mL (equivalent to phenytoin sodium 50 mg/mL), net price 10-mL vial = £40.00

Electrolytes phosphate 3.7 micromol/mg fosphenytoin sodium (phosphate 5.6 micromol/mg phenytoin sodium)

LORAZEPAM

Indications status epilepticus; febrile convulsions (section 4.8.3); convulsions due to poisoning (see p. 33); other indications (section 4.1.2 and section 15.1.4.1)

Cautions see Diazepam, section 4.1.2

Contra-indications see Diazepam, section 4.1.2

Hepatic impairment see Benzodiazepines, section 4.1.2

Renal impairment see Benzodiazepines, section 4.1.2

Pregnancy see Benzodiazepines, section 4.1.2, and Pregnancy, p. 280

Breast-feeding see Benzodiazepines, section 4.1.2

Side-effects see Diazepam, section 4.1.2

Dose

- By slow intravenous injection (into large vein), 4 mg repeated once after 10 minutes if necessary; CHILD under 12 years 100 micrograms/kg (max. 4 mg) repeated once after 10 minutes if necessary

Preparations

Section 4.1.2

MIDAZOLAM

Indications status epilepticus [unlicensed indication]; febrile convulsions [unlicensed] (section 4.8.3); other indications (section 15.1.4.1)

Cautions see Midazolam, section 15.1.4.1

Contra-indications see Midazolam, section 15.1.4.1

Hepatic impairment see Midazolam, section 15.1.4.1

Renal impairment see Midazolam, section 15.1.4.1

Pregnancy see Midazolam, section 15.1.4.1, and Pregnancy, p. 280

Breast-feeding see Midazolam, section 15.1.4.1

Side-effects see Midazolam, section 15.1.4.1

Dose

- By buccal administration [unlicensed], ADULT and CHILD over 10 years, 10 mg repeated once after 10 minutes if necessary; CHILD up to 6 months, 300 micrograms/kg (max. 2.5 mg); 6 months–1 year, 2.5 mg; 1–5 years, 5 mg; 5–10 years, 7.5 mg

Note Midazolam injection solution may be given by buccal administration

Midazolam (Non-proprietary) CD

Buccal liquid, midazolam 10 mg/mL

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Injection

Section 15.1.4

PARALDEHYDE

Indications status epilepticus

Cautions bronchopulmonary disease; **interactions:** Appendix 1 (paraldehyde)

Contra-indications gastric disorders; rectal administration in colitis

Hepatic impairment use with caution

Pregnancy avoid unless essential—crosses the placenta

Breast-feeding avoid unless essential—present in milk

Side-effects rashes

Dose

- By rectum (doses expressed as undiluted paraldehyde), ADULT 20 mL as a single dose; NEONATE 0.4 mL/kg; CHILD 1 month–18 years 0.4 mL/kg (max. 10 mL) as a single dose

Administration for *rectal administration*, do not administer paraldehyde undiluted

Paraldehyde (Non-proprietary) PoM

Enema, 8–50%, available from 'special-order' manufacturers or specialist importing companies, see p. 988

PHENOBARBITAL SODIUM

(Phenobarbitone sodium)

Indications status epilepticus; other forms of epilepsy except absence seizures (section 4.8.1)

Cautions see Phenobarbital, section 4.8.1; **interactions:** see p. 279 and Appendix 1 (phenobarbital)

Hepatic impairment see Phenobarbital, section 4.8.1

Renal impairment see Phenobarbital, section 4.8.1

Pregnancy see Pregnancy, p. 280

Breast-feeding see Phenobarbital, section 4.8.1

Side-effects see Phenobarbital, section 4.8.1

Dose

- Status epilepticus, by intravenous injection (dilute injection 1 in 10 with water for injections), 10 mg/kg at a rate of not more than 100 mg/minute; max. 1 g

Note For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect

Phenobarbital (Non-proprietary) CD

Injection, phenobarbital sodium 200 mg/mL, net price 1-mL amp = £2.00

Excipients include propylene glycol 90% (see Excipients, p. 2)

Note Must be diluted before intravenous administration (see under Dose)

Oral preparations

Section 4.8.1

PHENYTOIN SODIUM

Indications status epilepticus; seizures in neurosurgery

Cautions see notes above; respiratory depression; hypotension and heart failure; resuscitation facilities must be available; injection solutions alkaline (irritant to tissues); see also p. 288; **interactions:** see p. 279 and Appendix 1 (phenytoin)

Contra-indications sinus bradycardia, sino-atrial block, and second- and third-degree heart block; Stokes-Adams syndrome; acute porphyria (section 9.8.2)

Hepatic impairment see Phenytoin, section 4.8.1

Pregnancy see Phenytoin, section 4.8.1, and Pregnancy, p. 280

Breast-feeding see Phenytoin, section 4.8.1

Side-effects intravenous injection may cause cardiovascular and CNS depression (particularly if injection too rapid) with arrhythmias, hypotension, and cardiovascular collapse; alterations in respiratory function (including respiratory arrest); *also reported* tonic seizures, purple glove syndrome; see also p. 288

Dose

- By slow intravenous injection *or* infusion (with blood pressure and ECG monitoring), status epilepticus, 20 mg/kg at a rate not exceeding 50 mg per minute, as a loading dose (see also notes above); maintenance doses of about 100 mg should be given thereafter at intervals of every 6–8 hours, monitored by measurement of plasma concentrations; rate and dose reduced according to weight; CHILD 20 mg/kg as a loading dose (NEONATE 20 mg/kg at rate of 1–3 mg/kg/minute)

  Note To avoid local venous irritation each injection or infusion should be preceded and followed by an injection of sterile physiological saline through the same needle or catheter

  Note Phenytoin sodium doses in BNF may differ from those in product literature

Phenytoin (Non-proprietary) PoM

Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £3.40

Epanutin® Ready-Mixed Parenteral (Pfizer) PoM

Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £4.88

Electrolytes 1.1 mmol Na^+ per 5 mL ampoule

Oral preparations

Section 4.8.1

4.8.3 Febrile convulsions

Brief febrile convulsions need no specific treatment; antipyretic medication, e.g. **paracetamol** (section 4.7.1) is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. *Prolonged febrile convulsions* (those lasting 5 minutes or longer), *recurrent convulsions*, or those occurring in a child at known risk must be treated more actively, as there is the possibility of resulting brain damage. **Diazepam** is the drug of choice given either by slow intravenous injection or preferably rectally in solution (section 4.8.2). The rectal route is preferred as satisfactory absorption is achieved within minutes and administration is much easier. Suppositories are not suitable because absorption is too slow.

Intermittent prophylaxis (i.e. the anticonvulsant administered at the onset of fever) is possible in only a small proportion of children. Again **diazepam** is the treatment of choice, orally or rectally.

Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated. Anticonvulsant treatment needs to be considered only for children at risk from prolonged or complex febrile convulsions, including those whose first seizure occurred at under 14 months or who have neurological abnormalities or who have had previous prolonged or focal convulsions.

4.9 Drugs used in parkinsonism and related disorders

4.9.1 Dopaminergic drugs used in Parkinson's disease
4.9.2 Antimuscarinic drugs used in parkinsonism
4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Parkinson's disease

In idiopathic Parkinson's disease, the progressive degeneration of pigmented neurones in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. The resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness. Drug therapy does not prevent disease progression, but it improves most patients' quality of life.

Patients with suspected Parkinson's disease should be referred to a specialist to confirm the diagnosis; the diagnosis should be reviewed every 6–12 months.

Features resembling those of Parkinson's disease can occur in diseases such as progressive supranuclear palsy and multiple system atrophy, but they do not normally show a sustained response to the drugs used in the treatment of idiopathic Parkinson's disease.

When initiating treatment, patients should be advised about its limitations and possible side-effects. About 5–10% of patients with Parkinson's disease respond poorly to treatment.

Treatment is usually not started until symptoms cause significant disruption of daily activities. **Levodopa** (p. 302), **non-ergot-derived dopamine-receptor agonists** (p. 298), or **monoamine-oxidase-B inhibitors** (p. 304) can be prescribed for initial treatment in early Parkinson's disease. Therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses. Most patients eventually require levodopa and subsequently develop motor complications.

Elderly Antiparkinsonian drugs can cause confusion in the elderly. It is particularly important to initiate treatment with low doses and to increase the dose gradually.

4.9.1 Dopaminergic drugs used in Parkinson's disease

Dopamine-receptor agonists

The dopamine-receptor agonists, **bromocriptine**, **cabergoline**, **pergolide**, **pramipexole**, **ropinirole**, and **rotigotine** have a direct action on dopamine receptors. Initial treatment of Parkinson's disease is often with dopamine-receptor agonists. They are also used with levodopa in more advanced disease. If a dopamine-receptor agonist is added to levodopa therapy, the dose of levodopa needs to be reduced (see individual monographs).

When used alone, dopamine-receptor agonists cause fewer motor complications in long-term treatment compared with levodopa treatment but the overall motor performance improves slightly less. The dopamine-receptor agonists are associated with more psychiatric side-effects than levodopa. The ergot-derived dopamine-receptor agonists bromocriptine, cabergoline, and pergolide, are associated with fibrotic reactions (see notes below). Patients should be monitored for signs of cardiac fibrosis, before and at regular intervals during treatment with cabergoline or pergolide. Ergot-derived dopamine-receptor agonists should not be used as first-line treatment for Parkinson's disease.

Treatment with dopamine-receptor agonists is associated with impulse control disorders, including pathological gambling, binge eating, and hypersexuality. Patients taking dopamine-receptor agonists, and their carers, should be informed about the risk of impulse control disorders. There is no evidence that ergot- and non-ergot-derived dopamine-receptor agonists differ in their propensity to cause impulse control disorders, so switching between dopamine-receptor agonists to control these side-effects is not recommended. If the patient develops an impulse control disorder, the dopamine-receptor agonist should be discontinued or the dose titrated downwards, until the symptoms resolve.

Apomorphine is a potent dopamine-receptor agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment. Apomorphine should be initiated in a specialist clinic with at least two days pretreatment with domperidone (p. 253) for nausea and vomiting. After an overnight withdrawal of oral antiparkinsonian medication to induce an 'off' episode, the threshold dose of apomorphine is determined. Oral antiparkinsonian medication is then restarted. The patient must be taught to self-administer apomorphine by subcutaneous injection into the lower abdomen or outer thigh at the first sign of an 'off' episode. Once treatment has been established it may be possible to gradually reduce other antiparkinsonian medications and reduce or withdraw domperidone therapy. Treatment with apomorphine should remain under specialist supervision.

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

Fibrotic reactions

Ergot-derived dopamine-receptor agonists, bromocriptine, cabergoline, and pergolide, have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions.

Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson's disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline or pergolide should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

Driving

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa, co-beneldopa, and dopamine-receptor agonists.

Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery. Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped recurring.

Management of excessive daytime sleepiness should focus on the identification of an underlying cause, such as depression or concomitant medication that can disturb sleep. Patients should be counselled on improving sleep behaviour.

Hypotensive reactions Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

APOMORPHINE HYDROCHLORIDE

Indications refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by co-beneldopa or co-careldopa or other dopaminergics (for capable and motivated patients under specialist supervision)

Cautions see notes above; pulmonary disease, cardiovascular disease, history of postural hypotension (special care on initiation); susceptibility to QT-interval prolongation; neuropsychiatric conditions; monitor hepatic, haemopoietic, renal, and cardiovascular function; *with concomitant levodopa* test initially and every 6 months for haemolytic anaemia and thrombocytopenia (development calls for specialist haematological care with dose reduction and possible discontinuation); **interactions:** Appendix 1 (apomorphine)

Contra-indications respiratory depression, dementia, hypersensitivity to opioids, psychosis; avoid if 'on'

response to levodopa marred by severe dyskinesia or dystonia

Hepatic impairment avoid

Renal impairment use with caution

Pregnancy avoid unless clearly necessary

Breast-feeding no information available; may suppress lactation

Side-effects see notes above; also nausea, vomiting (see notes above); yawning; drowsiness (including sudden onset of sleep), confusion, hallucinations; *less commonly* postural hypotension, dyspnoea, dyskinesia during 'on' periods (may require discontinuation), haemolytic anaemia and thrombocytopenia with levodopa (see Cautions), and rash; *rarely* eosinophilia; peripheral oedema, compulsive behaviour, and dizziness also reported

Dose

- By subcutaneous injection, ADULT over 18 years, to determine threshold dose (see also notes above), initially 1 mg at the first sign of 'off' episode; if inadequate or no response after 30 minutes, then a further 2 mg should be given; thereafter increase dose at minimum 40-minute intervals until satisfactory response obtained; usual range 3–30 mg daily in divided doses; subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses daily; max. single dose 10 mg
- By continuous subcutaneous infusion, ADULT over 18 years, (those requiring division into more than 10 injections daily) initially 1 mg/hour increased according to response (not more often than every 4 hours) in max. steps of 500 micrograms/hour, to usual rate of 1–4 mg/hour (15–60 micrograms/kg/hour); change infusion site every 12 hours and give during waking hours only (tolerance may occur unless there is a 4-hour treatment-free period at night—24-hour infusions not recommended unless severe night-time symptoms); intermittent bolus boosts may be needed

Note Total daily dose by either route (or combined routes) max. 100 mg

Apomorphine (Non-proprietary) PoM

Injection, apomorphine hydrochloride 10 mg/mL, net price 2-mL amp = £7.21, 5-mL amp = £13.89. Label: 10, counselling, driving, see notes above

APO-go® (Genus) PoM

Injection, apomorphine hydrochloride 10 mg/mL, net price 2-mL amp = £7.59, 5-mL amp = £14.62. Label: 10, counselling, driving, see notes above
Excipients include sulphites

Injection (APO-go® Pen), apomorphine hydrochloride 10 mg/mL, net price 3-mL pen injector = £24.78. Label: 10, counselling, driving, see notes above
Excipients include sulphites

Injection (APO-go® PFS), apomorphine hydrochloride 5 mg/mL, net price 10-mL prefilled syringe = £14.62. Label: 10, counselling, driving, see notes above
Excipients include sulphites

BROMOCRIPTINE

Indications Parkinson's disease; endocrine disorders (section 6.7.1)

Cautions see Bromocriptine in section 6.7.1 and notes above

Contra-indications see Bromocriptine, section 6.7.1

Hepatic impairment see Bromocriptine, section 6.7.1

Pregnancy see Bromocriptine, section 6.7.1

Breast-feeding see Bromocriptine, section 6.7.1

Side-effects see notes above and Bromocriptine, section 6.7.1

Dose

- First week 1–1.25 mg at night, second week 2–2.5 mg at night, third week 2.5 mg twice daily, fourth week 2.5 mg 3 times daily then increasing by 2.5 mg every 3–14 days according to response to a usual range of 10–30 mg daily; taken with food

Preparations

Section 6.7.1

CABERGOLINE

Indications alone or as adjunct to co-beneldopa or co-careldopa in Parkinson's disease where dopamine-receptor agonists other than ergot derivative not appropriate; endocrine disorders (section 6.7.1)

Cautions see Cabergoline in section 6.7.1 and notes above

Contra-indications see Cabergoline, section 6.7.1

Hepatic impairment see Cabergoline, section 6.7.1

Pregnancy see Cabergoline, section 6.7.1

Breast-feeding see Cabergoline, section 6.7.1

Side-effects see notes above and Cabergoline, section 6.7.1

Dose

- Initially 1 mg daily, increased by increments of 0.5–1 mg at 7 or 14 day intervals; max. 3 mg daily
  Note Concurrent dose of levodopa may be decreased gradually while dose of cabergoline is increased

Cabergoline (Non-proprietary) PoM

Tablets, scored, cabergoline 1 mg, net price 20-tab pack = £59.08; 2 mg, 20-tab pack = £71.13. Label: 10, 21, counselling, driving, see notes above
Note Dispense in original container (contains desiccant)

Cabaser® (Pharmacia) PoM

Tablets, scored, cabergoline 1 mg, net price 20-tab pack = £83.00; 2 mg, 20-tab pack = £83.00. Label: 10, 21, counselling, driving, see notes above
Note Dispense in original container (contains desiccant)

PERGOLIDE

Indications alone or as adjunct to co-beneldopa or co-careldopa in Parkinson's disease where dopamine-receptor agonists other than ergot derivative not appropriate

Cautions see notes above; arrhythmias or underlying cardiac disease; history of confusion, psychosis, or hallucinations, dyskinesia (may exacerbate); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (pergolide)

Contra-indications history of fibrotic disorders; cardiac valvulopathy (exclude before treatment, see Fibrotic Reactions, p. 298)

Pregnancy use only if potential benefit outweighs risk

Breast-feeding may suppress lactation

Side-effects see notes above; also nausea, vomiting, dyspepsia, abdominal pain; dyspnoea, rhinitis; hallucinations, dyskinesia, drowsiness (including sudden onset of sleep); diplopia; also reported constipation,

diarrhoea, hiccups, tachycardia, atrial premature contractions, palpitation, hypotension, syncope, Raynaud's phenomenon, compulsive behaviour, insomnia, confusion, dizziness, fever, erythromelalgia, and rash

Dose

- Monotherapy, 50 micrograms at night on day 1, then 50 micrograms twice daily on days 2–4, then increased by 100–250 micrograms daily every 3–4 days to 1.5 mg daily in 3 divided doses at day 28; after day 30, further increases every 3–4 days of up to 250 micrograms daily; usual maintenance dose 2.1–2.5 mg daily; max. 3 mg daily
- Adjunctive therapy with levodopa, 50 micrograms daily for 2 days, increased gradually by 100–150 micrograms every 3 days over next 12 days, usually given in 3 divided doses; further increases of 250 micrograms every 3 days; max. 3 mg daily; during pergolide titration levodopa dose may be reduced cautiously

Pergolide (Non-proprietary) PoM

Tablets, pergolide (as mesilate) 50 micrograms, net price 100-tab pack = £17.42; 250 micrograms, 100-tab pack = £14.68; 1 mg, 100-tab pack = £41.95. Label: 10, counselling, driving, see notes above

Celance® (Lilly) PoM

Tablets, scored, pergolide (as mesilate) 50 micrograms (ivory), net price 100-tab pack = £20.70; 250 micrograms (green), 100-tab pack = £21.12; 1 mg (pink), 100-tab pack = £43.44. Label: 10, counselling, driving, see notes above

Note Caution if splitting tablets—may cause eye irritation, nasal irritation, and headache

PRAMIPEXOLE

Indications Parkinson's disease, used alone or as an adjunct to co-beneldopa or co-careldopa; moderate to severe restless legs syndrome

Cautions see notes above; psychotic disorders; ophthalmological testing recommended (risk of visual disorders); severe cardiovascular disease; risk of postural hypotension (especially on initiation)—monitor blood pressure; **interactions:** Appendix 1 (pramipexole)

Renal impairment

- for *immediate-release* tablets in Parkinson's disease, initially 88 micrograms twice daily (max. 1.57 mg daily in 2 divided doses) if eGFR 20–50 mL/minute/1.73m^2; initially 88 micrograms once daily (max. 1.1 mg once daily) if eGFR less than 20 mL/minute/1.73 m^2; if renal function declines during treatment, reduce dose by the same percentage as the decline in eGFR
- for *immediate-release* tablets in restless legs syndrome, reduce dose if eGFR less than 20 mL/minute/1.73 m^2
- for *modified-release* tablets, initially 260 micrograms on alternate days if eGFR 30–50 mL/minute/1.73m^2, increased to 260 micrograms once daily after 1 week, further increased if necessary by 260 micrograms daily at weekly intervals to max. 1.57 mg daily; avoid if eGFR less than 30 mL/minute/1.73m^2

Pregnancy use only if potential benefit outweighs risk—no information available

Breast-feeding may suppress lactation; avoid—present in milk in *animal* studies

Side-effects see notes above; also nausea, constipation, vomiting, weight changes, hypotension (including postural hypotension), peripheral oedema, dizziness, dyskinesia, drowsiness (including sudden onset of sleep), amnesia, headache, sleep disturbances, confusion, hallucinations, restlessness, visual disturbances; *less commonly* syncope, pneumonia, dyspnoea, compulsive behaviour, delusion, paranoia, pruritus, rash; *also reported* paradoxical worsening of restless legs syndrome

Dose

Important Doses and strengths are stated in terms of pramipexole (base); equivalent strengths in terms of pramipexole dihydrochloride monohydrate (salt) are as follows:
88 micrograms base ≡ 125 micrograms salt;
180 micrograms base ≡ 250 micrograms salt;
350 micrograms base ≡ 500 micrograms salt;
700 micrograms base ≡ 1 mg salt

- Parkinson's disease, ADULT over 18 years, initially 88 micrograms 3 times daily, dose doubled every 5–7 days if tolerated to 350 micrograms 3 times daily; further increased if necessary by 180 micrograms 3 times daily at weekly intervals; max. 3.3 mg daily in 3 divided doses

  Note During dose titration and maintenance, levodopa dose may be reduced
- Restless legs syndrome, ADULT over 18 years, initially 88 micrograms once daily 2–3 hours before bedtime, dose doubled every 4–7 days if necessary; max. 540 micrograms daily

  Note Repeat dose titration if restarting treatment after an interval of more than a few days

Mirapexin® (Boehringer Ingelheim) PoM

Tablets, pramipexole 88 micrograms, net price 30-tab pack = £9.55; 180 micrograms (scored), 30-tab pack = £19.10, 100-tab pack = £63.67; 350 micrograms (scored), 30-tab pack = £38.20, 100-tab pack = £127.34; 700 micrograms (scored), 30-tab pack = £76.40, 100-tab pack = £254.69. Label: 10, counselling, driving, see notes above

Modified release

Mirapexin® Prolonged Release (Boehringer Ingelheim) PoM

Tablets, m/r, pramipexole 260 micrograms, net price 30-tab pack = £28.65; 520 micrograms, 30-tab pack = £57.30; 1.05 mg, 30-tab pack = £114.60; 1.57 mg, 30-tab pack = £171.90; 2.1 mg, 30-tab pack = £229.20; 2.62 mg, 30-tab pack = £286.50; 3.15 mg, 30-tab pack = £343.80. Label: 10, 25, counselling, driving, see notes above

Important Doses and strengths are stated in terms of pramipexole (base); equivalent strengths in terms of pramipexole dihydrochloride monohydrate (salt) are as follows:
260 micrograms base ≡ 375 micrograms salt;
520 micrograms base ≡ 750 micrograms salt;
1.05 mg base ≡ 1.5 mg salt;
1.57 mg base ≡ 2.25 mg salt;
2.1 mg base ≡ 3 mg salt;
2.62 mg base ≡ 3.75 mg salt;
3.15 mg base ≡ 4.5 mg salt

Dose Parkinson's disease (with or without co-beneldopa or co-careldopa), ADULT over 18 years, initially 260 micrograms once daily, dose doubled every 5–7 days to 1.05 mg once daily; further increased if necessary by 520 micrograms daily at weekly intervals; max. 3.15 mg once daily

Note During dose titration and maintenance, levodopa dose may be reduced

ROPINIROLE

Indications Parkinson's disease, either used alone or as adjunct to co-beneldopa or co-careldopa; moderate to severe restless legs syndrome

Cautions see notes above; severe cardiovascular disease, major psychotic disorders; dose adjustment may be necessary if smoking started or stopped during treatment; **interactions**: Appendix 1 (ropinirole)

Hepatic impairment caution in moderate impairment; avoid in severe impairment

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid unless potential benefit outweighs risk—toxicity in *animal* studies

Breast-feeding may suppress lactation—avoid

Side-effects see notes above; also nausea, vomiting, abdominal pain, dyspepsia, constipation; hypotension; syncope, peripheral oedema; drowsiness (including sudden onset of sleep, see p. 298), dizziness, nervousness, fatigue, dyskinesia, hallucinations, confusion; *less commonly* psychosis, compulsive behaviour; *very rarely* hepatic disorders; *also reported* paradoxical worsening of restless legs syndrome

Dose

- Parkinson's disease, initially 750 micrograms daily in 3 divided doses, increased by increments of 750 micrograms at weekly intervals to 3 mg daily; further increased by increments of up to 3 mg at weekly intervals according to response; usual range 9–16 mg daily (but higher doses may be required if used with levodopa); max. 24 mg daily
  Note When administered as adjunct to levodopa, concurrent dose of levodopa may be reduced by approx. 20%; ropinirole doses in the BNF may differ from those in product literature
- Restless legs syndrome, ADULT over 18 years initially 250 micrograms at night for 2 days, increased if tolerated to 500 micrograms at night for 5 days and then to 1 mg at night for 7 days; further increased at weekly intervals in steps of 500 micrograms daily according to response; usual dose 2 mg at night; max. 4 mg daily
  Note Repeat dose titration if restarting after interval of more than a few days

Ropinirole (Non-proprietary) PoM
Tablets, ropinirole (as hydrochloride) 250 micrograms, net price 12-tab pack = £2.79; 500 micrograms, 28-tab pack = £7.72; 1 mg, 84-tab pack = £27.65; 2 mg, 84-tab pack = £54.43; 5 mg, 84-tab pack = £107.55. Label: 10, 21, counselling, driving, see notes above

Adartrel® (GSK) PoM
Tablets, f/c, ropinirole (as hydrochloride) 250 micrograms (white), net price 12-tab pack = £3.94; 500 micrograms (yellow), 28-tab pack = £15.75, 84-tab pack = £47.26; 2 mg (pink), 28-tab pack = £31.51, 84-tab pack = £94.53. Label: 10, 21, counselling, driving, see notes above
The *Scottish Medicines Consortium* has advised (June 2006) that *Adartrel®* should be restricted for use in patients with a baseline score of 24 points or more on the International Restless Legs Scale

Requip® (GSK) PoM
Tablets, f/c, ropinirole (as hydrochloride) 1 mg (green), net price 84-tab pack = £47.26; 2 mg (pink), 84-tab pack = £94.53; 5 mg (blue), 84-tab pack = £163.27; 28-day starter pack of 42 × 250-microgram (white) tablets, 42 × 500-microgram (yellow) tablets, and 21 × 1-mg (green) tablets = £40.10; 28-day follow-on pack of 42 × 500-microgram (yellow) tablets, 42 × 1-mg (green) tablets, and 63 × 2-mg (pink) tablets = £74.40. Label: 10, 21, counselling, driving, see notes above

Modified release

Requip® XL (GSK) ▼ PoM
Tablets, m/r, f/c, ropinirole (as hydrochloride) 2 mg (pink), net price 28-tab pack = £31.36; 4 mg (brown), 28-tab pack = £62.72; 8 mg (red), 28-tab pack = £105.28. Label: 10, 25, counselling, driving, see notes above

Dose stable Parkinson's disease in patients transferring from ropinirole immediate-release tablets, initially *Requip® XL* once daily substituted for total daily dose equivalent of ropinirole immediate-release tablets; if control not maintained after switching, *in patients receiving less than 8 mg once daily*, increase in steps of 2 mg at intervals of at least 1 week to 8 mg once daily according to response; *in patients receiving 8 mg once daily or more*, increase in steps of 2 mg at intervals of at least 2 weeks according to response; max. 24 mg once daily

Note When administered as adjunct to levodopa, concurrent dose of levodopa may be reduced

ROTIGOTINE

Indications Parkinson's disease, either used alone or as adjunct to co-beneldopa or co-careldopa; moderate to severe restless legs syndrome

Cautions see notes above; ophthalmic testing recommended; avoid exposure of patch to heat; withdraw gradually; **interactions**: Appendix 1 (rotigotine)

Hepatic impairment caution in severe impairment—no information available

Pregnancy avoid—no information available

Breast-feeding may suppress lactation; avoid—present in milk in *animal* studies

Side-effects see notes above; also constipation, dry mouth, dyspepsia, nausea, vomiting, weight changes; hypertension, postural hypotension, palpitation, peripheral oedema; hiccup; asthenia, dizziness, drowsiness (including sudden onset of sleep), sleep disturbances, dyskinesia, hallucinations, headache, syncope, sweating, rash, pruritus; *less commonly* abdominal pain, atrial fibrillation, hypotension, confusion, paranoia, compulsive behaviour, erectile dysfunction, and visual disturbances; *rarely* tachycardia, seizures, irritability, obsessive compulsive disorder, and psychotic disorder

Dose

- Monotherapy in Parkinson's disease, initially apply '2 mg/24 hours' patch, increased in steps of 2 mg/24 hours at weekly intervals if required; max. 8 mg/24 hours
- Adjunctive therapy with levodopa in Parkinson's disease, initially apply '4 mg/24 hours' patch, increased in steps of 2 mg/24 hours at weekly intervals if required; max. 16 mg/24 hours
- Restless legs syndrome, initially apply '1 mg/24 hours' patch, increased in steps of 1 mg/24 hours at weekly intervals if required; max. 3 mg/24 hours

Note Apply patch to dry, non-irritated skin on torso, thigh, or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same area for 14 days)

Neupro® (UCB Pharma) ▼ PoM
Patches, self-adhesive, beige, rotigotine 1 mg/24 hours, net price 28 = £77.24; 2 mg/24 hours, 28 = £77.24; 3 mg/24 hours, 28 = £97.48; 4 mg/24 hours,

28 = £117.71; 6 mg/24 hours, 28 = £142.79; 8 mg/24 hours, 28 = £142.79; 28-day starter pack of 7 × 2 mg/24 hours, 7 × 4 mg/24 hours, 7 × 6 mg/24 hours, and 7 × 8 mg/24 hours patches = £142.79. Label: 10, counselling, driving, see notes above

Note Remove patch (aluminium-containing) before magnetic resonance imaging or cardioversion

Note The *Scottish Medicines Consortium* (p. 4) has advised that *Neupro®* is accepted as monotherapy for the treatment of early-stage idiopathic Parkinson's disease (June 2007) and for restricted use for the treatment of advanced Parkinson's disease in combination with levodopa where the transdermal route would facilitate treatment (July 2007)

Note The *Scottish Medicines Consortium* (p. 4) has advised (April 2009) that rotigotine (*Neupro®*) is accepted for restricted use within NHS Scotland for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome in adults with a baseline score of 15 points or more on the International Restless Legs Scale

Levodopa

Levodopa, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine; it is given with an extracerebral **dopa-decarboxylase inhibitor** that reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as nausea, vomiting and cardiovascular effects. Additionally, effective brain-dopamine concentrations can be achieved with lower doses of levodopa. The extracerebral dopa-decarboxylase inhibitors used with levodopa are benserazide (in **co-beneldopa**) and carbidopa (in **co-careldopa**).

Levodopa, in combination with a dopa-decarboxylase inhibitor, is useful in the elderly or frail, in patients with other significant illnesses, and in those with more severe symptoms. It is effective and well tolerated in the majority of patients.

Levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patient.

Note When co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects.

Nausea and vomiting with co-beneldopa or co-careldopa are rarely dose-limiting but domperidone (section 4.6) may be useful in controlling these effects.

Levodopa treatment is associated with potentially troublesome motor complications including response fluctuations and dyskinesias. Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'End-of-dose' deterioration with progressively shorter duration of benefit also occurs. Modified-release preparations may help with 'end-of-dose' deterioration or nocturnal immobility and rigidity. Motor complications are particularly problematic in young patients treated with levodopa.

Cautions Levodopa should be used with caution in severe pulmonary or cardiovascular disease (including history of myocardial infarction with residual arrhythmia), psychiatric illness (avoid if severe and discontinue if deterioration), endocrine disorders (including hyperthyroidism, Cushing's syndrome, diabetes mellitus, osteomalacia, and phaeochromocytoma), and in those with a history of convulsions or peptic ulcer. Levodopa should be used with caution in patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Patients should be advised to avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), and to be aware of the potential for excessive drowsiness and sudden onset of sleep (see Driving, p. 298); **interactions:** Appendix 1 (levodopa).

Pregnancy Levodopa should be used with caution in pregnancy—toxicity has occurred in *animal* studies.

Breast-feeding Levodopa may suppress lactation. It is present in milk—avoid.

Side-effects Side-effects of levodopa include nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, palpitations, postural hypotension, syncope, drowsiness (see Driving, p. 298), fatigue, dementia, psychosis, confusion, euphoria, abnormal dreams, insomnia, depression (*very rarely* with suicidal ideation), anxiety, dizziness, dystonia, dyskinesia, and chorea.

Less commonly weight changes, constipation, diarrhoea, hypersalivation, dysphagia, flatulence, hypertension, chest pain, oedema, hoarseness, ataxia, hand tremor, malaise, weakness, muscle cramps, and reddish discoloration of the urine and other body fluids may occur. *Rare* side-effects include abdominal pain, gastrointestinal bleeding, duodenal ulcer, dyspepsia, phlebitis, dyspnoea, agitation, paraesthesia, bruxism, trismus, hiccups, neuroleptic malignant syndrome (associated with abrupt withdrawal), convulsions, reduced mental acuity, disorientation, headache, urinary retention, urinary incontinence, priapism, activation of malignant melanoma, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, blurred vision, blepharospasm, diplopia, activation of Horner's syndrome, pupil dilatation, oculogyric crisis, flushing, alopecia, exanthema, Henoch-Schönlein purpura, and sweating; *very rarely* angle-closure glaucoma may occur; compulsive behaviour and false positive tests for urinary ketones have also been reported.

CO-BENELDOPA

A mixture of benserazide hydrochloride and levodopa in mass proportions corresponding to 1 part of benserazide and 4 parts of levodopa

Indications Parkinson's disease, see notes above

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- See preparations

Madopar® (Roche) PoM

Capsules (*Madopar®-62.5* mg), blue/grey, co-beneldopa 12.5/50 (benserazide 12.5 mg (as hydrochloride), levodopa 50 mg), net price 100-cap pack = £4.96. Label: 10, 14, counselling, driving, see notes above

Capsules (*Madopar®-125* mg), blue/pink, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride), levodopa 100 mg), net price 100-cap pack = £6.91. Label: 10, 14, counselling, driving, see notes above

Capsules (*Madopar®-250* mg), blue/caramel, co-beneldopa 50/200 (benserazide 50 mg (as hydrochloride), levodopa 200 mg), net price 100-cap pack = £11.78. Label: 10, 14, counselling, driving, see notes above

Dispersible tablets, scored, co-beneldopa 12.5/50 (benserazide 12.5 mg (as hydrochloride), levodopa 50 mg), net price 100-tab pack = £5.90. Label: 10, 14, counselling, administration, see below, driving, see notes above

Dispersible tablets, scored, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride) levodopa 100 mg), net price 100-tab pack = £10.45. Label: 10, 14, counselling, administration, see below, driving, see notes above

Counselling The dispersible tablets can be dispersed in water or orange squash (not orange juice) or swallowed whole

Dose expressed as levodopa, initially 50 mg 3–4 times daily (100 mg 3 times daily in advanced disease), increased by 100 mg daily once or twice weekly according to response; usual maintenance dose 400–800 mg daily in divided doses; ELDERLY initially 50 mg once or twice daily, increased by 50 mg daily every 3–4 days according to response

Note When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued 12 hours before (although interval can be shorter)

Modified release

Madopar® CR (Roche) PoM

Capsules, m/r, dark green/light blue, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride), levodopa 100 mg), net price 100-cap pack = £12.77. Label: 5, 10, 14, 25, counselling, driving, see notes above

Dose patients not taking levodopa/dopa-decarboxylase inhibitor therapy, initially 1 capsule 3 times daily (max. initial dose 6 capsules daily)

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, initially 1 capsule substituted for every 100 mg of levodopa and given at same dosage frequency, increased every 2–3 days according to response; average increase of 50% needed over previous levodopa dose and titration may take up to 4 weeks

Supplementary dose of immediate-release *Madopar®* may be needed with first morning dose; if response still poor to total daily dose of *Madopar® CR* plus *Madopar®* corresponding to 1.2 g levodopa, consider alternative therapy

CO-CARELDOPA

A mixture of carbidopa and levodopa; the proportions are expressed in the form *x/y* where *x* and *y* are the strengths in milligrams of carbidopa and levodopa respectively

Indications Parkinson's disease, see notes above

Cautions see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- Expressed as levodopa, initially 100 mg (with carbidopa 25 mg) 3 times daily, increased by 50–100 mg (with carbidopa 12.5–25 mg) daily or on alternate days according to response, up to 800 mg (with carbidopa 200 mg) daily in divided doses
- Alternatively, initially 50–100 mg (with carbidopa 10–12.5 mg) 3–4 times daily, increased by 50–100 mg daily or on alternate days according to response, up to 800 mg (with carbidopa 80–100 mg) daily in divided doses
- Alternatively, initially 125 mg (with carbidopa 12.5 mg, as ½ tablet of co-careldopa 25/250) 1–2 times daily, increased by 125 mg (with carbidopa 12.5 mg) daily or on alternate days according to response

Note At least 70 mg carbidopa daily is necessary to achieve full inhibition of peripheral dopa-decarboxylase. When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued at least 12 hours before

Co-careldopa (Non-proprietary) PoM

Tablets, co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £7.30. Label: 10, 14, counselling, driving, see notes above

Tablets, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £24.45. Label: 10, 14, counselling, driving, see notes above

Tablets, co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 100-tab pack = £34.58. Label: 10, 14, counselling, driving, see notes above

Sinemet® (MSD) PoM

Tablets (*Sinemet®-62.5*), yellow, scored, co-careldopa 12.5/50 (carbidopa 12.5 mg (anhydrous), levodopa 50 mg), net price 90-tab pack = £6.28. Label: 10, 14, counselling, driving, see notes above

Note 2 tablets *Sinemet®-62.5* ≡ 1 tablet *Sinemet Plus®*

Tablets (*Sinemet®-110*), blue, scored, co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £6.57. Label: 10, 14, counselling, driving, see notes above

Tablets (*Sinemet®-Plus*), yellow, scored, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £9.66. Label: 10, 14, counselling, driving, see notes above

Note Co-careldopa 25/100 provides an adequate dose of carbidopa when low doses of levodopa are needed

Tablets (*Sinemet®-275*), blue, scored, co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 90-tab pack = £13.72. Label: 10, 14, counselling, driving, see notes above

For use with enteral tube

Duodopa® (Abbott Healthcare) ▼ PoM

Intestinal gel, co-careldopa 5/20 (carbidopa 5 mg as monohydrate, levodopa 20 mg)/mL, net price 100 mL cassette (for use with *Duodopa®* portable pump) = £77.00. Label: 10, 14, counselling, driving, see notes above

Dose severe Parkinson's disease inadequately controlled by other preparations, consult product literature

Modified release

Caramet® CR (TEVA UK) PoM

Tablets, m/r, orange-brown, co-careldopa 25/100 (carbidopa 25 mg (as monohydrate), levodopa 100 mg), net price 60-tab pack = £11.47; co-careldopa 50/200 (carbidopa 50 mg (as monohydrate), levodopa 200 mg), 60-tab pack = £11.47. Label: 10, 14, 25, counselling, driving, see notes above

Dose patients not receiving levodopa/dopa-decarboxylase inhibitor preparations, expressed as levodopa, initially 100–200 mg twice daily (at least 6 hours between doses); dose adjusted according to response at intervals of at least 2 days

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, discontinue previous preparation at least 12 hours before first dose of *Caramet® CR*; substitute *Caramet® CR* to provide a similar amount of levodopa daily and extend dosing interval by 30–50%; dose then adjusted according to response at intervals of at least 2 days

Half Sinemet® CR (MSD) PoM

Tablets, m/r, pink, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 60-tab pack = £11.60. Label: 10, 14, 25, counselling, driving, see notes above

Dose for fine adjustment of *Sinemet® CR* dose (see below)

Sinemet® CR (MSD) PoM

Tablets, m/r, peach, scored, co-careldopa 50/200 (carbidopa 50 mg (anhydrous), levodopa 200 mg), net price 60-tab pack = £11.60. Label: 10, 14, 25, counselling, driving, see notes above

Dose patients not receiving levodopa/dopa-decarboxylase inhibitor therapy, initially, 1 *Sinemet® CR* tablet twice daily; both dose and interval then adjusted according to response at intervals of not less than 3 days

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, 1 *Sinemet® CR* tablet twice daily can be substituted for a daily dose of levodopa 300–400 mg in immediate-release *Sinemet®* tablets (substitute *Sinemet® CR* to provide approx. 10% more levodopa per day and extend dosing interval by 30–50%); dose and interval then adjusted according to response at intervals of not less than 3 days

With entacapone

For Parkinson's disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

Stalevo® (Orion) PoM

Tablets, f/c, brown, levodopa 50 mg, carbidopa 12.5 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 10 tablets daily

Tablets, f/c, brown, levodopa 75 mg, carbidopa 18.75 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 10 tablets daily

Tablets, f/c, brown, levodopa 100 mg, carbidopa 25 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 10 tablets daily

Tablets, f/c, brown, levodopa 125 mg, carbidopa 31.25 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 10 tablets daily

Tablets, f/c, brown, levodopa 150 mg, carbidopa 37.5 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 10 tablets daily

Tablets, f/c, brown, levodopa 200 mg, carbidopa 50 mg, entacapone 200 mg, net price 30-tab pack = £20.79, 100-tab pack = £69.31. Label: 10, 14 (urine reddish-brown), 25, counselling, driving, see notes above

Dose only 1 tablet to be taken for each dose; max. 7 tablets daily

Note Patients receiving standard-release co-careldopa or co-beneldopa alone, initiate *Stalevo®* at a dose that provides similar (or slightly lower) amount of levodopa

Patients with dyskinesia or receiving more than 800 mg levodopa daily, introduce entacapone before transferring to *Stalevo®* (levodopa dose may need to be reduced by 10–30% initially)

Patients receiving entacapone and standard-release co-careldopa or co-beneldopa, initiate *Stalevo®* at a dose that provides similar (or slightly higher) amount of levodopa

Monoamine-oxidase-B inhibitors

Rasagiline, a monoamine-oxidase-B inhibitor, is licensed for the management of Parkinson's disease used alone or as an adjunct to levodopa for 'end-of-dose' fluctuations.

Selegiline is a monoamine-oxidase-B inhibitor used in conjunction with levodopa to reduce 'end-of-dose' deterioration in advanced Parkinson's disease. Early treatment with selegiline alone can delay the need for levodopa therapy. When combined with levodopa, selegiline should be avoided or used with great caution in postural hypotension.

RASAGILINE

Indications Parkinson's disease, used alone or as adjunct to co-beneldopa or co-careldopa

Cautions avoid abrupt withdrawal; **interactions:** Appendix 1 (rasagiline)

Hepatic impairment use with caution in mild impairment; avoid in moderate to severe impairment

Pregnancy use with caution

Breast-feeding use with caution—may suppress lactation

Side-effects dry mouth, dyspepsia, constipation, flatulence; angina; headache, depression, anorexia, weight loss, abnormal dreams, vertigo, hallucinations; influenza-like symptoms; urinary urgency; leucopenia; arthralgia; conjunctivitis; rhinitis; rash, skin carcinoma; *less commonly* myocardial infarction, and cerebrovascular accident

Dose

- 1 mg daily

Azilect® (Teva) PoM

Tablets, rasagiline (as mesilate) 1 mg, net price 28-tab pack = £70.72

SELEGILINE HYDROCHLORIDE

Indications Parkinson's disease, used alone or as adjunct to co-beneldopa or co-careldopa

Cautions avoid abrupt withdrawal; gastric and duodenal ulceration (avoid in active ulceration), uncontrolled hypertension, arrhythmias, angina, psychosis, side-effects of levodopa may be increased, concurrent levodopa dosage can be reduced by 10–30%; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (selegiline)

Hepatic impairment use with caution in severe impairment

Renal impairment use with caution in severe impairment

Pregnancy avoid—no information available

Breast-feeding avoid—no information available

Side-effects nausea, constipation, diarrhoea, dry mouth; postural hypotension; dyskinesia, vertigo, sleeping disorders, confusion, hallucinations; arthralgia, myalgia; mouth ulcers with oral lyophilisate; *rarely* arrhythmias, agitation, headache, micturition difficulties, skin reactions; *very rarely* hypersexuality; also reported chest pain

Dose

- 10 mg in the morning, or 5 mg at breakfast and midday; ELDERLY see below

  Elderly To avoid initial confusion and agitation, it may be appropriate to start treatment with a dose of 2.5 mg daily

  Note 1.25-mg oral lyophilisate is equivalent to 10-mg tablet

Selegiline Hydrochloride (Non-proprietary) PoM

Tablets, selegiline hydrochloride 5 mg, net price 60-tab pack = £5.59; 10 mg, 30-tab pack = £6.87

Eldepryl® (Orion) PoM

Tablets, scored, selegiline hydrochloride 5 mg, net price 60-tab pack = £9.91; 10 mg, 30-tab pack = £9.67

Oral liquid, selegiline hydrochloride 10 mg/5 mL, net price 200 mL = £17.93

Oral lyophilisate

Zelapar® (Cephalon) PoM

Oral lyophilisates (= freeze-dried tablets), yellow, selegiline hydrochloride 1.25 mg, net price 30-tab pack = £43.16. Counselling, administration

Excipients include aspartame (section 9.4.1)

Dose 1.25 mg daily before breakfast

Counselling Tablets should be placed on the tongue and allowed to dissolve. Advise patient not to drink, rinse, or wash mouth out for 5 minutes after taking the tablet

Note Patients receiving 10 mg conventional selegiline hydrochloride tablets can be switched to *Zelapar®* 1.25 mg

Catechol-*O*-methyltransferase inhibitors

Entacapone and **tolcapone** prevent the peripheral breakdown of levodopa, by inhibiting catechol-*O*-methyltransferase, allowing more levodopa to reach the brain. They are licensed for use as an adjunct to co-beneldopa or co-careldopa for patients with Parkinson's disease who experience 'end-of-dose' deterioration and cannot be stabilised on these combinations. Due to the risk of hepatotoxicity, tolcapone should be prescribed under specialist supervision only, when other catechol-*O*-methyltransferase inhibitors combined with co-beneldopa or co-careldopa are ineffective.

ENTACAPONE

Indications adjunct to co-beneldopa or co-careldopa in Parkinson's disease and 'end-of-dose' motor fluctuations

Cautions ischaemic heart disease; avoid abrupt withdrawal; concurrent levodopa dose may need to be reduced by about 10–30%; **interactions:** Appendix 1 (entacapone)

Contra-indications phaeochromocytoma; history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis

Hepatic impairment avoid

Pregnancy avoid—no information available

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, vomiting, abdominal pain, constipation, diarrhoea, urine may be coloured reddish-brown, dry mouth; ischaemic heart disease; confusion, dizziness, abnormal dreams, fatigue, insomnia, dystonia, dyskinesia, hallucinations; sweating; *less commonly* myocardial infarction; *rarely* rash; *very rarely* anorexia, weight loss, agitation, and urticaria; *also reported* hepatitis, colitis, neuroleptic malignant syndrome, rhabdomyolysis, and skin, hair, and nail discoloration

Dose

- 200 mg with each dose of levodopa with dopa-decarboxylase inhibitor; max. 2 g daily

Comtess® (Orion) PoM

Tablets, f/c, brown/orange, entacapone 200 mg, net price 30-tab pack = £17.24, 100-tab pack = £57.45. Label: 14, (urine reddish-brown), counselling, driving, see notes above, avoid iron-containing products at the same time of day

TOLCAPONE

Indications adjunct to co-beneldopa or co-careldopa in Parkinson's disease and 'end-of-dose' motor fluctuations if another inhibitor of peripheral catechol-*O*-methyltransferase inappropriate (under specialist supervision)

Cautions avoid abrupt withdrawal; most patients receiving more than 600 mg levodopa daily require reduction of levodopa dose by about 30%; **interactions:** Appendix 1 (tolcapone)

Hepatotoxicity Potentially life-threatening hepatotoxicity including fulminant hepatitis reported rarely, usually in women and during the first 6 months, but late-onset liver injury also reported; test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and then every 8 weeks thereafter (restart monitoring schedule if dose increased); discontinue if abnormal liver function tests or symptoms of liver disorder (counselling, see below); do not re-introduce tolcapone once discontinued

Counselling Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop

Contra-indications severe dyskinesia, phaeochromocytoma, previous history of neuroleptic malignant syndrome, rhabdomyolysis, or hyperthermia

Hepatic impairment avoid; see also under Cautions

Renal impairment caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy toxicity in *animal* studies—use only if potential benefit outweighs risk

Breast-feeding avoid—present in milk in *animal* studies

Side-effects diarrhoea, constipation, dyspepsia, abdominal pain, nausea, vomiting, anorexia, xerostomia, hepatotoxicity (see above); chest pain; confusion, dystonia, dyskinesia, drowsiness, headache, dizziness, sleep disturbances, excessive dreaming, hallucinations; syncope; urine discoloration; sweating; neuroleptic malignant syndrome and rhabdomyolysis reported on dose reduction or withdrawal

Dose

- 100 mg 3 times daily, leave 6 hours between each dose; max. 200 mg 3 times daily in exceptional circumstances; first daily dose should be taken at the same time as levodopa with dopa-decarboxylase inhibitor
  Note Continue beyond 3 weeks **only** if substantial improvement

Tasmar® (Meda) ▼ PoM
Tablets, f/c, yellow, tolcapone 100 mg, net price 100-tab pack = £95.20. Label: 14, 25

Amantadine

Amantadine is a weak dopamine agonist with modest antiparkinsonian effects. Tolerance to its effects may develop and confusion and hallucinations may occasionally occur.

AMANTADINE HYDROCHLORIDE

Indications Parkinson's disease; antiviral (section 5.3.4)

Cautions congestive heart disease (may exacerbate oedema), confused or hallucinatory states, elderly; avoid abrupt withdrawal in Parkinson's disease; **interactions:** Appendix 1 (amantadine)
Driving May affect performance of skilled tasks (e.g. driving)

Contra-indications epilepsy; history of gastric ulceration

Hepatic impairment caution

Renal impairment reduce dose; avoid if eGFR less than 15 mL/minute/1.73 m^2

Pregnancy avoid; toxicity in *animal* studies

Breast-feeding avoid; present in milk; toxicity in infant reported

Side-effects gastro-intestinal disturbances, anorexia, dry mouth; palpitation, peripheral oedema, postural hypotension; anxiety, mood changes, dizziness, headache, lethargy, hallucinations, insomnia, impaired concentration, slurred speech; myalgia; sweating and livedo reticularis; *less commonly* confusion, psychosis, tremor, movement disorders, seizure, neuroleptic malignant syndrome, urinary retention, urinary incontinence, visual disturbances, and rash; heart failure, leucopenia, and photosensitisation also reported

Dose

- Parkinson's disease, 100 mg daily increased after one week to 100 mg twice daily, usually in conjunction with other treatment; some patients may require higher doses, max. 400 mg daily; ELDERLY 65 years and over, 100 mg daily adjusted according to response
- Post-herpetic neuralgia, 100 mg twice daily for 14 days, continued for a further 14 days if necessary

Symmetrel® (Alliance) PoM
Capsules, red-brown, amantadine hydrochloride 100 mg. Net price 56-cap pack = £16.22. Counselling, driving, see Cautions

Syrup, amantadine hydrochloride 50 mg/5 mL. Net price 150-mL pack = £5.33. Counselling, driving, see Cautions

Lysovir® (Alliance) PoM
Section 5.3

4.9.2 Antimuscarinic drugs used in parkinsonism

Antimuscarinic drugs exert their antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency. Antimuscarinic drugs can be useful in drug-induced parkinsonism, but they are generally not used in idiopathic Parkinson's disease because they are less effective than dopaminergic drugs and they are associated with cognitive impairment.

The antimuscarinic drugs **orphenadrine**, **procyclidine**, and **trihexyphenidyl** reduce the symptoms of parkinsonism induced by antipsychotic drugs, but there is no justification for giving them routinely in the absence of parkinsonian side-effects. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

In idiopathic Parkinson's disease, antimuscarinic drugs reduce tremor and rigidity but they have little effect on bradykinesia. They may be useful in reducing sialorrhoea.

No important differences exist between the antimuscarinic drugs, but some patients tolerate one better than another.

Procyclidine can be given parenterally and is effective emergency treatment for acute drug-induced dystonic reactions.

Cautions Antimuscarinics should be used with caution in cardiovascular disease, hypertension, psychotic disorders, prostatic hypertrophy, pyrexia, in those susceptible to angle-closure glaucoma, and in the elderly. Antimuscarinics should not be withdrawn abruptly in patients receiving long-term treatment. Antimuscarinics are liable to abuse. **Interactions:** Appendix 1 (Antimuscarinics)

Driving May affect performance of skilled tasks (e.g. driving)

Contra-indications Antimuscarinics should be avoided in gastro-intestinal obstruction and myasthenia gravis.

Hepatic and renal impairment Orphenadrine, procyclidine, and trihexyphenidyl should be used with caution in patients with hepatic or renal impairment.

Side-effects Side-effects of antimuscarinics include constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, confusion, euphoria, hallucinations, impaired memory, anxiety, restlessness, urinary retention, blurred vision, and rash. Angle-closure glaucoma may occur very rarely.

ORPHENADRINE HYDROCHLORIDE

Indications parkinsonism; drug-induced extrapyramidal symptoms (but not tardive dyskinesia, see notes above)

Cautions see notes above

Contra-indications see notes above; also acute porphyria (section 9.8.2)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy caution

Breast-feeding caution

Side-effects see notes above; *less commonly* seizures, drowsiness, insomnia, and impaired coordination

Dose

- Initially 150 mg daily in divided doses, increased gradually in steps of 50 mg every 2–3 days according to response; usual dose range 150–300 mg daily in divided doses; max. 400 mg daily; ELDERLY preferably lower end of range

Orphenadrine Hydrochloride (Non-proprietary) PoM

Tablets, orphenadrine hydrochloride 50 mg, net price 100-tab pack = £63.68. Counselling, driving, see notes above

Oral solution, orphenadrine hydrochloride 50 mg/5 mL, net price 200 mL = £9.47. Counselling, driving, see notes above

Biorphen® (Alliance) PoM

Liquid, sugar-free, orphenadrine hydrochloride 25 mg/5 mL, net price 200 mL = £8.48. Counselling, driving, see notes above

Disipal® (Astellas) PoM

Tablets, yellow, s/c, orphenadrine hydrochloride 50 mg, net price 250-tab pack = £8.59. Counselling, driving, see notes above

Excipients include tartrazine

PROCYCLIDINE HYDROCHLORIDE

Indications parkinsonism; drug-induced extrapyramidal symptoms (but not tardive dyskinesia, see notes above)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding no information available

Side-effects see notes above, but causes sedation rather than stimulation; also gingivitis

Dose

- By mouth, 2.5 mg 3 times daily, increased gradually in steps of 2.5–5 mg daily every 2–3 days if necessary; usual max. 30 mg daily in 2–4 divided doses (60 mg daily in exceptional circumstances); ELDERLY preferably lower end of range
- By intramuscular *or* intravenous injection, acute dystonia, 5–10 mg (occasionally more than 10 mg), usually effective in 5–10 minutes but may need 30 minutes for relief; ELDERLY preferably lower end of range

Procyclidine (Non-proprietary) PoM

Tablets, procyclidine hydrochloride 5 mg, net price 28-tab pack = £2.77. Counselling, driving, see notes above

Arpicolin® (Rosemont) PoM

Syrup, sugar-free, procyclidine hydrochloride 2.5 mg/5 mL, net price 150 mL = £4.22; 5 mg/5 mL, 150 mL pack = £7.54. Counselling, driving, see notes above

Kemadrin® (Aspen) PoM

Tablets, scored, procyclidine hydrochloride 5 mg, net price 100-tab pack = £4.72. Counselling, driving, see notes above

Kemadrin® (Auden Mckenzie) PoM

Injection, procyclidine hydrochloride 5 mg/mL, net price 2-mL amp = £1.49

TRIHEXYPHENIDYL HYDROCHLORIDE

(Benzhexol hydrochloride)

Indications parkinsonism; drug-induced extrapyramidal symptoms (but not tardive dyskinesia, see notes above)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy use only if potential benefit outweighs risk

Breast-feeding avoid

Side-effects see notes above

Dose

- 1 mg daily, increased gradually; usual maintenance dose 5–15 mg daily in 3–4 divided doses (max. 20 mg daily); ELDERLY preferably lower end of range; CHILD under 18 years see *BNF for Children*

Trihexyphenidyl (Non-proprietary) PoM

Tablets, trihexyphenidyl hydrochloride 2 mg, net price 84-tab pack = £19.60; 5 mg, 84-tab pack = £18.59, 100-tab pack = £15.60. Counselling, with or after food, driving, see notes above

Broflex® (Alliance) PoM

Syrup, pink, black currant, trihexyphenidyl hydrochloride 5 mg/5 mL, net price 200 mL = £7.44. Counselling, driving, see notes above

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Tetrabenazine is mainly used to control movement disorders in Huntington's chorea and related disorders. Tetrabenazine can also be prescribed for the treatment of tardive dyskinesia if switching or withdrawing the causative antipsychotic drug is not effective. It may act by depleting nerve endings of dopamine. It is effective in only a proportion of patients and its use may be limited by the development of depression.

Haloperidol (p. 219) can improve motor tics and symptoms of Tourette syndrome and related choreas. Other treatments for Tourette syndrome include **pimozide** (p. 220) [unlicensed indication] (**important**: ECG monitoring required), **clonidine** (p. 278) [unlicensed indication], and **sulpiride** (p. 221) [unlicensed indication]. **Trihexyphenidyl** (above) in high dosage can also improve some movement disorders; it is sometimes necessary to build the dose up over many weeks, to 20 to 30 mg daily or higher. **Chlorpromazine** (p. 218) and **haloperidol** (p. 219) are used to relieve intractable hiccup.

Propranolol or another beta-adrenoceptor blocking drug (section 2.4) may be useful in treating essential tremor or tremors associated with anxiety or thyrotoxicosis.

Primidone (p. 288) in some cases provides relief from benign essential tremor; the dose is increased slowly to reduce side-effects.

Piracetam is used as an adjunctive treatment for myoclonus of cortical origin.

Riluzole is used to extend life in patients with motor neurone disease who have amyotrophic lateral sclerosis.

NICE guidance

Riluzole for motor neurone disease (January 2001)

Riluzole is recommended for treating the amyotrophic lateral sclerosis (ALS) form of motor neurone disease (MND). Treatment should be initiated by a specialist in MND but it can then be supervised under a shared-care arrangement involving the general practitioner.

PIRACETAM

Indications adjunctive treatment of cortical myoclonus

Cautions avoid abrupt withdrawal; elderly; haemostasis, major surgery, or severe haemorrhage

Contra-indications cerebral haemorrhage; Huntington's chorea

Hepatic impairment avoid

Renal impairment use two-thirds of normal dose if eGFR 50–80 mL/minute/1.73 m^2; use one-third of normal dose in 2 divided doses if eGFR 30–50 mL/minute/1.73 m^2; use one-sixth normal dose as a single dose if eGFR 20–30 mL/minute/1.73 m^2; avoid if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding avoid

Side-effects weight gain, nervousness, hyperkinesia; *less commonly* drowsiness, depression, asthenia,; *also reported* abdominal pain, nausea, vomiting, diarrhoea, headache, anxiety, confusion, hallucination, vertigo, ataxia, insomnia, and rash

Dose

- Initially 7.2 g daily in 2–3 divided doses, increased according to response by 4.8 g daily every 3–4 days to max. 20 g daily (subsequently, attempts should be made to reduce dose of concurrent therapy); CHILD under 16 years not recommended
  Oral solution Follow the oral solution with a glass of water (or soft drink) to reduce bitter taste.

Nootropil® (UCB Pharma) PoM

Tablets, f/c, scored, piracetam 800 mg, net price 90-tab pack = £11.75; 1.2 g, 60-tab pack = £10.97. Label: 3

Oral solution, piracetam, 333.3 mg/mL, net price 300-mL pack = £16.31. Label: 3

RILUZOLE

Indications to extend life in patients with amyotrophic lateral sclerosis, initiated by specialists experienced in the management of motor neurone disease

Cautions history of abnormal hepatic function (consult product literature for details)
Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever occur; white blood cell counts should be determined in febrile illness; neutropenia requires discontinuation of riluzole
Interstitial lung disease Perform chest radiography if symptoms such as dry cough or dyspnoea develop; discontinue if interstitial lung disease is diagnosed
Driving Dizziness or vertigo may affect performance of skilled tasks (e.g. driving)

Hepatic impairment avoid; see also under Cautions

Renal impairment avoid—no information available

Pregnancy avoid—no information available

Breast-feeding avoid—no information available

Side-effects nausea, vomiting, diarrhoea, abdominal pain; tachycardia; asthenia, headache, dizziness, drowsiness, oral paraesthesia; *less commonly* interstitial lung disease, pancreatitis, angioedema, and anaemia; *rarely* neutropenia; *very rarely* hepatitis

Dose

- 50 mg twice daily; CHILD not recommended

Rilutek® (Sanofi-Aventis) PoM

Tablets, f/c, riluzole 50 mg. Net price 56-tab pack = £278.55. Counselling, blood disorders, driving, see Cautions

TETRABENAZINE

Indications see Dose

Cautions **interactions:** Appendix 1 (tetrabenazine)
Driving May affect performance of skilled tasks (e.g. driving)

Pregnancy inadequate information but no evidence of harm

Breast-feeding avoid

Side-effects drowsiness, gastro-intestinal disturbances, depression, extrapyramidal dysfunction, hypotension; rarely parkinsonism; neuroleptic malignant syndrome reported

Dose

- Movement disorders due to Huntington's chorea, hemiballismus, senile chorea, and related neurological conditions, initially 12.5 mg twice daily (elderly 12.5 mg daily) gradually increased to 12.5–25 mg 3 times daily; max. 200 mg daily
- Moderate to severe tardive dyskinesia, initially 12.5 mg daily, gradually increased according to response

Xenazine® 25 (Alliance) PoM

Tablets, yellow, scored, tetrabenazine 25 mg. Net price 112-tab pack = £100.00. Label: 2

Torsion dystonias and other involuntary movements

Botulinum toxin type A should be used under specialist supervision.

Botox® and *Dysport®* are licensed for the treatment of focal spasticity (including arm symptoms in conjunction with physiotherapy, dynamic equinus foot deformity caused by spasticity in ambulant paediatric cerebral palsy patients over 2 years, and hand and wrist disability associated with stroke), blepharospasm, hemifacial spasm, and spasmodic torticollis. *Botox®* is also licensed for severe hyperhidrosis of the axillae, and for the prophylaxis of headaches in adults with chronic migraine (section 4.7.4.2).

Azzalure®, *Bocouture®*, and *Vistabel®* are licensed for the temporary improvement of moderate to severe wrinkles between the eyebrows in adults under 65 years.

Xeomin® is licensed for the treatment of blepharospasm, spasmodic torticollis, and post-stroke spasticity of the upper limb.

BOTULINUM TOXIN TYPE A

Indications see notes above; preparations are **not** interchangeable and should be used under specialist supervision

Cautions history of dysphagia or aspiration; chronic respiratory disorder; neurological disorders (can lead to increased sensitivity and exaggerated muscle weakness)

Specific cautions for blepharospasm or hemifacial spasm Caution if risk of angle-closure glaucoma; reduced blinking can lead to corneal exposure, persistent epithelial defect and corneal ulceration (especially in those with VIIth nerve disorders)—careful testing of corneal sensation in previously operated eyes, avoidance of injection in lower lid area to avoid ectropion, and vigorous treatment of epithelial defect needed

Contra-indications generalised disorders of muscle activity (e.g. myasthenia gravis); infection at injection site

Pregnancy low risk of systemic absorption but avoid unless essential

Breast-feeding low risk of systemic absorption but avoid unless essential

Side-effects increased electrophysiologic jitter in some distant muscles; misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles; influenza-like symptoms; *rarely* arrhythmias, myocardial infarction, seizures, and antibody formation (substantial deterioration in response); *very rarely* exaggerated muscle weakness, dysphagia, and aspiration (seek medical attention if swallowing, speech, or respiratory disorders)

Specific side-effects for blepharospasm or hemifacial spasm ptosis; keratitis, lagophthalmos, dry eye, irritation, photophobia, lacrimation; facial oedema; *less commonly* dry mouth, facial weakness (including drooping), dizziness, paraesthesia, headache, tiredness, ectropion, entropion, diplopia, visual disturbances, conjunctivitis, dermatitis; *rarely* eyelid bruising and swelling (minimised by applying gentle pressure at injection site immediately after injection); *very rarely* angle-closure glaucoma, corneal ulceration

Specific side-effects in paediatric cerebral palsy drowsiness, paraesthesia, urinary incontinence, myalgia

Specific side-effects for temporary improvement of moderate to severe wrinkles between the eyebrows facial oedema, headache; ptosis; *less commonly* nausea, dry mouth, dizziness, asthenia, anxiety, paraesthesia, muscle cramp, visual disturbances, tinnitus, blepharitis, photosensitivity reactions, and dry skin

Specific side-effects in spasmodic torticollis dysphagia and pooling of saliva (occurs most frequently after injection into sternomastoid muscle), nausea, dry mouth; rhinitis; drowsiness, headache, dizziness, malaise, numbness, stiffness, hypertonia, back pain, weakness; *less commonly* diarrhoea, vomiting, colitis, dyspnoea, voice alteration, tremor, skeletal pain, myalgia, diplopia, eye pain, ptosis, and sweating

Specific side-effects in axillary hyperhidrosis non-axillary sweating, hot flushes; *less commonly* myalgia and joint pain

Specific side-effects in focal upper-limb spasticity associated with stroke dysphagia; hypertonia, purpura; *less commonly* nausea, dry mouth, cough, haematoma, peripheral oedema, depression, insomnia, vertigo, amnesia, malaise, paraesthesia, dysaesthesia, headache, pain in extremities, arthralgia, and bursitis

Dose

- Consult product literature (**important:** specific to **each individual preparation** and **not interchangeable**)

Azzalure® (Galderma) PoM
Injection, powder for reconstitution, botulinum toxin type A-haemagglutinin complex, net price 125-unit vial = £64.00

Bocouture® (Merz) PoM
Injection, powder for reconstitution, botulinum toxin type A, net price 50-unit vial = £72.00

Botox® (Allergan) PoM
Injection, powder for reconstitution, botulinum toxin type A complex, net price 50-unit vial = £77.50, 100-unit vial = £138.20, 200-unit vial = £276.40

Dysport® (Ipsen) PoM
Injection, powder for reconstitution, botulinum type A toxin-haemagglutinin complex, net price 500-unit vial = £154.00

Vistabel® (Allergan) PoM
Injection, powder for reconstitution, botulinum toxin type A, net price 50-unit vial = £85.00

Xeomin® (Merz) PoM
Injection, powder for reconstitution, botulinum toxin type A, net price 100-unit vial = £129.90

BOTULINUM TOXIN TYPE B

Indications spasmodic torticollis (cervical dystonia)—specialist use only

Cautions history of dysphagia or aspiration; inadvertent injection into a blood vessel; tolerance may occur

Contra-indications neuromuscular or neuromuscular junctional disorders

Pregnancy low risk of systemic absorption but avoid unless essential

Breast-feeding low risk of systemic absorption but avoid unless essential

Side-effects increased electrophysiologic jitter in some distant muscles; dry mouth, dyspepsia, worsening torticollis, neck pain, myasthenia, voice changes, taste disturbances; *very rarely* exaggerated muscle weakness, dysphagia, and aspiration (seek medical attention if swallowing, speech, or respiratory disorders)

Dose

- By intramuscular injection, initially 5000–10 000 units divided between 2–4 most affected muscles; adjust dose and frequency according to response; **important: not** interchangeable with other botulinum toxin preparations

NeuroBloc® (Eisai) PoM
Injection, botulinum toxin type B 5000 units/mL, net price 0.5-mL vial = £111.20; 1-mL vial = £148.27; 2-mL vial = £197.69

Note May be diluted with sodium chloride 0.9%

4.10 Drugs used in substance dependence

This section includes drugs used in alcohol dependence, cigarette smoking, and opioid dependence.

The UK health departments have produced guidance on the treatment of drug misuse in the UK. *Drug Misuse and Dependence: UK Guidelines on Clinical Management* (2007) is available at www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf.

4.10.1 Alcohol dependence

Excessive drinking of alcoholic beverages over a prolonged period of time can result in an alcohol withdrawal syndrome on abrupt cessation of, or marked reduction in, drinking; for some patients the withdrawal syndrome can be severe and even fatal.

Acute alcohol withdrawal Long-acting benzodiazepines, usually **chlordiazepoxide** (p. 214), are used to attenuate alcohol withdrawal symptoms. In primary care, fixed-dose reducing regimens are usually used, whilst a symptom-triggered flexible regimen is used in hospital or other settings where continued assessment and monitoring is carried out for 24–48 hours, usually followed by a fixed 5-day reducing dose schedule. Patients with decompensated liver disease should be treated under specialist supervision.

Carbamazepine [unlicensed indication] (p. 281) is sometimes used as an alternative treatment in acute alcohol withdrawal when benzodiazepines are contraindicated or not tolerated. **Clomethiazole** (p. 211) is licensed for use in acute alcohol withdrawal, but benzodiazepines are preferred. It should only be used in an inpatient setting and should not be prescribed if the patient is liable to continue drinking alcohol.

Patients with marked agitation or hallucinations and those at risk of delirium tremens (characterised by delirium, hallucinations, course tremor, and disorientation) may be prescribed antipsychotic drugs, such as **haloperidol** (p. 219) or **olanzapine** (p. 224) [unlicensed indication], as adjunctive therapy to benzodiazepines; antipsychotics should not be used alone because they do not treat alcohol withdrawal and may lower the seizure threshold. Delirium tremens is a medical emergency that requires specialist inpatient care.

If a patient taking a benzodiazepine as part of a withdrawal regimen develops alcohol withdrawal seizures, a fast-acting benzodiazepine (such as intravenous **lorazepam** [unlicensed indication] (p. 296) or rectal **diazepam** (p. 295)) should be prescribed; thereafter an increase in the dose of oral benzodiazepine should be considered to prevent further seizures from occurring.

Alcohol dependence **Acamprosate** and **disulfiram** are effective treatments for relapse prevention in patients with alcohol dependence (see below).

Patients with alcohol dependence are at risk of developing Wernicke's encephalopathy; patients at high-risk are those who are malnourished, at risk of malnourishment, or have decompensated liver disease. Parenteral **thiamine** (as *Pabrinex®*, section 9.6.2) should be prescribed for treatment of suspected or confirmed Wernicke's encephalopathy, and for prophylaxis in alcohol-dependent patients attending hospital for acute treatment (including treatment unrelated to alcohol dependence); parenteral prophylaxis may also be considered for high-risk patients being treated in primary care. High-dose oral thiamine (p. 616) should be prescribed following parenteral treatment until cognitive function is maximised. In primary care, prophylactic high-dose oral thiamine should be prescribed during acute withdrawal of alcohol, before planned withdrawal, and for patients not undergoing withdrawal but who are at high-risk of developing Wernicke's encephalopathy.

Patients with chronic alcohol-related pancreatitis who have symptoms of steatorrhoea or who have poor nutritional status due to exocrine pancreatic insufficiency should be prescribed **pancreatic enzyme supplements** (section 1.9.4); supplements are not indicated when pain is the only symptom.

Corticosteroids (section 6.3.2) are used in patients with severe acute alcohol-related hepatitis.

Acamprosate

Acamprosate, in combination with counselling, may be helpful for maintaining abstinence in alcohol-dependent patients. It is useful for patients who are concerned that strong cravings will result in relapse. It should be initiated as soon as possible *after* abstinence has been achieved and continued for 1 year; treatment should be maintained if the patient has a temporary relapse. Acamprosate is not effective in all patients, so efficacy should be regularly assessed.

ACAMPROSATE CALCIUM

Indications see notes above

Cautions continued alcohol abuse (risk of treatment failure)

Hepatic impairment avoid if severe

Renal impairment avoid if serum-creatinine greater than 120 micromol/litre

Pregnancy avoid

Breast-feeding avoid

Side-effects diarrhoea, nausea, vomiting, abdominal pain; fluctuation in libido; pruritus, maculopapular rash; *rarely* bullous skin reactions

Dose

- ADULT 18–65 years, body-weight 60 kg and over, 666 mg 3 times daily; body-weight less than 60 kg, 666 mg at breakfast, 333 mg at midday and 333 mg at night

Campral EC® (Merck Serono) PoM

Tablet, e/c, acamprosate calcium 333 mg, net price 168-tab pack = £24.00. Label: 21, 25

Electrolytes Ca^{2+} 0.8 mmol/tablet

Disulfiram

Disulfiram is used as an adjunct in the treatment of alcohol dependence (under specialist supervision). It gives rise to an extremely unpleasant systemic reaction after the ingestion of even a small amount of alcohol because it causes accumulation of acetaldehyde in the body; it is only effective if taken daily. Symptoms can occur within 10 minutes of ingesting alcohol and include flushing of the face, throbbing headache, palpitation, tachycardia, nausea, vomiting, and, with large doses of alcohol, arrhythmias, hypotension, and collapse; these reactions can last several hours. Small amounts of alcohol such as those included in many oral medicines may be sufficient to precipitate a reaction—even toiletries and mouthwashes that contain alcohol should be avoided. Alcohol should be avoided for at least 1 week after stopping treatment.

Before initiating disulfiram, prescribers should evaluate the patient's suitability for treatment, because some patient factors, for example memory impairment or social circumstances, make compliance to treatment or abstinence from alcohol difficult.

DISULFIRAM

Indications see notes above

Cautions ensure that alcohol not consumed for at least 24 hours before initiating treatment; see also notes above; alcohol challenge **not** recommended on routine basis (if considered essential—specialist units only with resuscitation facilities); respiratory disease, diabetes mellitus, epilepsy; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (disulfiram)

Contra-indications cardiac failure, coronary artery disease, history of cerebrovascular accident, hypertension, psychosis, severe personality disorder, suicide risk

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy high concentrations of acetaldehyde which occur in presence of alcohol may be teratogenic; avoid in first trimester

Breast-feeding avoid—no information available

Side-effects initially drowsiness and fatigue; nausea, vomiting, halitosis, reduced libido; rarely psychotic reactions (depression, paranoia, schizophrenia, mania), allergic dermatitis, peripheral neuritis, hepatic cell damage

Dose

- 800 mg as a single dose on first day, reducing over 5 days to 100–200 mg daily; should not be continued for longer than 6 months without review; CHILD not recommended

Antabuse® (Actavis) PoM

Tablets, scored, disulfiram 200 mg. Net price 50-tab pack = £24.78. Label: 2, counselling, alcohol reaction

4.10.2 Nicotine dependence

Smoking cessation interventions are a cost-effective way of reducing ill health and prolonging life. Smokers should be advised to stop and offered help with follow-up when appropriate. If possible, smokers should have access to smoking cessation services for behavioural support.

Therapy to aid smoking cessation is chosen according to the smoker's likely compliance, availability of counselling and support, previous experience of smoking-cessation aids, contra-indications and adverse effects of the products, and the smoker's preferences. **Nicotine replacement therapy**, **bupropion**, and **varenicline** are effective aids to smoking cessation. The use of nicotine replacement preparations in an individual who is already accustomed to nicotine introduces few new risks and it is widely accepted that there are no circumstances in which it is safer to smoke than to use nicotine replacement therapy.

Some patients benefit from having more than one type of nicotine replacement therapy prescribed, such as a combination of transdermal and oral preparations. The combination of nicotine replacement therapy with varenicline or bupropion is not recommended.

Concomitant medication Cigarette smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these drugs, in particular theophylline (p. 181), cinacalcet (p. 610), ropinirole (p. 301), and some antipsychotics (including clozapine (p. 223), olanzapine (p. 224), chlorpromazine (p. 218), and haloperidol (p. 219)), may need to be reduced. Regular monitoring for adverse effects is advised.

Buproprion

Bupropion has been used as an antidepressant but its mode of action in smoking cessation is not clear and may involve an effect on noradrenaline and dopamine neurotransmission.

BUPROPION HYDROCHLORIDE

(Amfebutamone hydrochloride)

Indications see notes above

Cautions elderly; predisposition to seizures (prescribe only if benefit clearly outweighs risk) including concomitant use of drugs that lower seizure threshold, alcohol abuse, history of head trauma, and diabetes; measure blood pressure before and during treatment; **interactions**: Appendix 1 (bupropion)

Driving May impair performance of skilled tasks (e.g. driving)

Contra-indications acute alcohol or benzodiazepine withdrawal; severe hepatic cirrhosis; CNS tumour; history of seizures, eating disorders, or bipolar disorder

Hepatic impairment reduce dose to 150 mg daily; avoid in severe hepatic cirrhosis

Renal impairment reduce dose to 150 mg daily

Pregnancy avoid—no information available

Breast-feeding present in milk—avoid

Side-effects dry mouth, gastro-intestinal disturbances, taste disturbance; agitation, anxiety, dizziness, depression, headache, impaired concentration, insomnia (reduced by avoiding dose at bedtime), tremor; fever; pruritus, rash, sweating; *less commonly* chest pain, flushing, hypertension, tachycardia, anorexia, asthenia, confusion, tinnitus, and visual disturbances; *rarely* hepatitis, jaundice, palpitation, postural hypotension, vasodilatation, abnormal dreams, ataxia, dystonia, depersonalisation, hallucinations, hostility, incoordination, irritability, impaired memory, paraesthesia, seizures, twitching, blood-glucose changes, urinary frequency, urinary retention, exacerbation of psoriasis, and Stevens-Johnson syndrome; *very rarely* aggression, delusions, paranoid ideation, and restlessness; *also reported* suicidal ideation

Dose

- ADULT over 18 years, start 1–2 weeks before target stop date, initially 150 mg daily for 6 days then 150 mg twice daily (max. single dose 150 mg, max. daily dose 300 mg; minimum 8 hours between doses); period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks; consider max. 150 mg daily in patients with risk factors for seizures; ELDERLY max. 150 mg daily

Zyban® (GSK) PoM

Tablets, m/r, f/c, bupropion hydrochloride 150 mg, net price 60-tab pack = £47.82. Label: 25, counselling, driving, see Cautions

Nicotine replacement therapy

Nicotine replacement therapy can be used in place of cigarettes after abrupt cessation of smoking, or alternatively to reduce the amount of cigarettes used in

advance of making a quit attempt. Nicotine replacement therapy can also be used to minimise passive smoking, and to treat cravings and reduce compensatory smoking after enforced abstinence in smoke-free environments. Smokers who find it difficult to achieve abstinence should consult a healthcare professional for advice.

Choice Nicotine patches are a prolonged-release formulation and are applied for 16 hours (with the patch removed overnight) or for 24 hours. If patients experience strong cravings for cigarettes on waking, a 24-hour patch may be more suitable. Immediate-release nicotine preparations (gum, lozenges, sublingual tablets, inhalator, nasal spray) are used whenever the urge to smoke occurs.

The choice of nicotine replacement preparation depends largely on patient preference, and should take into account what preparations, if any, have been tried before. Patients with a high level of nicotine dependence, or who have failed with nicotine replacement therapy previously, may benefit from using a combination of an immediate-release preparation and patches to achieve abstinence.

All preparations are licensed for adults and children over 12 years (with the exception of *Nicotinell®* lozenges which are licensed for children under 18 years only when recommended by a doctor).

Cautions Most warnings for nicotine replacement therapy also apply to continued cigarette smoking, but the risk of continued smoking outweighs any risks of using nicotine preparations. Nicotine replacement therapy should be used with caution in haemodynamically unstable patients hospitalised with severe arrhythmias, myocardial infarction, or cerebrovascular accident, and in patients with phaeochromocytoma or uncontrolled hyperthyroidism. Care is also needed in patients with diabetes mellitus—blood-glucose concentration should be monitored closely when initiating treatment.

Specific cautions for individual preparations are usually related to the local effect of nicotine. *Oral preparations* should be used with caution in patients with oesophagitis, gastritis, or peptic ulcers because swallowed nicotine can aggravate these conditions. The *gum* may also stick to and damage dentures. Acidic beverages, such as coffee or fruit juice, may decrease the absorption of nicotine through the buccal mucosa and should be avoided for 15 minutes before the use of oral nicotine replacement therapy. Care should be taken with the *inhalation cartridges* in patients with obstructive lung disease, chronic throat disease, or bronchospastic disease. The *nasal spray* can cause worsening of bronchial asthma. *Patches* should not be placed on broken skin and should be used with caution in patients with skin disorders.

Hepatic impairment Nicotine replacement therapy should be used with caution in moderate to severe hepatic impairment.

Renal impairment Nicotine replacement therapy should be used with caution in severe renal impairment.

Pregnancy The use of nicotine replacement therapy in pregnancy is preferable to the continuation of smoking, but should be used only if smoking cessation without nicotine replacement fails. Intermittent therapy is preferable over patches but avoid liquorice-flavoured nicotine products. Patches are useful, however, if the patient is experiencing pregnancy-related nausea and vomiting. If patches are used, they should be removed before bed.

Breast-feeding Nicotine is present in milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.

Side-effects Some systemic effects occur on initiation of therapy, particularly if the patient is using high-strength preparations; however, the patient may confuse side-effects of the nicotine-replacement preparation with nicotine withdrawal symptoms. Common symptoms of nicotine withdrawal include malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, aphthous ulcers, decreased heart rate, and impaired concentration.

Mild topical reactions at the beginning of treatment are common because of the irritant effect of nicotine. *Oral preparations* and *inhalation cartridges* can cause irritation of the throat, *gum* and *lozenges* can cause increased salivation, and *patches* can cause minor skin irritation. The *nasal spray* commonly causes coughing, nasal irritation, epistaxis, sneezing, and watery eyes.

Gastro-intestinal disturbances are common and may be caused by swallowed nicotine. Nausea, vomiting, dyspepsia, and hiccup occur most frequently. Ulcerative stomatitis has also been reported. Dry mouth is a common side-effect of *lozenges*, *patches* and *sublingual tablets*. *Lozenges* cause diarrhoea, constipation, dysphagia, oesophagitis, gastritis, mouth ulcers, bloating, flatulence, and less commonly, taste disturbance, thirst, gingival bleeding, and halitosis.

Palpitations may occur with nicotine replacement therapy and rarely *patches* can cause arrhythmia. *Patches* and *lozenges* can cause chest pain.

Abnormal dreams can occur with *patches*; removal of the patch before bed may help. *Lozenges* may cause hot flushes; sweating, arthralgia, and myalgia can occur with *patches*.

Nicotine medicated chewing gum Individuals who smoke fewer than 20 cigarettes each day should use one piece of 2-mg strength gum when the urge to smoke occurs; individuals who smoke more than 20 cigarettes each day or who require more than 15 pieces of 2-mg strength gum each day should use the 4-mg strength. Patients should not exceed 15 pieces of 4-mg strength gum daily. If attempting smoking cessation, treatment should continue for 3 months before reducing the dose.

Administration Chew the gum until the taste becomes strong, then rest it between the cheek and gum; when the taste starts to fade, repeat this process. One piece of gum lasts for approximately 30 minutes.

Nicotine inhalation cartridge The cartridges can be used when the urge to smoke occurs or to prevent cravings, up to a maximum of 12 cartridges daily.

Administration Insert the cartridge into the device and draw in air through the mouthpiece. The amount of nicotine from 1 puff of the cartridge is less than that from a cigarette, therefore it is necessary to inhale more often than when smoking a cigarette. A single cartridge lasts for approximately 20 minutes of intense use.

Nicotine lozenge One lozenge should be used every 1–2 hours when the urge to smoke occurs. Individuals

who smoke less than 20 cigarettes each day should usually use the lower-strength lozenges; individuals who smoke more than 20 cigarettes each day and those who fail to stop smoking with the low-strength lozenges should use the higher-strength lozenges. Patients should not exceed 15 lozenges daily. If attempting smoking cessation, treatment should continue for 6–12 weeks before attempting a reduction in dose.

Administration Slowly allow each lozenge to dissolve in the mouth; periodically move the lozenge from one side of the mouth to the other. Lozenges last for 10–30 minutes, depending on their size.

Nicotine sublingual tablets Individuals who smoke fewer than 20 cigarettes each day should initially use 1 tablet each hour, increased to 2 tablets each hour if necessary; individuals who smoke more than 20 cigarettes each day should use 2 tablets each hour. Patients should not exceed 40 tablets daily. If attempting smoking cessation, treatment should continue for up to 3 months before reducing the dose.

Administration Each tablet should be placed under the tongue and allowed to dissolve.

Nicotine nasal spray Patients can use 1 spray in each nostril when the urge to smoke occurs, up to twice every hour for 16 hours daily (maximum 64 sprays daily). If attempting smoking cessation, treatment should continue for 8 weeks before reducing the dose.

Administration Initially 1 spray should be used in both nostrils but when withdrawing from therapy, the dose can be gradually reduced to 1 spray in 1 nostril.

Nicotine transdermal patches As a general guide for smoking cessation, individuals who smoke more than 10 cigarettes daily should apply a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks, and then the low-strength patch for the final 2 weeks; individuals who smoke fewer than 10 cigarettes daily can usually start with the medium-strength patch for 6–8 weeks, followed by the low-strength patch for 2–4 weeks. A slower titration schedule can be used in patients who are not ready to quit but want to reduce cigarette consumption before a quit attempt.

If abstinence isn't achieved, or if withdrawal symptoms are experienced, the strength of the patch used should be maintained or increased until the patient is stabilised. Patients using the high-strength patch who experience excessive side-effects, that do not resolve within a few days, should change to a medium-strength patch for the remainder of the initial period and then use the low-strength patch for 2–4 weeks.

Administration Patches should be applied on waking to dry, non-hairy skin on the hip, trunk, or upper arm and held in position for 10–20 seconds; place next patch on a different area and avoid using the same site for several days.

NICOTINE

Indications see notes above

Cautions see notes above; **interactions:** Appendix 1 (nicotine)

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- See notes above

Nicorette® (McNeil)

Tablets (sublingual) (*Nicorette Microtab®*), nicotine (as a cyclodextrin complex) 2 mg, net price starter pack of 2 × 15-tablet discs with dispenser = £4.46; pack of 100 = £12.12. Label: 26

Note Also available in lemon flavour; also available as *NicAssist®*

Excipients lemon flavour includes aspartame (section 9.4.1)

Chewing gum, sugar-free, nicotine (as resin) 2 mg, net price pack of 30 = £3.41, pack of 105 = £9.37, pack of 210 = £14.82; 4 mg, pack of 30 = £3.99, pack of 105 = £11.48, pack of 210 = £18.24

Note Also available in mint, freshfruit, freshmint, and icy white flavours. Also available as *NicAssist®*

Note *Nicorette® Combi patch + gum* (containing *Invisi* patches 15 mg and *Icy White* gum 2 mg) also available

Patches, self-adhesive, beige, nicotine, *'5 mg' patch* (releasing approx. 5 mg/16 hours), net price 7 = £9.07; *'10 mg' patch* (releasing approx. 10 mg/16 hours), 7 = £9.07; *'15 mg' patch* (releasing approx. 15 mg/16 hours), 2 = £2.85, 7 = £9.07

Note Also available as *NicAssist®*

Invisi patches, self-adhesive, beige, nicotine, *'10 mg' patch* (releasing approx. 10 mg/16 hours), net price 7 = £9.97; *'15 mg' patch* (releasing approx. 15 mg/16 hours), 7 = £9.97; *'25 mg' patch* (releasing approx. 25 mg/16 hours), 7 = £9.97

Note *Nicorette® Combi patch + gum* (containing *Invisi* patches 15 mg and *Icy White* gum 2 mg) also available

Nasal spray, nicotine 500 micrograms/metered spray, net price 200-spray unit = £13.40

Note Also available as *NicAssist®*

Inhalator (nicotine-impregnated plug for use in inhalator mouthpiece), nicotine 10 mg/cartridge, net price 6-cartridge (starter) pack = £4.46, 42-cartridge (refill) pack = £14.01. Counselling, administration, see notes above

Note Also available as *NicAssist®*

Nicotinell® (Novartis Consumer Health)

Chewing gum, sugar-free, nicotine (as polacrilin complex) 2 mg, net price pack of 12 = £1.71, pack of 24 = £3.01, pack of 96 = £8.26, pack of 204 = £14.23; 4 mg, pack of 12 = £1.70, pack of 24 = £3.30, pack of 96 = £10.26

Note Also available in fruit, liquorice and mint flavours

Mint lozenge, sugar-free, nicotine (as bitartrate) 1 mg, net price pack of 12 = £1.71, pack of 36 = £4.27, pack of 96 = £9.12; 2 mg, net price pack of 12 = £1.99, pack of 36 = £4.95, pack of 96 = £10.60. Label: 24

Excipients include aspartame (section 9.4.1)

TTS Patches, self-adhesive, all yellowish-ochre, nicotine, *'10' patch* (releasing approx. 7 mg/24 hours), net price 7 = £9.12; *'20' patch* (releasing approx. 14 mg/24 hours), net price 2 = £2.57, 7 = £9.40; *'30' patch* (releasing approx. 21 mg/24 hours), net price 2 = £2.85, 7 = £9.97, 21 = £24.51

NiQuitin® (GSK Consumer Healthcare)

Chewing gum, sugar-free, mint-flavour, nicotine 2 mg (white), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55; 4 mg (yellow), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55

Lozenges, sugar-free, nicotine (as resinate) 1.5 mg (cherry- and mint-flavoured), net price pack of 20 =

£3.18, pack of 60 = £8.93; nicotine (as polacrilex) 2 mg (mint-flavoured), pack of 36 = £ 5.12, pack of 72 = £9.97; nicotine (as resinate) 4 mg (mint-flavoured), pack of 20 = £3.18, pack of 60 = £8.93, nicotine (as polacrilex) 4 mg (mint-flavoured) pack of 36 = £5.12, pack of 72 = £9.97. Label: 24

Excipients include aspartame (section 9.4.1); contains 0.65 mmol Na^+/lozenge

Patches, self-adhesive, pink/beige, nicotine *'7 mg' patch* (releasing approx. 7 mg/24 hours), net price 7 = £9.97; *'14 mg' patch* (releasing approx. 14 mg/24 hours), 7 = £9.97; *'21 mg' patch* (releasing approx. 21 mg/24 hours), 7 = £9.97, 14 = £18.79

Note Also available as a clear patch

Varenicline

Varenicline is a selective nicotine-receptor partial agonist used as an aid for smoking cessation.

VARENICLINE

Indications see notes above

Cautions risk of relapse, irritability, depression, and insomnia on discontinuation (consider dose tapering on completion of 12-week course); history of psychiatric illness (may exacerbate underlying illness including depression)

MHRA/CHM advice

Suicidal behaviour and varenicline

Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood, or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline

Renal impairment if eGFR less than 30 mL/minute/1.73 m^2, initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies

Side-effects gastro-intestinal disturbances, appetite changes, dry mouth, taste disturbance; headache, drowsiness, dizziness, sleep disorders, abnormal dreams; *less commonly* thirst, weight gain, aphthous stomatitis, gingival pain, chest pain, hypertension, tachycardia, atrial fibrillation, palpitation, panic attack, mood swings, dysarthria, asthenia, tremor, incoordination, hypertonia, restlessness, hypoaesthesia, impaired temperature regulation, menorrhagia, vaginal discharge, sexual dysfunction, dysuria, arthralgia, muscle spasm, visual disturbances, eye pain, lacrimation, tinnitus, acne, sweating, rash, and pruritus; myocardial infarction, anxiety, depression, aggression, irrational behaviour, psychosis, suicidal ideation (see MHRA/CHM advice above), and Stevens-Johnson syndrome also reported

Dose

- ADULT over 18 years, start 1–2 weeks before target stop date, initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks (reduce to 500 micrograms twice daily if not tolerated); 12-week course can be repeated in abstinent individuals to reduce risk of relapse

Champix® (Pfizer) ▼ PoM

Tablets, f/c, varenicline (as tartrate) 500 micrograms (white), net price 56-tab pack = £54.60; 1 mg (blue) 28-tab pack = £27.30, 56-tab pack = £54.60; starter pack of 11 × 500-microgram tabs with 14 × 1-mg tabs = £27.30. Label: 3

4.10.3 Opioid dependence

The management of opioid dependence requires medical, social, and psychological treatment; access to a multidisciplinary team is recommended. Treatment for opioid dependence should be initiated under the supervision of an appropriately qualified prescriber.

Untreated heroin dependence shows early withdrawal symptoms within 8 hours, with peak symptoms at 36–72 hours; symptoms subside substantially after 5 days. Methadone or buprenorphine withdrawal occurs later, with longer-lasting symptoms.

Opioid substitution therapy

Methadone and **buprenorphine** are used as substitution therapy in opioid dependence. Substitute medication should be commenced with a short period of stabilisation, followed by either a withdrawal regimen or by maintenance treatment. Maintenance treatment enables patients to achieve stability, reduces drug use and crime, and improves health; it should be regularly reviewed to ensure the patient continues to derive benefit. The prescriber should monitor for signs of toxicity, and the patient should be told to be aware of warning signs of toxicity on initiation and during titration.

A withdrawal regimen after stabilisation with methadone or buprenorphine should be attempted only after careful consideration. Enforced withdrawal is ineffective for sustained abstinence, and it increases the risk of patients relapsing and subsequently overdosing because of loss of tolerance. Complete withdrawal from opioids usually takes up to 4 weeks in an inpatient or residential setting, and up to 12 weeks in a community setting. If abstinence is not achieved, illicit drug use is resumed, or the patient cannot tolerate withdrawal, the withdrawal regimen should be stopped and maintenance therapy should be resumed at the optimal dose. Following successful withdrawal treatment, further support and monitoring to maintain abstinence should be provided for a period of at least 6 months.

In younger patients (under 18 years), the harmful effects of drug misuse are more often related to acute intoxication than to dependence, and substitution therapy is therefore usually inappropriate. Maintenance treatment with opioid substitution therapy is therefore controversial in young people; however, it may be useful for the older adolescent who has a history of opioid use to undergo a period of stabilisation with buprenorphine or methadone before starting a withdrawal regimen.

Missed doses

Patients who miss 3 days or more of their regular prescribed dose of opioid maintenance therapy are at risk of overdose because of loss of tolerance. Consider reducing the dose in these patients.

If the patient misses 5 or more days of treatment, an assessment of illicit drug use is also recommended before restarting substitution therapy; this is particularly important for patients taking buprenorphine, because of the risk of precipitated withdrawal.

NICE guidance

Methadone and buprenorphine for the management of opioid dependence (January 2007)

Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

Buprenorphine Buprenorphine is an opioid-receptor partial agonist (it has opioid agonist and antagonist properties). Buprenorphine is preferred by some patients because it is less sedating than methadone; for this reason it may be more suitable for employed patients or those undertaking other skilled tasks such as driving. Buprenorphine is safer than methadone when used in conjunction with other sedating drugs, and has fewer drug interactions. Dose reductions may be easier than with methadone because the withdrawal symptoms are milder, and patients generally require fewer adjunctive medications; there is also a lower risk of overdose. Buprenorphine can be given on alternate days in higher doses and it requires a shorter drug-free period than methadone before induction with naltrexone for prevention of relapse (p. 317).

Patients dependent on high doses of opioids may be at increased risk of precipitated withdrawal. Precipitated withdrawal may occur in any patient if buprenorphine is administered when other opioid agonist drugs are in circulation. Precipitated opioid withdrawal, if it occurs, starts within 1–3 hours of the first buprenorphine dose and peaks at around 6 hours. Non-opioid adjunctive therapy, such as lofexidine (p. 317), may be required if symptoms are severe.

The first dose of buprenorphine should be given when the patient is exhibiting signs of withdrawal, or 6–12 hours after the last use of heroin (or other short-acting opioid), or 24–48 hours after the last dose of methadone. It is possible to titrate the dose of buprenorphine within one week—more rapidly than with methadone therapy—but care is still needed to avoid toxicity or precipitated withdrawal; dividing the dose on the first day may be useful.

In patients taking methadone who want to switch to buprenorphine, the dose of methadone should be reduced to a maximum of 30 mg daily before starting buprenorphine treatment. If the dose of methadone is over 10 mg daily, buprenorphine can be started at a dose of 4 mg daily and titrated according to requirements; if the methadone dose is below 10 mg daily, buprenorphine can be started at a dose of 2 mg daily.

Buprenorphine should not normally be used in patients with liver dysfunction. Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy, and regular liver function tests should be performed throughout treatment.

A combination preparation containing buprenorphine with naloxone (*Suboxone®*, p. 316) can be prescribed for patients when there is a risk of dose diversion for parenteral administration; the naloxone component precipitates withdrawal if the preparation is injected, but it has little effect when the preparation is taken sublingually.

Methadone Methadone, a long-acting opioid agonist, is usually administered in a single daily dose as methadone oral solution 1 mg/mL. Patients with a long history of opioid misuse, those who typically abuse a variety of sedative drugs and alcohol, and those who experience increased anxiety during withdrawal of opioids may prefer methadone to buprenorphine because it has a more pronounced sedative effect.

Methadone is initiated at least 8 hours after the last heroin dose, provided that there is objective evidence of withdrawal symptoms. A supplementary dose on the first day may be considered if there is evidence of persistent opioid withdrawal symptoms. Because of the long half-life, blood levels progressively rise during initial treatment even if the patient remains on the same daily dose (it takes 3–10 days for plasma levels to reach steady-state in patients on a stable dose); a dose tolerated on the first day of treatment may become a toxic dose on the third day as cumulative toxicity develops. Thus, titration to the optimal dose in methadone maintenance treatment may take several weeks.

Pregnancy Acute withdrawal of opioids should be avoided in pregnancy because it can cause fetal death. Opioid substitution therapy is recommended during pregnancy because it carries a lower risk to the fetus than continued use of illicit drugs. If a woman who is stabilised on methadone or buprenorphine for treatment of opioid dependence becomes pregnant, therapy should be continued [buprenorphine is not licensed for use in pregnancy]. Many pregnant patients choose a withdrawal regimen, but withdrawal during the first trimester should be avoided because it is associated with an increased risk of spontaneous miscarriage. Withdrawal of methadone or buprenorphine should be undertaken gradually during the second trimester; for example, the dose of methadone may be reduced by 2–3 mg every 3–5 days. If illicit drug use occurs, the patient should be re-stabilised at the optimal maintenance dose and consideration should be given to stopping the withdrawal regimen.

Further withdrawal of methadone or buprenorphine in the third trimester is not recommended because maternal withdrawal, even if mild, is associated with fetal distress, stillbirth, and the risk of neonatal mortality. Drug metabolism can be increased in the third trimester; it may be necessary to either increase the dose of methadone or change to twice-daily consumption (or a combination of both strategies) to prevent withdrawal symptoms from developing.

The neonate should be monitored for respiratory depression and signs of withdrawal if the mother is prescribed high doses of opioid substitute.

Signs of neonatal withdrawal from opioids usually develop 24–72 hours after delivery but symptoms may be delayed for up to 14 days, so monitoring may be required for several weeks. Symptoms include a high-pitched cry, rapid breathing, hungry but ineffective suckling, and excessive wakefulness; severe, but rare, symptoms include hypertonicity and convulsions.

Breast-feeding The dose of methadone should be kept as low as possible in breast-feeding mothers and the infant should be monitored for sedation (high doses of methadone carry an increased risk of sedation and respiratory depression in the neonate).

Buprenorphine is excreted in low levels in breast milk and has low oral bioavailability; however, neonates should be monitored for drowsiness, adequate weight gain, and developmental milestones.

Increased sleepiness, breathing difficulties, or limpness in breast-fed babies of mothers taking opioid substitutes should be reported urgently to a healthcare professional.

BUPRENORPHINE

Indications adjunct in the treatment of opioid dependence; premedication, peri-operative analgesia, analgesia in other situations (section 4.7.2)

Cautions see Buprenorphine in section 4.7.2 and notes above; caution if pre-existing liver enzyme abnormalities, hepatitis B or C infection, or concomitant use of hepatotoxic drugs

Contra-indications see notes in section 4.7.2

Hepatic impairment see notes in section 4.7.2

Renal impairment see notes in section 4.7.2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see Buprenorphine, section 4.7.2; also hepatic necrosis and hepatitis

Dose

- By sublingual administration, ADULT and CHILD over 16 years, initially, 0.8–4 mg on day 1, adjusted if necessary by 2–4 mg daily to usual dose of 12–24 mg daily (max. 32 mg daily); withdraw gradually

Buprenorphine (Non-proprietary) CD

Tablets (sublingual), buprenorphine (as hydrochloride) 400 micrograms, net price 7-tab pack = £1.57; 2 mg, 7-tab pack = £7.74; 8 mg, 7-tab pack = £20.54. Label: 2, 26

Subutex® (Reckitt Benckiser) CD

Tablets (sublingual), buprenorphine (as hydrochloride) 400 micrograms, net price 7-tab pack = £1.54; 2 mg, 7-tab pack = £6.46; 8 mg, 7-tab pack = £19.40. Label: 2, 26

With naloxone

Suboxone® (Schering-Plough) ▼ CD

Suboxone 2 mg/500 micrograms tablets (sublingual), buprenorphine (as hydrochloride) 2 mg, naloxone (as hydrochloride) 500 micrograms, net price 28-tab pack = £25.87. Label: 2, 26

Suboxone 8 mg/2 mg tablets (sublingual), buprenorphine (as hydrochloride) 8 mg, naloxone (as hydrochloride) 2 mg, net price 28-tab pack = £77.61. Label: 2, 26

Dose expressed as buprenorphine, ADULT and CHILD over 15 years, initially 2-4 mg once daily (an additional dose of 2–4 mg may be administered on day 1 depending on the individual patient's requirement), increased in steps of 2–8 mg according to response; max. 24 mg daily; total weekly dose may be divided and given on alternate days or 3 times weekly (but max. 24 mg daily)

Note The *Scottish Medicines Consortium* (p. 4) has advised (February 2007) that *Suboxone®* should be restricted for use in patients in whom methadone is not suitable

METHADONE HYDROCHLORIDE

Indications adjunct in treatment of opioid dependence, see notes above; analgesia (section 4.7.2); cough in terminal disease (section 3.9.1)

Cautions see Methadone, section 4.7.2

Contra-indications see Methadone, section 4.7.2

Hepatic impairment see notes in section 4.7.2

Renal impairment see notes in section 4.7.2

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see Methadone, section 4.7.2; **overdosage:** see Emergency Treatment of Poisoning, p. 36

Important Methadone, even in low doses is a **special hazard** for children; non-dependent adults are also at risk of toxicity; dependent adults are at risk if tolerance is incorrectly assessed during induction

Incompatibility Syrup preserved with hydroxybenzoate (parabens) esters may be incompatible with methadone hydrochloride.

Dose

- Initially 10–40 mg daily, increased by up to 10 mg daily (max. weekly increase 30 mg) until no signs of withdrawal or intoxication; usual dose range 60–120 mg daily; CHILD not recommended (see also important note above)

Note Methadone hydrochloride doses in the BNF may differ from those in the product literature

Methadone (Non-proprietary) CD

Oral solution 1 mg/mL, methadone hydrochloride 1 mg/mL, net price 20 mL = 29p, 30 mL = 62p, 40 mL = 58p, 50 mL = £1.04, 60 mL = 87p, 100 mL = £1.27, 500 mL = £11.34. Label: 2

Brands include *Metharose®* (sugar-free), *Physeptone* (sugar-free)

Important Methadone oral solution 1 mg/mL is 2½ times the strength of Methadone Linctus (section 3.9.1). Many preparations of Methadone oral solution are licensed for opioid drug addiction only but some are also licensed for analgesia in severe pain

Injection, methadone hydrochloride 25 mg/mL, net price 2-mL amp = £2.05; 50 mg/mL, 1-mL amp = £2.05

Brands include *Synastone®*

Methadose® (Rosemont) CD

Oral concentrate, methadone hydrochloride 10 mg/mL (blue), net price 150 mL = £12.01; 20 mg/mL (brown), 150 mL = £24.02. Label: 2

Note The final strength of the methadone mixture to be dispensed to the patient must be specified on the prescription

Important Care is required in prescribing and dispensing the **correct strength** since any confusion could lead to an overdose; this preparation should be dispensed only **after dilution** as appropriate with *Methadose® Diluent* (life of diluted solution 3 months) and is for drug dependent persons (see also p. 8)

Adjunctive therapy and symptomatic treatment

Adjunctive therapy may be required for the management of opioid withdrawal symptoms. **Loperamide** (p. 58) may be used for the control of diarrhoea; **mebeverine** (p. 48) for controlling stomach cramps; **paracetamol** (p. 259) and **non-steroidal anti-inflammatory drugs** (p. 630) for muscular pains and headaches; **metoclopramide** (p. 253) or **prochlorperazine** (p. 252) may be useful for nausea or vomiting. Topical **rubefacients** (p. 664) can be helpful for relieving muscle pain associated with methadone withdrawal. If a patient is suffering from insomnia, **benzodiazepines** (section 4.1) or **zopiclone** (p. 210) may be prescribed, but because of

the potential for abuse, prescriptions should be limited to a short course of a few days only. If anxiety or agitation is severe, specialist advice should be sought.

Lofexidine **Lofexidine** is an alpha$_2$-adrenergic agonist. It may alleviate some of the physical symptoms of opioid withdrawal by attenuating the increase in adrenergic neurotransmission that occurs during opioid withdrawal. Lofexidine can be prescribed as an adjuvant to opioid substitution therapy, initiated either at the same time as the opioid substitute, or during withdrawal of the opioid substitute. Alternatively, lofexidine may be prescribed instead of an opioid substitute in patients who have mild or uncertain dependence (including young people), and those with a short history of illicit drug use. The patient should take part of the dose at bedtime to offset insomnia associated with opioid withdrawal.

Monitoring of blood pressure and pulse rate is recommended on initiation, for at least 72 hours or until a stable dose is achieved, and on discontinuation; treatment should be discontinued gradually over 2–4 days to reduce the risk of rebound hypertension.

LOFEXIDINE HYDROCHLORIDE

Indications management of symptoms of opioid withdrawal

Cautions severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, bradycardia, hypotension (monitor pulse rate and blood pressure); history of QT prolongation, concomitant administration of drugs that prolong QT interval; metabolic disturbances; withdraw gradually over 2–4 days (or longer) to minimise risk of rebound hypertension and associated symptoms; depression; **interactions:** Appendix 1 (lofexidine)

Renal impairment caution in chronic impairment

Pregnancy use only if benefit outweighs risk—no information available

Breast-feeding use only if benefit outweighs risk—no information available

Side-effects dry mucous membranes; hypotension, bradycardia; dizziness, drowsiness; QT-interval prolongation also reported

Dose

- Initially, 800 micrograms daily in divided doses, increased as necessary in steps of 400–800 micrograms daily to max. 2.4 mg daily in divided doses; max. single dose 800 micrograms; recommended duration of treatment 7–10 days if no opioid use (but longer may be required)

BritLofex® (Genus) PoM
Tablets, peach, f/c, lofexidine hydrochloride 200 micrograms, net price 60-tab pack = £61.79. Label: 2

Opioid-receptor antagonists

Naloxone is an opioid-receptor antagonist used to reverse opioid overdose. Patients dependant on opioids can be given a supply of naloxone to be used in case of accidental overdose; see Emergency Treatment of Poisoning, p. 36.

Naltrexone is an opioid-receptor antagonist that precipitates withdrawal symptoms in opioid-dependent subjects. Because the effects of opioid-receptor agonists are blocked by naltrexone, it is prescribed as an aid to prevent relapse in formerly opioid-dependent patients.

NICE guidance
Naltrexone for the management of opioid dependence (January 2007)
Naltrexone is recommended for the prevention of relapse in formerly opioid-dependent patients who are motivated to remain in a supportive care abstinence programme. Naltrexone should be administered under supervision and its effectiveness in preventing opioid misuse reviewed regularly.

NALTREXONE HYDROCHLORIDE

Indications adjunct to prevent relapse in formerly opioid-dependent patients (who have remained opioid-free for at least 7–10 days)

Cautions liver function tests needed before and during treatment; test for opioid dependence with naloxone before treatment; avoid concomitant use of opioids but increased dose of opioid analgesic may be required for pain (monitor for opioid intoxication)
Note Patients should be warned that an attempt to overcome the blockade of opioid receptors by overdosing could result in acute opioid intoxication

Contra-indications patients currently dependent on opioids

Hepatic impairment avoid in acute hepatitis, hepatic failure, or severe impairment

Renal impairment avoid in severe impairment

Pregnancy use only if benefit outweighs risk

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, vomiting, abdominal pain, diarrhoea, constipation, reduced appetite, increased thirst; chest pain; anxiety, sleep disorders, headache, reduced energy, increased energy, irritability, emotional lability, dizziness; chills; urinary retention; delayed ejaculation, decreased potency; arthralgia, myalgia; increased lacrimation; rash, and increased sweating; *rarely* hepatic dysfunction, suicidal ideation, and speech disorders; *very rarely* hallucinations, tremor, and idiopathic thrombocytopenia

Dose

- ADULT over 18 years (initiate in specialist clinics only), 25 mg initially then 50 mg daily; total weekly dose (350 mg) may be divided and given on 3 days of the week for improved compliance (e.g. 100 mg on Monday and Wednesday, and 150 mg on Friday)

Nalorex® (Bristol-Myers Squibb) PoM
Tablets, yellow, f/c, scored, naltrexone hydrochloride 50 mg, net price 28-tab pack = £22.34

Opizone® (Genus) PoM
Tablets, beige, f/c, scored, naltrexone hydrochloride 50 mg, net price 28-tab pack = £23.00

4.11 Drugs for dementia

Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer's disease, specifically for mild to moderate disease. Rivastigmine is also licensed for

mild to moderate dementia associated with Parkinson's disease. The evidence to support the use of these drugs relates to their cognitive enhancement.

Treatment with drugs for dementia should be initiated and supervised only by a specialist experienced in the management of dementia.

Benefit is assessed by repeating the cognitive assessment at around 3 months. Such assessment cannot demonstrate how the disease may have progressed in the absence of treatment but it can give a good guide to response. Up to half the patients given these drugs will show a slower rate of cognitive decline. Drugs for dementia should be discontinued in those thought not to be responding. Many specialists repeat the cognitive assessment 4 to 6 weeks after discontinuation to assess deterioration; if significant deterioration occurs during this short period, consideration should be given to restarting therapy.

Donepezil is a reversible inhibitor of acetylcholinesterase. **Galantamine** is a reversible inhibitor of acetylcholinesterase and it also has nicotinic receptor agonist properties. **Rivastigmine** is a reversible non-competitive inhibitor of acetylcholinesterases; it is also licensed for treating mild to moderate dementia in Parkinson's disease.

Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

Memantine is a glutamate receptor antagonist; it is licensed for treating moderate to severe Alzheimer's disease.

NICE guidance

Donepezil, galantamine, rivastigmine, and memantine for Alzheimer's disease (August 2009)

Donepezil, galantamine, and rivastigmine can be used for the treatment of moderate Alzheimer's disease in patients whose mini mental-state examination (MMSE) score is 10–20 points under the following conditions:

- Alzheimer's disease must be diagnosed in a specialist clinic; cognitive, global, and behavioural functioning, activities of daily living, and the likelihood of compliance with treatment must be assessed;
- treatment should be initiated by specialists but can be continued by general practitioners under a shared-care protocol;
- the carers' views of the condition should be sought before and during treatment;
- the patient should be assessed every 6 months and drug treatment should continue only if the MMSE score remains at or above 10 points and if treatment is considered to have a worthwhile effect on the global, functional, and behavioural condition.

Healthcare professionals should not rely solely on the MMSE score to assess the severity of Alzheimer's disease when the patient has learning or other disabilities, or other communication difficulties.

NICE does not recommend initiation of memantine for Alzheimer's disease except as part of clinical studies.

DONEPEZIL HYDROCHLORIDE

Indications mild to moderate dementia in Alzheimer's disease

Cautions sick sinus syndrome or other supraventricular conduction abnormalities; susceptibility to peptic ulcers; asthma, chronic obstructive pulmonary disease; **interactions:** Appendix 1 (parasympathomimetics)

Hepatic impairment caution in mild to moderate impairment, no information available for severe impairment

Side-effects nausea, vomiting, anorexia, diarrhoea; fatigue, insomnia, headache, dizziness, syncope, hallucinations, agitation, aggression; muscle cramps; urinary incontinence; rash, pruritus; *less commonly* gastric and duodenal ulcers, gastro-intestinal haemorrhage, bradycardia, seizures; *rarely* sino-atrial block, AV block, hepatitis, extrapyramidal symptoms; potential for bladder outflow obstruction

Dose

- Initially 5 mg once daily at bedtime, increased if necessary after one month to max. 10 mg daily

Aricept® (Eisai) PoM

Tablets, f/c, donepezil hydrochloride 5 mg (white), net price 28-tab pack = £59.85; 10 mg (yellow), 28-tab pack = £83.89.

Aricept Evess® (Eisai) PoM

Orodispersible tablets, donepezil hydrochloride 5 mg (white), net price 28-tab pack = £59.85; 10 mg (yellow), 28-tab pack = £83.89. Counselling, administration

Counselling *Aricept Evess®* should be placed on the tongue, allowed to disperse, and swallowed

GALANTAMINE

Indications mild to moderate dementia in Alzheimer's disease

Cautions cardiac disease (including sick sinus syndrome or other supraventricular conduction abnormalities, unstable angina, congestive heart failure); electrolyte disturbances; susceptibility to peptic ulcers; asthma, chronic obstructive pulmonary disease, pulmonary infection; avoid in urinary retention, gastro-intestinal obstruction, and while recovering from bladder or gastro-intestinal surgery; **interactions:** Appendix 1 (parasympathomimetics)

Hepatic impairment

- for *immediate-release* preparations in moderate impairment, initially 4 mg once daily (preferably in the morning) for at least 7 days, then 4 mg twice daily for at least 4 weeks; max. 8 mg twice daily; avoid in severe impairment
- for *modified-release* preparations in moderate impairment, initially 8 mg on alternate days (preferably in the morning) for 7 days, then 8 mg once daily for 4 weeks; max. 16 mg daily; avoid in severe impairment

Renal impairment avoid if eGFR less than 9 mL/minute/1.73m^2

Side-effects vomiting, nausea, abdominal pain, diarrhoea, dyspepsia, anorexia, weight loss, bradycardia, hypertension, syncope, hallucination, depression, dizziness, tremor, headache, drowsiness, malaise, muscle spasm, sweating; *less commonly* taste disturbance, palpitation, arrhythmias, first-degree AV block,

hypotension, flushing, paraesthesia, dehydration, muscular weakness, blurred vision, tinnitus; *rarely* hepatitis, exacerbation of Parkinson's disease, seizures

Dose

- Initially 4 mg twice daily for 4 weeks increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily

Reminyl® (Shire) PoM

Tablets, f/c, galantamine (as hydrobromide) 8 mg (pink), net price 56-tab pack = £68.32; 12 mg (orange-brown), 56-tab pack = £84.00 Label: 3, 21

Oral solution, galantamine (as hydrobromide) 4 mg/mL, net price 100 mL with pipette = £120.00. Label: 3, 21

Modified release

Reminyl® XL (Shire) PoM

Capsules, m/r, galantamine (as hydrobromide) 8 mg (white), net price 28-cap pack = £51.88; 16 mg (pink), 28-cap pack = £64.90; 24 mg (beige), 28-cap pack = £79.80. Label: 3, 21, 25

Dose initially 8 mg once daily for 4 weeks increased to 16 mg once daily for 4 weeks; maintenance 16–24 mg daily

MEMANTINE HYDROCHLORIDE

Indications moderate to severe dementia in Alzheimer's disease

Cautions history of convulsions; **interactions**: Appendix 1 (memantine)

Hepatic impairment avoid in severe impairment—no information available

Renal impairment reduce dose to 10 mg daily if eGFR 30–49 mL/minute/1.73 m^2, if well tolerated after at least 7 days dose can be increased in steps to 20 mg daily; reduce dose to 10 mg daily if eGFR 5–29 mL/minute/1.73 m^2; avoid if eGFR less than 5 mL/minute/1.73 m^2

Side-effects constipation; hypertension; dyspnoea; headache, dizziness, drowsiness; *less commonly* vomiting, thrombosis, heart failure, confusion, fatigue, hallucinations, and abnormal gait; *very rarely* seizures; pancreatitis, psychosis, depression, and suicidal ideation also reported

Dose

- Initially 5 mg once daily, increased in steps of 5 mg at weekly intervals; max. 20 mg daily

Ebixa® (Lundbeck) PoM

Tablets, f/c, scored, memantine hydrochloride 10 mg, net price 28-tab pack = £34.50, 56-tab pack = £69.01, 112-tab pack = £138.01; 20 mg, 28-tab pack = £69.01; treatment initiation pack, 7 × 5 mg, 7 × 10 mg, 7 × 15 mg, and 7 × 20 mg = £43.13

Oral solution, memantine hydrochloride 5 mg/actuation (10 mg/mL), net price 50-g pump pack = £61.61, 100-g pump pack = £123.23

Counselling Solution should be dosed onto a spoon or into a glass of water

RIVASTIGMINE

Indications mild to moderate dementia in Alzheimer's disease or in Parkinson's disease

Cautions gastric or duodenal ulcers (or susceptibility to ulcers); monitor body-weight; sick sinus syndrome, conduction abnormalities; history of asthma or chronic obstructive pulmonary disease; history of seizures; bladder outflow obstruction; **interactions**: Appendix 1 (parasympathomimetics)

Hepatic impairment use with caution; avoid in severe impairment

Renal impairment use with caution

Side-effects nausea, vomiting, diarrhoea, dyspepsia, anorexia, weight loss, increased salivation, abdominal pain, bradycardia, dizziness, headache, drowsiness, malaise, agitation, anxiety, restlessness, confusion, insomnia, extrapyramidal symptoms (and worsening of Parkinson's disease), dehydration, sweating; *less commonly* atrial fibrillation, AV block, depression, syncope; *rarely* gastric and duodenal ulceration, angina, seizures, rash; *very rarely* gastro-intestinal haemorrhage, pancreatitis, tachycardia, hypertension, hallucinations

Note Transdermal administration less likely to cause gastro-intestinal disturbance

Dose

- See under preparations

Exelon® (Novartis) PoM

Capsules, rivastigmine (as hydrogen tartrate) 1.5 mg (yellow), net price 28-cap pack = £33.25, 56-cap pack = £66.51; 3 mg (orange), 28-cap pack = £33.25, 56-cap pack = £66.51; 4.5 mg (red), 28-cap pack = £33.25, 56-cap pack = £66.51; 6 mg (red/orange), 28-cap pack = £33.25, 56-cap pack = £66.51. Label: 21, 25

Oral solution, rivastigmine (as hydrogen tartrate) 2 mg/mL, net price 120 mL (with oral syringe) = £99.14. Label: 21

Dose initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to response and tolerance; usual range 3–6 mg twice daily; max. 6 mg twice daily; if treatment interrupted for more than several days, treatment should be retitrated from 1.5 mg twice daily

Patches, self-adhesive, beige, rivastigmine 4.6 mg/24 hours, net price 30 = £77.97; 9.5 mg/24 hours, 30 = £77.97

Dose initially apply 4.6 mg/24 hours patch to clean, dry, non-hairy, non-irritated skin on back, upper arm, or chest, removing after 24 hours and siting a replacement patch on a different area (avoid using the same area for 14 days); if well tolerated increase to 9.5 mg/24 hours patch daily after at least 4 weeks; if treatment interrupted for more than several days, treatment should be retitrated from 4.6 mg/24 hours patch

Note When switching from oral to transdermal therapy, patients taking 3–6 mg by mouth daily should initially switch to 4.6 mg/24 hours patch (then titrate as above); patients taking 9–12 mg by mouth daily should switch to 9.5 mg/24 hours patch. The first patch should be applied on the day following the last oral dose

Note The *Scottish Medicines Consortium* (p. 4) has advised (October 2007) that *Exelon®* patches should be restricted for use in patients with moderately severe Alzheimer's disease under the conditions of the NICE guidance (September 2007) and when a transdermal patch is an appropriate choice of formulation

5 Infections

5.1 Antibacterial drugs 321
5.1.1 Penicillins 332
5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin 333
5.1.1.2 Penicillinase-resistant penicillins 334
5.1.1.3 Broad-spectrum penicillins 335
5.1.1.4 Antipseudomonal penicillins 339
5.1.1.5 Mecillinams 340
5.1.2 Cephalosporins, carbapenems, and other beta-lactams 340
5.1.2.1 Cephalosporins 340
5.1.2.2 Carbapenems 344
5.1.2.3 Other beta-lactam antibiotics 346
5.1.3 Tetracyclines 346
5.1.4 Aminoglycosides 349
5.1.5 Macrolides 352
5.1.6 Clindamycin 354
5.1.7 Some other antibacterials 355
5.1.8 Sulfonamides and trimethoprim 359
5.1.9 Antituberculosis drugs 361
5.1.10 Antileprotic drugs 366
5.1.11 Metronidazole and tinidazole 367
5.1.12 Quinolones 368
5.1.13 Urinary-tract infections 371
5.2 Antifungal drugs 373
5.2.1 Triazole antifungals 374
5.2.2 Imidazole antifungals 377
5.2.3 Polyene antifungals 378
5.2.4 Echinocandin antifungals 378
5.2.5 Other antifungals 379
5.3 Antiviral drugs 381
5.3.1 HIV infection 381
5.3.2 Herpesvirus infections 392
5.3.2.1 Herpes simplex and varicella–zoster infection 392
5.3.2.2 Cytomegalovirus infection 395
5.3.3 Viral hepatitis 397
5.3.4 Influenza 399
5.3.5 Respiratory syncytial virus 400
5.4 Antiprotozoal drugs 402
5.4.1 Antimalarials 402
5.4.2 Amoebicides 411
5.4.3 Trichomonacides 412
5.4.4 Antigiardial drugs 412
5.4.5 Leishmaniacides 412
5.4.6 Trypanocides 413
5.4.7 Drugs for toxoplasmosis 413
5.4.8 Drugs for pneumocystis pneumonia 413
5.5 Anthelmintics 415
5.5.1 Drugs for threadworms 415
5.5.2 Ascaricides 416
5.5.3 Drugs for tapeworm infections 416
5.5.4 Drugs for hookworms 416
5.5.5 Schistosomicides 416
5.5.6 Filaricides 416
5.5.7 Drugs for cutaneous larva migrans 417
5.5.8 Drugs for strongyloidiasis 417

This chapter also includes advice on the drug management of the following:

- anthrax, p. 368
- *Clostridium difficile* infection, p. 322
- bacterial infections: table 1, summary of antibacterial treatment, p. 322
- bacterial infections: table 2, summary of antibacterial prophylaxis, p. 330
- Lyme disease, p. 336
- MRSA infections, p. 334
- oral infections, p. 321, p. 328, p. 373

Notifiable diseases

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

Anthrax	Mumps
Botulism	Paratyphoid fever
Brucellosis	Plague
Cholera	Poliomyelitis, acute
Diarrhoea (infectious bloody)	Rabies
Diphtheria	Rubella
Encephalitis, acute	SARS
Food poisoning	Scarlet fever
Haemolytic uraemic syndrome	Smallpox
Haemorrhagic fever (viral)	Streptococcal disease (Group A, invasive)
Hepatitis, viral	
Legionnaires' disease	Tetanus
Leprosy	Tuberculosis
Malaria	Typhoid fever
Measles	Typhus
Meningitis	Whooping cough
Meningococcal septicaemia	Yellow fever

Note It is good practice for doctors to also inform the consultant in communicable disease control of instances of other infections (e.g. psittacosis) where there could be a public health risk.

5.1 Antibacterial drugs

Choice of a suitable drug Before selecting an antibacterial the clinician must first consider two factors—the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties.

An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a patient complaining of nausea and symptoms of a urinary-tract infection in early pregnancy. The organism is reported as being resistant to ampicillin but sensitive to nitrofurantoin (can cause nausea), gentamicin (can be given only by injection and best avoided in pregnancy), tetracycline (causes dental discoloration) and trimethoprim (folate antagonist therefore theoretical teratogenic risk), and cefalexin. The safest antibiotics in pregnancy are the penicillins and cephalosporins; therefore, cefalexin would be indicated for this patient.

The principles involved in selection of an antibacterial must allow for a number of variables including changing renal and hepatic function, increasing bacterial resistance, and new information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

Antibacterial policies Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Before starting therapy The following precepts should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials may be used to treat secondary bacterial infection (e.g. bacterial pneumonia secondary to influenza);
- Samples should be taken for culture and sensitivity testing; **'blind'** antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of **prevalent organisms** and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication (e.g. life-threatening sepsis);
- The **dose** of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. The prescribing of the so-called 'standard' dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;
- The **route** of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;
- **Duration** of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections.

Oral bacterial infections Antibacterial drugs should only be prescribed for the *treatment* of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The 'blind' prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. In severe oral infections, a sample should always be taken for bacteriology.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be required if treatment has to be delayed, in immunocompromised patients, or in those with conditions such as diabetes or Paget's disease. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig's angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be changed, preferably on the basis of bacteriological

investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or erythromycin) with metronidazole may sometimes be helpful for the treatment of severe oral infections or oral infections that have not responded to initial antibacterial treatment.

See also **Penicillins** (section 5.1.1), **Cephalosporins** (section 5.1.2), **Tetracyclines** (section 5.1.3), **Macrolides** (section 5.1.5), **Clindamycin** (section 5.1.6), **Metronidazole** (section 5.1.11), **Fusidic acid** (section 13.10.1.2).

Superinfection In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. *fungal infections* or *antibiotic-associated colitis* (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Therapy Suggested treatment is shown in table 1. When the pathogen has been isolated treatment may be changed to a more appropriate antibacterial if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds. Infections for which prophylaxis is useful are listed in table 2.

Table 1. Summary of antibacterial therapy

If treating a patient suspected of suffering from a notifiable disease, the consultant in communicable disease control should be informed (see p. 320)

Gastro-intestinal system

Gastro-enteritis
Frequently self-limiting and may not be bacterial.
Antibacterial not usually indicated

Campylobacter enteritis
Frequently self-limiting; treat if immunocompromised or if severe infection.
Clarithromycin[1]
Alternative, ciprofloxacin

Salmonella (non-typhoid)
Treat invasive or severe infection. Do not treat less severe infection unless there is a risk of developing invasive infection (e.g. immunocompromised patients, those with haemoglobinopathy, the elderly, or children under 6 months of age).
Ciprofloxacin *or* cefotaxime

Shigellosis
Antibacterial not indicated for mild cases.
Ciprofloxacin *or* azithromycin
Alternatives if micro-organism sensitive, amoxicillin *or* trimethoprim

Typhoid fever
Infections from Middle-East, South Asia, and South-East Asia may be multiple-antibacterial-resistant and sensitivity should be tested.
Cefotaxime[2]
Azithromycin may be an alternative in mild or moderate disease caused by multiple-antibacterial-resistant organisms.
Alternative, ciprofloxacin
Strains with decreased sensitivity to ciprofloxacin being isolated

***Clostridium difficile* infection**
Oral metronidazole
Suggested duration of treatment 10–14 days
For third or subsequent episode of infection, for severe infection, for infection not responding to metronidazole, or in patients intolerant of metronidazole, oral vancomycin
Suggested duration of treatment 10–14 days
For infection not responding to vancomycin, or for life-threatening infection, or in patients with ileus, oral vancomycin + i/v metronidazole
Suggested duration of treatment 10–14 days

Biliary-tract infection
Ciprofloxacin *or* gentamicin *or* a cephalosporin

1. Where clarithromycin is suggested azithromycin or erythromycin may be used
2. Where cefotaxime is suggested ceftriaxone may be used

Peritonitis

A cephalosporin + metronidazole *or* gentamicin + metronidazole *or* gentamicin + clindamycin *or* piperacillin with tazobactam alone

Peritonitis: peritoneal dialysis-associated

Vancomycin[1] + ceftazidime added to dialysis fluid *or* vancomycin added to dialysis fluid + ciprofloxacin by mouth

Suggested duration of treatment 14 days or longer

Cardiovascular system

Endocarditis: initial 'blind' therapy

Flucloxacillin (*or* benzylpenicillin if symptoms less severe) + gentamicin

If cardiac prostheses present, or if penicillin-allergic, or if meticillin-resistant Staphylococcus aureus suspected, vancomycin + rifampicin + gentamicin

Endocarditis caused by staphylococci

Flucloxacillin

Add rifampicin for at least 2 weeks in prosthetic valve endocarditis.

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

If penicillin-allergic or if meticillin-resistant Staphylococcus aureus, vancomycin + rifampicin

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

Native-valve endocarditis caused by fully-sensitive streptococci (e.g. viridans streptococci)

Benzylpenicillin

Suggested duration of treatment 4 weeks

Alternative if a large vegetation, intracardial abscess, or infected emboli are absent, benzylpenicillin + gentamicin

Suggested duration of treatment 2 weeks

If penicillin-allergic, vancomycin

Suggested duration of treatment 4 weeks

Native-valve endocarditis caused by less-sensitive streptococci

Benzylpenicillin + gentamicin

Suggested duration of treatment 4–6 weeks (stop gentamicin after 2 weeks for micro-organisms moderately sensitive to penicillin)

If aminoglycoside cannot be used and if streptococci moderately sensitive to penicillin, benzylpenicillin

Suggested duration of treatment 4 weeks

If penicillin-allergic or highly penicillin-resistant, vancomycin[1] + gentamicin

Suggested duration of treatment 4–6 weeks (stop gentamicin after 2 weeks for micro-organisms moderately sensitive to penicillin)

Prosthetic valve endocarditis caused by streptococci

Benzylpenicillin + gentamicin

Suggested duration of treatment at least 6 weeks (stop gentamicin after 2 weeks if micro-organisms fully sensitive to penicillin)

If penicillin-allergic or highly penicillin-resistant, vancomycin[1] + gentamicin

Suggested duration of treatment at least 6 weeks (stop gentamicin after 2 weeks if micro-organisms fully sensitive to penicillin)

Endocarditis caused by enterococci (e.g. *Enterococcus faecalis*)

Amoxicillin[2] + gentamicin

If gentamicin-resistant, substitute gentamicin with streptomycin.

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

If penicillin-allergic or penicillin-resistant, vancomycin[1] + gentamicin

If gentamicin-resistant, substitute gentamicin with streptomycin.

Suggested duration of treatment at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis)

Endocarditis caused by haemophilus, actinobacillus, cardiobacterium, eikenella, and kingella species ('HACEK' micro-organisms)

Amoxicillin[2] + low-dose gentamicin

Suggested duration of treatment 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

If amoxicillin-resistant, ceftriaxone + low-dose gentamicin

Suggested duration of treatment 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

1. Where vancomycin is suggested teicoplanin may be used
2. Where amoxicillin is suggested ampicillin may be used

Respiratory system

Haemophilus influenzae epiglottitis

Cefotaxime[1]

If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol

Chronic bronchitis: acute exacerbations

Treat if increase in sputum purulence accompanied by an increase in sputum volume or increase in dyspnoea.

Amoxicillin[2] *or* tetracycline

Some pneumococci and *Haemophilus influenzae* strains tetracycline-resistant; approx. 20% *H. influenzae* strains amoxicillin-resistant.

Suggested duration of treatment 5 days; longer treatment may be necessary in severely ill patients

Alternative, clarithromycin[3]

Suggested duration of treatment 5 days; longer treatment may be necessary in severely ill patients

Pneumonia: low-severity community-acquired

Amoxicillin[2]

Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
If atypical pathogens suspected, add clarithromycin[3].
If staphylococci suspected (e. g. in influenza or measles), add flucloxacillin.
Suggested duration of treatment 7 days (14–21 days for infections caused by staphylococci)

Alternatives, doxycycline *or* clarithromycin[3]

Suggested duration of treatment 7 days (14–21 days for infections caused by staphylococci)

Pneumonia: moderate-severity community-acquired

Amoxicillin[2] + clarithromycin[3] *or* doxycycline alone

Pneumococci with decreased penicillin sensitivity being isolated, but not yet common in UK.
If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin[4].
Suggested duration of treatment 7 days (14–21 days for infections caused by staphylococci)

Pneumonia: high-severity community-acquired

Co-amoxiclav + clarithromycin[3]

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin[4].
Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

Alternatives, cefuroxime + clarithromycin[3] *or* cefotaxime[1] + clarithromycin[3]

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin[4].
Suggested duration of treatment 7–10 days (may extend treatment to 14–21 days in some cases e.g. if staphylococci or Gram-negative enteric bacilli suspected)

Pneumonia possibly caused by atypical pathogens

Clarithromycin[3]

If high-severity Legionella infection, add rifampicin for the first few days.
Suggested duration of treatment 14 days (usually 7–10 days for Legionella)

Alternative if Legionella infection suspected, a quinolone

If high-severity Legionella infection, add clarithromycin[3] or rifampicin for the first few days.
Suggested duration of treatment usually 7–10 days

Alternative for chlamydial or mycoplasma infections, doxycycline

Suggested duration of treatment 14 days

Pneumonia: hospital-acquired

Early-onset infection (less than 5 days after admission to hospital), co-amoxiclav *or* cefuroxime

If life-threatening infection, or if history of antibacterial treatment in the last 3 months, or if resistant micro-organisms suspected, treat as for late-onset hospital-acquired pneumonia.
Suggested duration of treatment 7 days

Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam) *or* a broad-spectrum cephalosporin (e.g. ceftazidime) *or* another antipseudomonal beta-lactam *or* a quinolone (e.g. ciprofloxacin)

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin.
For severe illness caused by *Pseudomonas aeruginosa*, consider adding an aminoglycoside.
Suggested duration of treatment 7 days (longer if *Pseudomonas aeruginosa* confirmed)

1. Where cefotaxime is suggested ceftriaxone may be used
2. Where amoxicillin is suggested ampicillin may be used
3. Where clarithromycin is suggested azithromycin or erythromycin may be used
4. Where vancomycin is suggested teicoplanin may be used

Central nervous system

Meningitis: initial empirical therapy

- Transfer patient to hospital urgently
- If *meningococcal disease* (meningitis with non-blanching rash or meningococcal septicaemia) suspected, benzylpenicillin (see p. 334 for dose) can be given before transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, benzylpenicillin (see p. 334 for dose) can be given before the transfer. Cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol (section 5.1.7) may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.
- In hospital, consider adjunctive treatment with dexamethasone (particularly if pneumococcal meningitis suspected in adults; section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery.
- In hospital, if aetiology unknown:

Adult and child 3 months–50 years, cefotaxime[1]

Consider adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.

Suggested duration of treatment at least 10 days

Adult over 50 years, cefotaxime[1] + amoxicillin[2]

Consider adding vancomycin if prolonged or multiple use of other antibacterials in the last 3 months, or if travelled, in the last 3 months, to areas outside the UK with highly penicillin- and cephalosporin-resistant pneumococci.

Suggested duration of treatment at least 10 days

Meningitis caused by meningococci

Benzylpenicillin *or* cefotaxime[1]

Suggested duration of treatment 7 days.

To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol

Suggested duration of treatment 7 days.

To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

Meningitis caused by pneumococci

Cefotaxime[1]

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial (may reduce penetration of vancomycin into cerebrospinal fluid).

If micro-organism penicillin-sensitive, replace cefotaxime with benzylpenicillin.

If micro-organism highly penicillin- and cephalosporin-resistant, add vancomycin and if necessary rifampicin.

Suggested duration of antibacterial treatment 14 days

Meningitis caused by *Haemophilus influenzae*

Cefotaxime[1]

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.

Suggested duration of antibacterial treatment 10 days.

For *H. influenzae* type b give rifampicin for 4 days before hospital discharge (see Table 2, section 5.1)

If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if micro-organism resistant to cefotaxime, chloramphenicol

Consider adjunctive treatment with dexamethasone (section 6.3.2), preferably starting before or with first dose of antibacterial, but no later than 12 hours after starting antibacterial.

Suggested duration of antibacterial treatment 10 days.

For *H. influenzae* type b give rifampicin for 4 days before hospital discharge (see Table 2, section 5.1)

Meningitis caused by Listeria

Amoxicillin[2] + gentamicin

Suggested duration of treatment 21 days.

Consider stopping gentamicin after 7 days

If history of immediate hypersensitivity reaction to penicillin, co-trimoxazole

Suggested duration of treatment 21 days

1. Where cefotaxime is suggested ceftriaxone may be used
2. Where amoxicillin is suggested ampicillin may be used

Urinary tract

Pyelonephritis: acute

A broad-spectrum cephalosporin *or* a quinolone

Suggested duration of treatment 10–14 days (longer treatment may be necessary in complicated pyelonephritis)

Prostatitis: acute

Ciprofloxacin *or* ofloxacin

Suggested duration of treatment 28 days

Alternative, trimethoprim

Suggested duration of treatment 28 days

Urinary-tract infection: 'lower'

Trimethoprim *or* nitrofurantoin

Suggested duration of treatment 7 days, but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women. See also section 5.1.13

Alternative, amoxicillin[1] *or* oral cephalosporin

Suggested duration of treatment 7 days, but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women. See also section 5.1.13

Genital system

Early syphilis (infection of less than 2 years)

Contact tracing recommended.

Benzathine benzylpenicillin [unlicensed]

Suggested duration of treatment single-dose (repeat dose after 7 days for women in the third trimester of pregnancy)

Alternatives, doxycycline *or* erythromycin

Suggested duration of treatment 14 days

Late latent syphilis (asymptomatic infection of more than 2 years)

Contact tracing recommended.

Benzathine benzylpenicillin [unlicensed]

Suggested duration of treatment once weekly for 2 weeks

Alternative, doxycycline

Suggested duration of treatment 28 days

Asymptomatic contacts of patients with infectious syphilis

Doxycycline

Suggested duration of treatment 14 days

Gonorrhoea: uncomplicated

Contact tracing recommended. Remember chlamydia. Choice of antibacterial depends on locality where infection acquired.

Cefixime

Suggested duration of treatment single-dose

Alternative if micro-organism sensitive, ciprofloxacin

Suggested duration of treatment single-dose

Pharyngeal infection, ceftriaxone

Suggested duration of treatment single-dose

Uncomplicated genital chlamydial infection, non-gonococcal urethritis and non-specific genital infection

Contact tracing recommended.

Azithromycin *or* doxycycline

Suggested duration of treatment azithromycin as a single dose or doxycycline for 7 days

Alternative, erythromycin

Suggested duration of treatment 14 days

Pelvic inflammatory disease

Contact tracing recommended.

Doxycycline + metronidazole + i/m ceftriaxone *or* ofloxacin + metronidazole

Suggested duration of treatment 14 days (use i/m ceftriaxone as a single dose).

In severely ill patients initial treatment with doxycycline + i/v ceftriaxone (as a single dose) + i/v metronidazole, then switch to oral treatment with doxycycline + metronidazole to complete 14 days' treatment

1. Where amoxicillin is suggested ampicillin may be used

Bacterial vaginosis

Oral metronidazole

Suggested duration of treatment 5–7 days (or high-dose metronidazole as a single dose)

Alternative, topical metronidazole *or* topical clindamycin

Suggested duration of treatment 5 days with metronidazole or 7 days with clindamycin

Blood

Septicaemia: community-acquired

A broad-spectrum antipseudomonal penicillin (e.g. piperacillin with tazobactam, ticarcillin with clavulanic acid) *or* a broad-spectrum cephalosporin (e.g. cefuroxime)

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin[1].
If anaerobic infection suspected, add metronidazole to broad-spectrum cephalosporin.
If other resistant micro-organisms suspected, use a more broad-spectrum beta-lactam antibacterial (e.g. meropenem)

Septicaemia: hospital-acquired

A broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam, ticarcillin with clavulanic acid, ceftazidime, imipenem with cilastatin, *or* meropenem)

If meticillin-resistant *Staphylococcus aureus* suspected, add vancomycin[1].
If anaerobic infection suspected, add metronidazole to broad-spectrum cephalosporin

Septicaemia related to vascular catheter

Vancomycin[1]

If Gram-negative sepsis suspected, especially in the immunocompromised, add a broad-spectrum antipseudomonal beta-lactam.
Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus*, pseudomonas, or *Candida* species

Meningococcal septicaemia

If meningococcal disease suspected, a single dose of benzylpenicillin (see p. 334 for dose) can be given before urgent transfer to hospital, so long as this does not delay the transfer; cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins.

Benzylpenicillin or cefotaxime[2]

To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

If history of immediate hypersensitivity reaction to penicillin or to cephalosporins, chloramphenicol

To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

Musculoskeletal system

Osteomyelitis

Seek specialist advice if chronic infection or prostheses present.

Flucloxacillin

Consider adding fusidic acid or rifampicin for initial 2 weeks.
Suggested duration of treatment 6 weeks for acute infection

If penicillin-allergic, clindamycin

Consider adding fusidic acid or rifampicin for initial 2 weeks.
Suggested duration of treatment 6 weeks for acute infection

If meticillin-resistant Staphylococcus aureus suspected, vancomycin[1]

Consider adding fusidic acid or rifampicin for initial 2 weeks.
Suggested duration of treatment 6 weeks for acute infection

Septic arthritis

Seek specialist advice if prostheses present.

Flucloxacillin

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If penicillin-allergic, clindamycin

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If meticillin-resistant Staphylococcus aureus suspected, vancomycin[1]

Suggested duration of treatment 4–6 weeks (longer if infection complicated)

If gonococcal arthritis or Gram-negative infection suspected, cefotaxime[2]

Suggested duration of treatment 4–6 weeks (longer if infection complicated; treat gonococcal infection for 2 weeks)

1. Where vancomycin is suggested teicoplanin may be used
2. Where cefotaxime is suggested ceftriaxone may be used

Eye

Purulent conjunctivitis

Chloramphenicol eye-drops

See also section 11.3.1

Ear, nose, and oropharynx

Pericoronitis

Antibacterial required only in presence of systemic features of infection, or of trismus, or persistent swelling despite local treatment.

Metronidazole

Suggested duration of treatment 3 days or until symptoms resolve

Alternative, amoxicillin

Suggested duration of treatment 3 days or until symptoms resolve

Gingivitis: acute necrotising ulcerative

Antibacterial required only if systemic features of infection.

Metronidazole

Suggested duration of treatment 3 days or until symptoms resolve

Alternative, amoxicillin

Suggested duration of treatment 3 days or until symptoms resolve

Periapical or periodontal abscess

Antibacterial required only in severe disease with cellulitis or if systemic features of infection.

Amoxicillin

Suggested duration of treatment 5 days

Alternative, metronidazole

Suggested duration of treatment 5 days

Periodontitis

Antibacterial used as an adjunct to debridement in severe disease or disease unresponsive to local treatment alone.

Metronidazole

Alternative, doxycycline

Throat infections

Most throat infections are caused by viruses and many do not require antibacterial therapy. Consider antibacterial, if history of valvular heart disease, if marked systemic upset, if peritonsillar cellulitis or abscess, or if at increased risk from acute infection (e.g. in immunosuppression, cystic fibrosis); prescribe antibacterial for beta-haemolytic streptococcal pharyngitis.

Phenoxymethylpenicillin

In severe infection, initial parenteral therapy with benzylpenicillin, then oral therapy with phenoxymethylpenicillin *or* amoxicillin[1]. **Avoid** amoxicillin if possibility of glandular fever, see section 5.1.1.3.

Suggested duration of treatment 10 days

If penicillin-allergic, clarithromycin[2]

Suggested duration of treatment 10 days

Sinusitis

Antibacterial should usually be used only for persistent symptoms and purulent discharge lasting at least 7 days or if severe symptoms. Also, consider antibacterial for those at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis).

Amoxicillin[1] *or* doxycycline *or* clarithromycin[2]

Suggested duration of treatment 7 days.

Consider oral co-amoxiclav if no improvement after 48 hours.

In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime may be required

Otitis externa

Consider systemic antibacterial if spreading cellulitis or patient systemically unwell.

For topical preparations see section 12.1.1.

Flucloxacillin

If penicillin-allergic, clarithromycin[2]

If pseudomonas suspected, ciprofloxacin (*or* an aminoglycoside)

1. Where amoxicillin is suggested ampicillin may be used
2. Where clarithromycin is suggested azithromycin or erythromycin may be used

Otitis media

Many infections caused by viruses. Most uncomplicated cases resolve without antibacterial treatment. In children without systemic features, antibacterial treatment may be started after 72 hours if no improvement. Consider earlier treatment if deterioration, if systemically unwell, if at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis present, or in children under 2 years of age with bilateral otitis media.

Amoxicillin[1]

Consider co-amoxiclav if no improvement after 48 hours.
In severe infection, initial parenteral therapy with co-amoxiclav or cefuroxime.
Suggested duration of treatment 5 days (longer if severely ill)

If penicillin-allergic, clarithromycin[2]

Suggested duration of treatment 5 days (longer if severely ill)

Skin

Impetigo: small areas of skin infected

Seek local microbiology advice before using topical treatment in hospital.

Topical fusidic acid

Suggested duration of treatment 7 days is usually adequate (max. 10 days)

Alternative if meticillin-resistant Staphylococcus aureus, topical mupirocin

Suggested duration of treatment 7 days is usually adequate (max. 10 days)

Impetigo: widespread infection

Oral flucloxacillin

If streptococci suspected in severe infection, add phenoxymethylpenicillin.
Suggested duration of treatment 7 days

If penicillin-allergic, oral clarithromycin[2]

Suggested duration of treatment 7 days

Erysipelas

Phenoxymethylpenicillin *or* benzylpenicillin

If staphylococci suspected, replace phenoxymethylpenicillin or benzylpenicillin with flucloxacillin.
Suggested duration of treatment at least 7 days

If penicillin-allergic, clindamycin *or* clarithromycin[2]

Suggested duration of treatment at least 7 days

Cellulitis: mild or moderate

Flucloxacillin

If streptococcal infection confirmed, replace flucloxacillin with phenoxymethylpenicillin or benzylpenicillin.
If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials

If penicillin-allergic, clindamycin *or* clarithromycin[2]

If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials

Cellulitis: severe

Benzylpenicillin + flucloxacillin

If oral treatment required, replace benzylpenicillin with phenoxymethylpenicillin.
If streptococcal infection confirmed, discontinue flucloxacillin.
If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials

If penicillin-allergic, clindamycin *or* clarithromycin[2]

If Gram-negative bacteria or anaerobes suspected, use broad-spectrum antibacterials

Animal and human bites

Cleanse wound thoroughly. For tetanus-prone wound, give human tetanus immunoglobulin (with a tetanus-containing vaccine if necessary, according to immunisation history and risk of infection), see under Tetanus Vaccines, section 14.4. Consider rabies prophylaxis (section 14.4) for bites from animals in endemic countries; assess risk of blood-borne viruses.

Co-amoxiclav

If penicillin-allergic, doxycycline + metronidazole

Acne

See section 13.6

1. Where amoxicillin is suggested ampicillin may be used
2. Where clarithromycin is suggested azithromycin or erythromycin may be used

Table 2. Summary of antibacterial prophylaxis

Prevention of recurrence of rheumatic fever

Phenoxymethylpenicillin 250 mg twice daily *or* sulfadiazine 1 g daily (500 mg daily for patients under 30 kg)

Prevention of secondary case of invasive group A streptococcal infection[1]

Phenoxymethylpenicillin 250–500 mg every 6 hours for 10 days; CHILD under 1 year 62.5 mg every 6 hours, 1–5 years 125 mg every 6 hours, 6–12 years 250 mg every 6 hours

Patients who are penicillin allergic,

either erythromycin ADULT and CHILD over 8 years, 250–500 mg every 6 hours for 10 days; CHILD under 2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours

or azithromycin [unlicensed indication] 500 mg once daily for 5 days; CHILD over 6 months, 12 mg/kg (max. 500 mg) once daily

Prevention of secondary case of meningococcal meningitis[2]

Rifampicin 600 mg every 12 hours for 2 days; CHILD 10 mg/kg (under 1 year, 5 mg/kg) every 12 hours for 2 days

or ciprofloxacin 500 mg as a single dose; CHILD [unlicensed] 2–5 years 125 mg; 5–12 years 250 mg

or i/m ceftriaxone [unlicensed indication] 250 mg as a single dose; CHILD under 12 years 125 mg

Prevention of secondary case of *Haemophilus influenzae* type b disease[2]

Rifampicin 600 mg once daily for 4 days (regimen of choice for adults); CHILD 1–3 months 10 mg/kg once daily for 4 days, over 3 months 20 mg/kg once daily for 4 days (max. 600 mg daily)

Prevention of secondary case of diphtheria in non-immune patient

Erythromycin[3] 500 mg every 6 hours for 7 days; CHILD up to 2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days' treatment. For immunisation against diphtheria see section 14.4

Prevention of secondary case of pertussis in non-immune patient or partially immune patient

Erythromycin[3] ADULT and CHILD over 8 years, 250–500 mg every 6 hours for 7 days; CHILD under 2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours

Prevention of pneumococcal infection in asplenia or in patients with sickle-cell disease

Phenoxymethylpenicillin 500 mg every 12 hours; CHILD under 5 years 125 mg every 12 hours, 6–12 years 250 mg every 12 hours—if cover also needed for *H. influenzae* in CHILD give amoxicillin instead (under 5 years 125 mg every 12 hours, over 5 years 250 mg every 12 hours)

Note Antibiotic prophylaxis is not fully reliable; for vaccines in asplenia see p. 749

Prevention of gas-gangrene in high lower-limb amputations

Benzylpenicillin 300–600 mg every 6 hours for 5 days *or* if penicillin-allergic metronidazole 400–500 mg every 8 hours

Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive[4]

Isoniazid 300 mg daily for 6 months; CHILD 5 mg/kg daily (max. 300 mg daily)

or isoniazid 300 mg daily + rifampicin 600 mg daily (450 mg if less than 50 kg) for 3 months; CHILD isoniazid 5 mg/kg daily (max. 300 mg daily) + rifampicin 10 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)

or (if isoniazid-resistant tuberculosis in patients under 35 years) rifampicin 600 mg daily (450 mg if less than 50 kg) for 6 months; CHILD 10 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)

Prevention of infection in gastro-intestinal procedures

Operations on stomach or oesophagus[5]

Single dose[6] of i/v gentamicin *or* i/v cefuroxime *or* i/v co-amoxiclav

Add i/v teicoplanin[7] if high risk of meticillin-resistant *Staphylococcus aureus*

1. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency Laboratory)
2. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis
3. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used
4. For details of those who should receive chemoprophylaxis contact the lead clinician for local tuberculosis services (or a consultant in communicable disease control). See also section 5.1.9, for advice on immunocompromised patients and on prevention of tuberculosis
5. Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure
6. Additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss
7. Where teicoplanin is suggested vancomycin may be used

Open biliary surgery[1]

Single dose[2] of i/v cefuroxime + i/v metronidazole[3] *or* i/v gentamicin + i/v metronidazole[3] *or* i/v co-amoxiclav alone

Add i/v teicoplanin[4] if high risk of meticillin-resistant *Staphylococcus aureus*

Resections of colon and rectum for carcinoma, and resections in inflammatory bowel disease, and appendicectomy[1]

Single dose[2] of i/v gentamicin + i/v metronidazole[3] *or* i/v cefuroxime + i/v metronidazole[3] *or* i/v co-amoxiclav alone

Add i/v teicoplanin[4] if high risk of meticillin-resistant *Staphylococcus aureus*

Endoscopic retrograde cholangiopancreatography[1]

Single dose of i/v gentamicin *or* oral *or* i/v ciprofloxacin

Prophylaxis recommended if pancreatic pseudocyst, immunocompromised, history of liver transplantation, or risk of incomplete biliary drainage. For biliary complications following liver transplantation, add i/v amoxicillin or i/v vancomycin

Percutaneous endoscopic gastrostomy or jejunostomy[1]

Single dose of i/v co-amoxiclav *or* i/v cefuroxime

Use single dose of i/v teicoplanin[4] if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*

Prevention of infection in orthopaedic surgery

Joint replacement including hip and knee[1]

Single dose[2] of i/v cefuroxime alone *or* i/v flucloxacillin + i/v gentamicin

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant *Staphylococcus aureus*, use single dose[2] of i/v teicoplanin[4] + i/v gentamicin

Closed fractures[1]

Single dose[2] of i/v cefuroxime *or* i/v flucloxacillin

If history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant *Staphylococcus aureus*, use single dose[2] of i/v teicoplanin[4]

Open fractures

i/v co-amoxiclav alone *or* i/v cefuroxime + i/v metronidazole (*or* i/v clindamycin alone if history of allergy to penicillins or to cephalosporins)

Add i/v teicoplanin[4] if high risk of meticillin-resistant *Staphylococcus aureus*. Start prophylaxis within 3 hours of injury and continue until soft tissue closure (max. 72 hours); at first debridement also use a single dose of i/v cefuroxime + i/v metronidazole + i/v gentamicin *or* i/v co-amoxiclav + i/v gentamicin (*or* i/v clindamycin + i/v gentamicin if history of allergy to penicillins or to cephalosporins). At time of skeletal stabilisation and definitive soft tissue closure[1] use a single dose of i/v gentamicin + i/v teicoplanin[4]

1. Intravenous antibacterial prophylaxis should be given up to 30 minutes before the procedure
2. Additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss
3. Metronidazole may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery
4. Where teicoplanin is suggested vancomycin may be used

Prevention of infection in urological procedures

Transrectal prostate biopsy[1]

Single dose[2] of oral ciprofloxacin + oral metronidazole *or* i/v gentamicin + i/v metronidazole[3]

Use single dose[2] of i/v gentamicin + i/v metronidazole[3] if high risk of meticillin-resistant *Staphylococcus aureus*

Transurethral resection of prostate[1]

Single dose[2] of oral ciprofloxacin *or* i/v gentamicin *or* i/v cefuroxime

Use single dose[2] of i/v gentamicin if high risk of meticillin-resistant *Staphylococcus aureus*

Prevention of infection in obstetric and gynaecological surgery

Caesarean section

Single dose[2] of i/v cefuroxime

Administer immediately after umbilical cord is clamped. Substitute i/v clindamycin if history of allergy to penicillins or cephalosporins. Add i/v teicoplanin[4] if high risk of meticillin-resistant *Staphylococcus aureus*

Hysterectomy[1]

Single dose[2] of i/v cefuroxime + i/v metronidazole[3] *or* i/v gentamicin + i/v metronidazole[3] *or* i/v co-amoxiclav alone

Use single dose[2] of i/v gentamicin + i/v metronidazole[3] or add i/v teicoplanin[4] to other regimens if high risk of meticillin-resistant *Staphylococcus aureus*

Termination of pregnancy

Single dose[2] of oral metronidazole

If genital chlamydial infection cannot be ruled out, give doxycycline (section 5.1.3) postoperatively

Prevention of infection in cardiology procedures

Cardiac pacemaker insertion[1]

Single dose[2] of i/v cefuroxime alone *or* i/v flucloxacillin + i/v gentamicin *or* i/v teicoplanin[4] + i/v gentamicin

Use single dose[2] of i/v teicoplanin[4] + i/v cefuroxime *or* i/v teicoplanin[4] + i/v gentamicin if high risk of meticillin-resistant *Staphylococcus aureus*

Prevention of infection in vascular surgery

Reconstructive arterial surgery of abdomen, pelvis or legs[1]

Single dose[2] of i/v cefuroxime alone *or* i/v flucloxacillin + i/v gentamicin

Add i/v metronidazole for patients at risk from anaerobic infections including those with diabetes, gangrene, or undergoing amputation. Use single dose[2] of i/v teicoplanin[4] + i/v gentamicin if history of allergy to penicillins or cephalosporins, or if high risk of meticillin-resistant *Staphylococcus aureus*

Prevention of endocarditis

NICE guidance

Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (March 2008)

Antibacterial prophylaxis and chlorhexidine mouthwash are **not** recommended for the prevention of endocarditis in patients undergoing dental procedures.

Antibacterial prophylaxis is **not** recommended for the prevention of endocarditis in patients undergoing procedures of the:

- upper and lower respiratory tract (including ear, nose, and throat procedures and bronchoscopy);
- genito-urinary tract (including urological, gynaecological, and obstetric procedures);
- upper and lower gastro-intestinal tract.

Whilst these procedures can cause bacteraemia, there is no clear association with the development of infective endocarditis. Prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Any infection in patients at risk of endocarditis[1] should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

If patients at risk of endocarditis[1] are undergoing a gastro-intestinal or genito-urinary tract procedure at a site where infection is suspected, they should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis.

Patients at risk of endocarditis[1] should be:

- advised to maintain good oral hygiene;
- told how to recognise signs of infective endocarditis, and advised when to seek expert advice.

Dermatological procedures

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who undergo dermatological procedures[2] do not require antibacterial prophylaxis against endocarditis.

1. Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis
2. The British Association of Dermatologists Therapy Guidelines and Audit Subcommittee advise that such dermatological procedures include skin biopsies and excision of moles or of malignant lesions

Joint prostheses and dental treatment

Joint prostheses and dental treatment

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive.

The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

Immunosuppression and indwelling intraperitoneal catheters

Immunosuppression and indwelling intraperitoneal catheters

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis.

The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

5.1.1 Penicillins

5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin
5.1.1.2 Penicillinase-resistant penicillins
5.1.1.3 Broad-spectrum penicillins
5.1.1.4 Antipseudomonal penicillins
5.1.1.5 Mecillinams

The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

Hypersensitivity reactions The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins. Indi-

viduals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive a penicillin. Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. As patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics; aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients and can be used with caution. If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity (see also p. 340).

Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other beta-lactam antibiotics (including cephalosporins) can be used in these patients.

Other side-effects A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation. This may result from excessively high doses or in patients with severe renal failure. The penicillins should **not** be given by intrathecal injection because they can cause encephalopathy which may be fatal.

Another problem relating to high doses of penicillin, or normal doses given to patients with renal failure, is the accumulation of electrolyte since most injectable penicillins contain either sodium or potassium.

Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic-associated colitis.

5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin sodium (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax (section 5.1.12), diphtheria, gas-gangrene, leptospirosis, and treatment of Lyme disease (section 5.1.1.3). Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; benzylpenicillin is no longer the drug of first choice for pneumococcal meningitis. Although benzylpenicillin is effective in the treatment of tetanus, metronidazole (section 5.1.11) is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gut is low; therefore it is best given by injection.

Benzathine benzylpenicillin (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is used for the treatment of early syphilis and late latent syphilis; it is given by intramuscular injection.

Phenoxymethylpenicillin (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.

Oral infections Phenoxymethylpenicillin is effective for dentoalveolar abscess.

BENZYLPENICILLIN SODIUM
(Penicillin G)

Indications throat infections, otitis media, endocarditis, meningococcal disease, pneumonia, cellulitis (Table 1, section 5.1); anthrax; intrapartum prophylaxis against group B streptococcal infection; prophylaxis in limb amputation (Table 2, section 5.1); see also notes above

Cautions history of allergy; false-positive urinary glucose (if tested for reducing substances); **interactions:** Appendix 1 (penicillins)

Contra-indications penicillin hypersensitivity

Renal impairment reduce dose—consult product literature; high doses may cause cerebral irritation, convulsions, or coma

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction; *rarely* CNS toxicity including convulsions (especially with high doses or in severe renal impairment), interstitial nephritis, haemolytic anaemia, leucopenia, thrombocytopenia, and coagulation disorders; also reported diarrhoea (including antibiotic-associated colitis)

Dose

- By intramuscular *or* by slow intravenous injection *or* by infusion, 0.6–1.2 g every 6 hours, increased if necessary in more serious infections (single doses over 1.2 g intravenous route only; see also below); NEONATE under 7 days, 25 mg/kg every 12 hours, dose doubled in severe infection; NEONATE 7–28 days, 25 mg/kg every 8 hours, dose doubled in severe infection; CHILD 1 month–18 years, 25 mg/kg every 6 hours (increased in severe infection to 50 mg/kg every 4–6 hours (max. 2.4 g every 4 hours); intravenous route recommended in neonates and infants
- Endocarditis (in combination with another antibacterial if necessary, see Table 1, section 5.1), by slow intravenous injection *or* by infusion, 1.2 g every 4 hours, increased if necessary (e.g. in enterococcal endocarditis or if benzylpenicillin used alone) to 2.4 g every 4 hours; CHILD 1 month–18 years see *BNF for Children*
- Anthrax (in combination with other antibacterials, see also section 5.1.12), by slow intravenous injection *or* by infusion, 2.4 g every 4 hours; CHILD 37.5 mg/kg every 6 hours

- Intrapartum prophylaxis against group B streptococcal infection, by slow intravenous injection *or* by infusion, initially 3 g then 1.5 g every 4 hours until delivery
- Meningitis, meningococcal disease, by slow intravenous injection *or* by infusion, 2.4 g every 4 hours; NEONATE, 75 mg/kg every 8 hours; CHILD 1 month–18 years, 50 mg/kg every 4–6 hours (max. 2.4 g every 4 hours)

  Important. If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) is suspected, a single dose of benzylpenicillin can be given before transferring the patient to hospital urgently, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently, a single dose of benzylpenicillin can be given before the transfer. Suitable doses of benzylpenicillin by intravenous injection (or by intramuscular injection) are: ADULT 1.2 g; INFANT under 1 year 300 mg; CHILD 1–9 years 600 mg, 10 years and over as for adult. In **penicillin allergy**, cefotaxime (section 5.1.2) may be an alternative; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins
- By intrathecal injection, **not** recommended

Note Benzylpenicillin doses in BNF may differ from those in product literature

Crystapen® (Genus) PoM

Injection, powder for reconstitution, benzylpenicillin sodium (unbuffered), net price 600-mg vial = 95p, 2-vial 'GP pack' = £2.64; 1.2-g vial = £1.89

Electrolytes Na^+ 1.68 mmol/600-mg vial; 3.36 mmol/1.2-g vial

PHENOXYMETHYLPENICILLIN
(Penicillin V)

Indications oral infections (see notes above); tonsillitis, otitis media, erysipelas, cellulitis; group A streptococcal infection, rheumatic fever and pneumococcal infection prophylaxis (Table 2, section 5.1)

Cautions see under Benzylpenicillin; **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Benzylpenicillin

Dose

- 500 mg every 6 hours increased up to 1 g every 6 hours in severe infections; CHILD up to 1 year 62.5 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections; 1–6 years, 125 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections; 6–12 years, 250 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections

Note Phenoxymethylpenicillin doses in the BNF may differ from those in product literature

Phenoxymethylpenicillin (Non-proprietary) PoM

Tablets, phenoxymethylpenicillin (as potassium salt) 250 mg, net price 28-tab pack = £1.27. Label: 9, 23

Dental prescribing on NHS Phenoxymethylpenicillin Tablets may be prescribed

Oral solution, phenoxymethylpenicillin (as potassium salt) for reconstitution with water, net price 125 mg/5 mL, 100 mL = £1.90; 250 mg/5 mL, 100 mL = £2.59. Label: 9, 23

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Phenoxymethylpenicillin Oral Solution may be prescribed

5.1.1.2 Penicillinase-resistant penicillins

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. **Flucloxacillin**, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection.

Flucloxacillin is well absorbed from the gut. For a warning on hepatic disorders see under Flucloxacillin.

Temocillin is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against *Pseudomonas aeruginosa* or *Acinetobacter* spp.

MRSA Infection from *Staphylococcus aureus* strains resistant to meticillin [now discontinued] (meticillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin (section 5.1.9) or **sodium fusidate** (section 5.1.7) should **not** be used alone because resistance may develop rapidly. A **tetracycline** alone or a combination of rifampicin and sodium fusidate can be used for *skin* and *soft-tissue infections* caused by MRSA; **clindamycin** alone is an alternative. A **glycopeptide** (e.g. vancomycin, section 5.1.7) can be used for severe skin and soft-tissue infections associated with MRSA; if a glycopeptide is unsuitable, **linezolid** (section 5.1.7) can be used on expert advice. As linezolid is **not** active against Gram-negative organisms, it can be used for mixed skin and soft-tissue infections only when other treatments are not available; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A combination of a glycopeptide and sodium fusidate *or* a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial.

Tigecycline (section 5.1.3) and **daptomycin** (section 5.1.7) are licensed for the treatment of complicated skin and soft-tissue infections involving MRSA.

A **tetracycline** or **clindamycin** can be used for *bronchiectasis* caused by MRSA. A **glycopeptide** can be used for *pneumonia* associated with MRSA; if a glycopeptide is unsuitable, **linezolid** can be used on expert advice. Linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms.

A **tetracycline** can be used for *urinary-tract infections* caused by MRSA; **trimethoprim** or **nitrofurantoin** are alternatives. A **glycopeptide** can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A **glycopeptide** can be used for *septicaemia* associated with MRSA.

For the management of *endocarditis*, *osteomyelitis*, or *septic arthritis* associated with MRSA, see Table 1, section 5.1.

Prophylaxis with vancomycin or teicoplanin (alone or in combination with another antibacterial active against

other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient's MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

For eradication of nasal carriage of MRSA, see section 12.2.3.

FLUCLOXACILLIN

Indications infections due to beta-lactamase-producing staphylococci including otitis externa; adjunct in pneumonia, impetigo, cellulitis, osteomyelitis and in staphylococcal endocarditis (Table 1, section 5.1)

Cautions see under Benzylpenicillin (section 5.1.1.1); risk of kernicterus in jaundiced neonates when high doses given parenterally; **interactions:** Appendix 1 (penicillins)

Hepatic disorders

Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. Healthcare professionals are reminded that:

- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;
- flucloxacillin should be used with caution in patients with hepatic impairment;
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Hepatic impairment see Cautions and Hepatic Disorders above

Renal impairment reduce dose if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Benzylpenicillin (section 5.1.1.1); also gastro-intestinal disturbances; *very rarely* hepatitis and cholestatic jaundice (see also Hepatic disorders above)

Dose

- By mouth, 250–500 mg every 6 hours, at least 30 minutes before food; NEONATE see *BNF for Children*; CHILD 1 month–2 years, 62.5–125 mg every 6 hours, at least 30 minutes before food; 2–10 years, 125–250 mg every 6 hours, at least 30 minutes before food
- By intramuscular injection, 250–500 mg every 6 hours; CHILD 1 month–18 years see *BNF for Children*
- By slow intravenous injection *or* by intravenous infusion, 0.25–2 g every 6 hours; CHILD under 18 years see *BNF for Children*

  Endocarditis (in combination with another antibacterial, see Table 1, section 5.1), body-weight under 85 kg, 8 g daily in 4 divided doses; body-weight over 85 kg, 12 g daily in 6 divided doses; CHILD 1 month–18 years see *BNF for Children*

  Osteomyelitis (see Table 1, section 5.1), up to 8 g daily in 3–4 divided doses; CHILD under 18 years see *BNF for Children*
- Surgical prophylaxis, by slow intravenous injection *or* by intravenous infusion, 1–2 g up to 30 minutes before the procedure; up to 4 further doses of 500 mg may be given every 6 hours by mouth, *or* by intramuscular injection, *or* by slow intravenous injection *or* by intravenous infusion for high risk procedures

Note Flucloxacillin doses in BNF may differ from those in product literature

Flucloxacillin (Non-proprietary) PoM

Capsules, flucloxacillin (as sodium salt) 250 mg, net price 28 = £2.07; 500 mg, 28 = £3.21. Label: 9, 23
Brands include *Floxapen®*, *Fluclomix®*, *Ladropen®*

Oral solution (= elixir or syrup), flucloxacillin (as sodium salt) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £4.41; 250 mg/5 mL, 100 mL = £31.28. Label: 9, 23
Brands include *Ladropen®*

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Injection, powder for reconstitution, flucloxacillin (as sodium salt), net price 250-mg vial = £1.23; 500-mg vial = £2.45; 1-g vial = £4.90

TEMOCILLIN

Indications septicaemia, urinary-tract infections, lower respiratory-tract infections caused by susceptible Gram-negative bacteria

Cautions see under Benzylpenicillin (section 5.1.1.1); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Renal impairment 1 g every 12 hours if eGFR 30–60 mL/minute/1.73 m^2; 1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m^2; 1 g every 48 hours *or* 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Benzylpenicillin (section 5.1.1.1)

Dose

- ADULT over 18 years, by intramuscular injection *or* by intravenous injection over 3–4 minutes, *or* by intravenous infusion, 1–2 g every 12 hours

Negaban® (Eumedica) PoM

Injection, powder for reconstitution, temocillin (as sodium salt), net price 1-g vial = £25.45
Electrolytes Na^+ 5 mmol/g

5.1.1.3 Broad-spectrum penicillins

Ampicillin is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by *Staphylococcus aureus* and by common Gram-negative bacilli such as *Escherichia coli*. Almost all staphylococci, approx. 60% of *E. coli* strains and approx. 20% of *Haemophilus influenzae* strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the 'blind' treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin is well excreted in the bile and urine. It is principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to *Streptococcus pneumoniae* and *H. influenzae*, and for urinary-tract infections (section 5.1.13).

Ampicillin can be given by mouth but less than half the dose is absorbed, and absorption is further decreased by the presence of food in the gut.

Maculopapular rashes commonly occur with ampicillin (and amoxicillin) but are not usually related to true penicillin allergy. They almost always occur in patients with glandular fever; broad-spectrum penicillins should not therefore be used for 'blind' treatment of a sore throat. The risk of rash is also increased in patients with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.

Amoxicillin is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach. Amoxicillin may also be used for the treatment of Lyme disease [not licensed], see below.

Co-amoxiclav consists of amoxicillin with the beta-lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of *Staph. aureus*, *E. coli*, and *H. influenzae*, as well as many *Bacteroides* and *Klebsiella* spp. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains.

A combination of ampicillin with flucloxacillin (as co-fluampicil) is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

Lyme disease Lyme disease should generally be treated by those experienced in its management. **Doxycycline** (p. 348), **amoxicillin** [unlicensed indication] or **cefuroxime axetil** are the antibacterials of choice for *early Lyme disease* or *Lyme arthritis*. If these antibacterials are contra-indicated, a **macrolide** (e.g. clarithromycin) can be used for early Lyme disease. Intravenous administration of **ceftriaxone**, **cefotaxime** (p. 340), or **benzylpenicillin** (p. 333) is recommended for Lyme disease associated with cardiac or neurological complications. The duration of treatment is usually 2–4 weeks; Lyme arthritis may require further treatment.

Oral infections Amoxicillin or ampicillin are as effective as phenoxymethylpenicillin (section 5.1.1.1) but they are better absorbed; however, they may encourage emergence of resistant organisms. Like phenoxymethylpenicillin, amoxicillin and ampicillin are ineffective against bacteria that produce beta-lactamases. Amoxicillin may be useful for short-course oral regimens. Co-amoxiclav is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

AMOXICILLIN

(Amoxycillin)

Indications see under Ampicillin; also oral infections, Lyme disease (see notes above); endocarditis treatment (Table 1, section 5.1); anthrax (section 5.1.12); adjunct in listerial meningitis (Table 1, section 5.1); *Helicobacter pylori* eradication (section 1.3)

Cautions see under Ampicillin; maintain adequate hydration with high doses (particularly during parenteral therapy); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Ampicillin

Renal impairment risk of crystalluria with high doses (particularly during parenteral therapy). Reduce dose in severe impairment; rashes more common

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Ampicillin

Dose

- By mouth, ADULT and CHILD over 5 years, 250 mg every 8 hours, dose doubled in severe infection; CHILD, 1 month–1 year, 62.5 mg every 8 hours, dose doubled in severe infection; 1–5 years, 125 mg every 8 hours, dose doubled in severe infection

  Otitis media, 500 mg every 8 hours; CHILD 40 mg/kg daily in 3 divided doses (max. 1.5 g daily)

  Pneumonia, ADULT over 18 years, 0.5–1 g every 8 hours

  Lyme disease (see also notes above), ADULT and CHILD over 5 years, 500 mg every 8 hours for 14–21 days (for 28 days in Lyme arthritis) [unlicensed indication]; CHILD 1 month–5 years see *BNF for Children*

  Anthrax (treatment and post-exposure prophylaxis—see also section 5.1.12), 500 mg every 8 hours; CHILD body-weight under 20 kg, 80 mg/kg daily in 3 divided doses, body-weight over 20 kg, adult dose
- *Short-course oral therapy*

  Dental abscess, ADULT over 18 years, 3 g repeated after 8 hours

  Urinary-tract infections, ADULT over 18 years, 3 g repeated after 10–12 hours
- By intramuscular injection, ADULT over 18 years, 500 mg every 8 hours
- By intravenous injection *or* infusion, 500 mg every 8 hours increased to 1 g every 6 hours in severe infection; CHILD 1 month–18 years, 20–30 mg/kg (max. 500 mg) every 8 hours; dose doubled in severe infection (max. 4 g daily)
- Listerial meningitis (in combination with another antibiotic, see Table 1, section 5.1), by intravenous infusion, ADULT over 18 years, 2 g every 4 hours for 10–14 days; CHILD under 18 years see *BNF for Children*
- Endocarditis (in combination with another antibiotic if necessary, see Table 1, section 5.1), by intravenous infusion, ADULT over 18 years, 2 g every 6 hours, increased to 2 g every 4 hours e.g. in enterococcal endocarditis or if amoxicillin used alone; CHILD under 18 years see *BNF for Children*

Note Amoxicillin doses in BNF may differ from those in product literature

Amoxicillin (Non-proprietary) PoM

Capsules, amoxicillin (as trihydrate) 250 mg, net price 21 = £1.07; 500 mg, 21 = £1.31. Label: 9

Brands include *Amix®*, *Amoram®*, *Amoxident®*, *Galenamox®*, *Rimoxallin®*

Dental prescribing on NHS Amoxicillin Capsules may be prescribed

Oral suspension, amoxicillin (as trihydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.22; 250 mg/5 mL, 100 mL = £1.39. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Amoram®*, *Galenamox®*, *Rimoxallin®*

Dental prescribing on NHS Amoxicillin Oral Suspension may be prescribed

Sachets, sugar-free, amoxicillin (as trihydrate) 3 g/sachet, net price 2-sachet pack = £8.34, 14-sachet pack = £31.94. Label: 9, 13
Dental prescribing on NHS Amoxicillin Sachets may be prescribed as Amoxicillin Oral Powder

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 250-mg vial = 32p; 500-mg vial = 66p; 1-g vial = £1.16

Amoxil® (GSK) PoM

Capsules, both maroon/gold, amoxicillin (as trihydrate), 250 mg, net price 21-cap pack = £3.45; 500 mg, 21-cap pack = £6.91. Label: 9

Paediatric suspension, amoxicillin 125 mg (as trihydrate)/1.25 mL when reconstituted with water, net price 20 mL (peach- strawberry- and lemon-flavoured) = £3.25. Label: 9, counselling , use of pipette
Excipients include sucrose 600 mg/1.25 mL

Sachets SF, powder, sugar-free, amoxicillin (as trihydrate) 3 g/sachet, 2-sachet pack (peach- strawberry- and lemon-flavoured) = £2.99. Label: 9, 13

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 500-mg vial = 56p; 1-g vial = £1.12
Electrolytes Na^+ 3.3 mmol/g

AMPICILLIN

Indications urinary-tract infections, otitis media, sinusitis, oral infections (see notes above), bronchitis, low or moderate-severity community-acquired pneumonia (Table 1, section 5.1), invasive salmonellosis; listerial meningitis (Table 1, section 5.1)

Cautions history of allergy; erythematous rashes common in glandular fever (see notes above); increased risk of erythematous rashes in cytomegalovirus infection, and acute or chronic lymphocytic leukaemia (see notes above); **interactions:** Appendix 1 (penicillins)

Contra-indications penicillin hypersensitivity

Renal impairment reduce dose if eGFR less than 10 mL/minute/1.73 m^2; rashes more common

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects nausea, vomiting, diarrhoea; rashes (discontinue treatment); rarely, antibiotic-associated colitis; see also under Benzylpenicillin (section 5.1.1.1)

Dose

- By mouth, 0.25–1 g every 6 hours, CHILD 1 month–1 year, 62.5 mg every 6 hours, dose doubled in severe infection; 1–5 years, 125 mg every 6 hours, dose doubled in severe infection; 5–12 years, 250 mg every 6 hours, dose doubled in severe infection

  Urinary-tract infections, ADULT and CHILD over 10 years, 500 mg every 8 hours; CHILD under 10 years, half adult dose
- By intramuscular injection *or* intravenous injection *or* infusion, 500 mg every 4–6 hours; CHILD under 18 years see *BNF for Children*
- Endocarditis (in combination with another antibiotic if necessary, see Table 1, section 5.1), by intravenous infusion, ADULT over 18 years, 2 g every 6 hours, increased to 2 g every 4 hours e.g. in enterococcal endocarditis or if ampicillin used alone; CHILD under 18 years see *BNF for Children*
- Listerial meningitis (in combination with another antibiotic, see Table 1, section 5.1), by intravenous infusion, ADULT over 18 years, 2 g every 4 hours for 10–14 days; CHILD under 18 years see *BNF for Children*

Note Ampicillin doses in BNF may differ from those in product literature

Ampicillin (Non-proprietary) PoM

Capsules, ampicillin 250 mg, net price 28 = £7.18; 500 mg, 28 = £32.93. Label: 9, 23
Brands include *Rimacillin®*
Dental prescribing on NHS Ampicillin Capsules may be prescribed

Oral suspension, ampicillin 125 mg/5 mL when reconstituted with water, net price 100 mL = £9.23; 250 mg/5 mL, 100 mL = £14.17. Label: 9, 23
Brands include *Rimacillin®*
Dental prescribing on NHS Ampicillin Oral Suspension may be prescribed

Injection, powder for reconstitution, ampicillin (as sodium salt), net price 500-mg vial = £7.83

Penbritin® (Chemidex) PoM

Capsules, grey/red, ampicillin (as trihydrate) 250 mg, net price 28-cap pack = £2.10; 500 mg, 28-cap pack = £5.28. Label: 9, 23

Syrup, apricot- caramel- and peppermint-flavoured, ampicillin (as trihydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £3.78; 250 mg/5 mL, 100 mL = £7.39. Label: 9, 23
Excipients include sucrose 3.6 g/5 mL

With flucloxacillin

See Co-fluampicil

CO-AMOXICLAV

A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form *x/y* where *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively

Indications infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, bone and joint infections, genito-urinary and abdominal infections, cellulitis, animal bites, severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial

Cautions see under Ampicillin and notes above; maintain adequate hydration with high doses (particularly during parenteral therapy); **interactions:** Appendix 1 (penicillins)
Cholestatic jaundice Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days

Contra-indications penicillin hypersensitivity, history of co-amoxiclav-associated or penicillin-associated jaundice or hepatic dysfunction

Hepatic impairment monitor liver function in liver disease; see also Cholestatic Jaundice above

Renal impairment risk of crystalluria with high doses (particularly during parenteral therapy).

Co-amoxiclav 250/125 tablets or 500/125 tablets: if eGFR 10–30 mL/minute/1.73 m^2, one *250/125* strength tablet every 12 hours *or* one *500/125* strength tablet every 12 hours; if eGFR less than

10 mL/minute/1.73 m^2, one *250/125* strength tablet every 24 hours *or* one *500/125* strength tablet every 24 hours.

Co-amoxiclav 400/57 suspension: avoid if eGFR less than 30 mL/minute/1.73 m^2.

Co-amoxiclav injection (expressed as co-amoxiclav): if eGFR 10–30 mL/minute/1.73 m^2, 1.2 g initially, then 600 mg every 12 hours; if eGFR less than 10 mL/minute/1.73 m^2, 1.2 g initially, then 600 mg every 24 hours

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Ampicillin; hepatitis, cholestatic jaundice (see above); Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; rarely prolongation of bleeding time, dizziness, headache, convulsions (particularly with high doses or in renal impairment); superficial staining of teeth with suspension, phlebitis at injection site

Dose

- By mouth, expressed as co-amoxiclav, one *250/125* strength tablet every 8 hours, increased in severe infections to one *500/125* strength tablet every 8 hours; NEONATE 0.25 mL/kg of *125/31* suspension every 8 hours; CHILD 1 month–1 year, 0.25 mL/kg of *125/31* suspension every 8 hours, dose doubled in severe infection; 1–6 years, 5 mL of *125/31* suspension every 8 hours *or* 0.25 mL/kg of *125/31* suspension every 8 hours, dose doubled in severe infection; 6–12 years, 5 mL of *250/62* suspension every 8 hours *or* 0.15 mL/kg of *250/62* suspension every 8 hours, dose doubled in severe infection

  Severe dental infections (but not generally first-line, see notes above), expressed as co-amoxiclav, ADULT and CHILD over 12 years, one *250/125* strength tablet every 8 hours for 5 days

- By intravenous injection over 3–4 minutes *or* by intravenous infusion, expressed as co-amoxiclav, 1.2 g every 8 hours; INFANTS up to 3 months 30 mg/kg every 8 hours (every 12 hours in the perinatal period and in premature infants); CHILD 3 months–18 years, 30 mg/kg (max. 1.2 g) every 8 hours

  Surgical prophylaxis, expressed as co-amoxiclav, 1.2 g up to 30 minutes before the procedure; for high risk procedures up to 2–3 further doses of 1.2 g may be given every 8 hours

Co-amoxiclav (Non-proprietary) PoM

Tablets, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £2.63. Label: 9

Dental prescribing on NHS Co-amoxiclav 250/125 Tablets may be prescribed

Tablets, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £4.38. Label: 9

Oral suspension, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £2.49. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Co-amoxiclav 125/31 Suspension may be prescribed

Oral suspension, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £6.29. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Co-amoxiclav 250/62 Suspension may be prescribed

Injection 500/100, powder for reconstitution, co-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt), net price per vial = £1.21

Injection 1000/200, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt), net price per vial = £2.63

Augmentin® (GSK) PoM

Tablets 375 mg, f/c, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £4.19. Label: 9

Tablets 625 mg, f/c, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £8.00. Label: 9

Suspension '125/31 SF', sugar-free, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL (raspberry-and orange-flavoured) = £4.08. Label: 9

Excipients include aspartame 12.5 mg/5 mL (section 9.4.1)

Suspension '250/62 SF', sugar-free, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL (raspberry-and orange-flavoured) = £5.74. Label: 9

Excipients include aspartame 12.5 mg/5 mL (section 9.4.1)

Injection 600 mg, powder for reconstitution, co-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt), net price per vial = £1.31

Electrolytes Na^+ 1.35 mmol, K^+ 0.5 mmol/600-mg vial

Injection 1.2 g, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt), net price per vial = £2.61

Electrolytes Na^+ 2.7 mmol, K^+ 1 mmol/1.2-g vial

Twice daily oral preparations

Co-amoxiclav (Non-proprietary) PoM

Suspension '400/57', co-amoxiclav 400/57 (amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/5 mL when reconstituted with water, net price 35 mL = £4.13, 70 mL = £5.79. Label: 9

Excipients may include aspartame (section 9.4.1)

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Augmentin-Duo®*

Dose CHILD 2 months–2 years 0.15 mL/kg twice daily, 2–6 years (13–21 kg) 2.5 mL twice daily, 7–12 years (22–40 kg) 5 mL twice daily, doubled in severe infections

CO-FLUAMPICIL

A mixture of equal parts by mass of flucloxacillin and ampicillin

Indications mixed infections involving beta-lactamase-producing staphylococci

Cautions see under Ampicillin and Flucloxacillin; **interactions:** Appendix 1 (penicillins)

Contra-indications see under Ampicillin and Flucloxacillin

Hepatic impairment see under Flucloxacillin

Renal impairment see under Ampicillin and Flucloxacillin

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Ampicillin and Flucloxacillin

Dose

- By mouth, co-fluampicil, 250/250 every 6 hours, dose doubled in severe infections; CHILD under 10 years half adult dose, dose doubled in severe infections
- By intramuscular *or* slow intravenous injection *or* by intravenous infusion, co-fluampicil 250/250 every 6 hours, dose doubled in severe infections; CHILD under 2 years quarter adult dose, 2–10 years half adult dose, dose doubled in severe infections

Co-fluampicil (Non-proprietary) PoM

Capsules, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as trihydrate), net price 28-cap pack = £14.73. Label: 9, 22

Brands include *Flu-Amp®*

Syrup, co-fluampicil 125/125 (flucloxacillin 125 mg as magnesium salt, ampicillin 125 mg as trihydrate)/5 mL when reconstituted with water, net price 100 mL = £4.99. Label: 9, 22

Magnapen® (Wockhardt) PoM

Injection 500 mg, powder for reconstitution, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as sodium salt), net price per vial = £1.33

Electrolytes Na^+ 1.3 mmol/vial

5.1.1.4 Antipseudomonal penicillins

Piperacillin, a ureidopenicillin, is only available in combination with the beta-lactamase inhibitor tazobactam. **Ticarcillin**, a carboxypenicillin, is only available in combination with the beta-lactamase inhibitor clavulanic acid (section 5.1.1.3). Both preparations have a broad spectrum of activity against a range of Gram-positive and Gram-negative bacteria, and anaerobes. Piperacillin with tazobactam has activity against a wider range of Gram-negative organisms than ticarcillin with clavulanic acid and it is more active against *Pseudomonas aeruginosa*. These antibacterials are not active against MRSA. They are used in the treatment of septicaemia, peritonitis, hospital-acquired pneumonia, complicated urinary-tract infections, and skin and soft-tissue infections.

For severe pseudomonas infections (especially in neutropenia or endocarditis) these antipseudomonal penicillins can be given with an aminoglycoside (e.g. gentamicin section 5.1.4) since they have a synergistic effect.

Owing to the sodium content of many of these antibiotics, high doses may lead to hypernatraemia.

PIPERACILLIN WITH TAZOBACTAM

Indications see under Dose

Cautions see under Benzylpenicillin (section 5.1.1.1); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Renal impairment max. 4.5 g every 8 hours if eGFR 20–80 mL/minute/1.73 m^2; max. 4.5 g every 12 hours if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy manufacturers advise use only if potential benefit outweighs risk

Breast-feeding present in milk—manufacturers advise use only if potential benefit outweighs risk

Side-effects see under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, diarrhoea; *less commonly* stomatitis, dyspepsia, constipation, jaundice, hypotension, headache, insomnia, and injection-site reactions; *rarely* abdominal pain, hepatitis, oedema, fatigue, and eosinophilia; *very rarely* hypoglycaemia, hypokalaemia, pancytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

Note Expressed as a combination of piperacillin and tazobactam (both as sodium salts) in a ratio of 8:1

- Lower respiratory-tract, urinary-tract, intra-abdominal and skin infections, and septicaemia, ADULT and CHILD over 12 years, by intravenous injection over 3–5 minutes *or* by intravenous infusion, 2.25–4.5 g every 6–8 hours, usually 4.5 g every 8 hours
- Complicated appendicitis, by intravenous injection over 3–5 minutes *or* by intravenous infusion, CHILD 2–12 years, 112.5 mg/kg (max. 4.5 g) every 8 hours for 5–14 days; CHILD under 2 years, not recommended
- Infections in neutropenic patients (in combination with an aminoglycoside), by intravenous injection over 3–5 minutes *or* by intravenous infusion, ADULT and CHILD over 50 kg, 4.5 g every 6 hours; CHILD less than 50 kg, 90 mg/kg every 6 hours

Piperacillin with tazobactam (Non-proprietary) PoM

Injection 2.25 g, powder for reconstitution, piperacillin 2 g (as sodium salt), tazobactam 250 mg (as sodium salt), net price 2.25-g vial = £7.16

Injection 4.5 g, powder for reconstitution, piperacillin 4 g (as sodium salt), tazobactam 500 mg (as sodium salt), net price 4.5-g vial = £14.21

Tazocin® (Wyeth) PoM

Injection 2.25 g, powder for reconstitution, piperacillin 2 g (as sodium salt), tazobactam 250 mg (as sodium salt), net price 2.25-g vial = £7.65

Electrolytes Na^+ 5.58 mmol/2.25-g vial

Injection 4.5 g, powder for reconstitution, piperacillin 4 g (as sodium salt), tazobactam 500 mg (as sodium salt), net price 4.5-g vial = £15.17

Electrolytes Na^+ 11.16 mmol/4.5-g vial

TICARCILLIN WITH CLAVULANIC ACID

Indications infections due to *Pseudomonas* and *Proteus* spp, see notes above

Cautions see under Benzylpenicillin (section 5.1.1.1); **interactions:** Appendix 1 (penicillins)

Cholestatic jaundice For a warning on cholestatic jaundice possibly associated with clavulanic acid, see under Co-amoxiclav, p. 337.

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Hepatic impairment manufacturer advises caution in severe impairment; also cholestatic jaundice, see under Co-amoxiclav, p. 337

Renal impairment reduce dose to 3.2 g every eight hours if eGFR 30–60 mL/minute/1.73 m^2; 1.6 g every eight hours if eGFR 10–30 mL/minute/1.73 m^2; 1.6 g every twelve hours if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy not known to be harmful

Breast-feeding trace amounts in milk

Side-effects see under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, coagulation disorders, haemorrhagic cystitis (more frequent in children), injection-site reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypokalaemia, eosinophilia

Dose

Note Expressed as a combination of ticarcillin (as sodium salt) and clavulanic acid (as potassium salt) in a ratio of 15:1

- By intravenous infusion, 3.2 g every 6–8 hours increased to every 4 hours in more severe infections; CHILD 1 month–18 years, body-weight under 40 kg, 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections; body-weight over 40 kg, adult dose

Timentin (GSK) PoM

Injection 3.2 g, powder for reconstitution, ticarcillin 3 g (as sodium salt), clavulanic acid 200 mg (as potassium salt). Net price per vial = £5.33

Electrolytes Na^+ 16 mmol, K^+ 1 mmol /3.2-g vial

5.1.1.5 Mecillinams

Pivmecillinam has significant activity against many Gram-negative bacteria including *Escherichia coli*, klebsiella, enterobacter, and salmonellae. It is not active against *Pseudomonas aeruginosa* or enterococci. Pivmecillinam is hydrolysed to mecillinam, which is the active drug.

PIVMECILLINAM HYDROCHLORIDE

Indications see under Dose below

Cautions see under Benzylpenicillin (section 5.1.1.1); also liver and renal function tests required in long-term use; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (penicillins)

Contra-indications see under Benzylpenicillin (section 5.1.1.1); also carnitine deficiency, oesophageal strictures, gastro-intestinal obstruction, infants under 3 months

Pregnancy not known to be harmful, but manufacturer advises avoid

Breast-feeding trace amounts in milk

Side-effects see under Benzylpenicillin (section 5.1.1.1); nausea, vomiting, dyspepsia; also reduced serum and total body carnitine (especially with long-term or repeated use)

Dose

- Acute uncomplicated cystitis, ADULT and CHILD over 40 kg, initially 400 mg then 200 mg every 8 hours for 3 days
- Chronic or recurrent bacteriuria, ADULT and CHILD over 40 kg, 400 mg every 6–8 hours
- Urinary-tract infections, CHILD under 40 kg, 20–40 mg/kg daily in 3–4 divided doses
- Salmonellosis, not recommended therefore no dose stated

Counselling Tablets should be swallowed whole with plenty of fluid during meals while sitting or standing

Selexid® (LEO) PoM

Tablets, f/c, pivmecillinam hydrochloride 200 mg, net price 10-tab pack = £4.50. Label 9, 21, 27, counselling, posture (see Dose above)

5.1.2 Cephalosporins, carbapenems, and other beta-lactams

Antibiotics in this section include the **cephalosporins**, such as cefotaxime, ceftazidime, cefuroxime, cefalexin and cefradine, the **monobactam**, aztreonam, and the **carbapenems**, imipenem (a thienamycin derivative), meropenem, doripenem, and ertapenem.

5.1.2.1 Cephalosporins

The cephalosporins are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime is a suitable cephalosporin for infections of the CNS (e.g meningitis).

The principal side-effect of the cephalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin. If a cephalosporin is essential in these patients because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, and cefradine should be avoided.

Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins, particularly second- and-third-generation cephalosporins.

Cefuroxime is a 'second generation' cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to the other drugs and has greater activity against *Haemophilus influenzae*.

Cefotaxime, **ceftazidime** and **ceftriaxone** are 'third generation' cephalosporins with greater activity than the 'second generation' cephalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably *Staphylococcus aureus*. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

Orally active cephalosporins The orally active 'first generation' cephalosporins, **cefalexin**, **cefradine**, and **cefadroxil** and the 'second generation' cephalosporin, **cefaclor**, have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy,

respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor has good activity against *H. influenzae*, but it is associated with protracted skin reactions especially in children. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against *H. influenzae*. **Cefuroxime axetil**, an ester of the 'second generation' cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed.

Cefixime and **cefpodoxime proxetil** are orally active 'third generation' cephalosporins. Cefixime has a longer duration of action than the other cephalosporins that are active by mouth. It is only licensed for acute infections. Cefpodoxime proxetil is more active than the other oral cephalosporins against respiratory bacterial pathogens and it is licensed for upper and lower respiratory-tract infections.

For treatment of Lyme disease, see section 5.1.1.3.

Oral infections The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cephalosporins. This is of importance in the case of patients who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin and cefradine have been used in the treatment of oral infections.

CEFACLOR

Indications infections due to sensitive Gram-positive and Gram-negative bacteria, but see notes above

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also notes above and p. 332); false positive urinary glucose (if tested for reducing substances) and false positive Coombs' test; **interactions:** Appendix 1 (cephalosporins)

Contra-indications cephalosporin hypersensitivity

Renal impairment no dose adjustment required—manufacturer advises caution

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration, but appropriate to use

Side-effects diarrhoea (rarely antibiotic-associated colitis), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia, and anaphylaxis; Stevens-Johnson syndrome, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia, and dizziness

Dose

- 250 mg every 8 hours, doubled for severe infections; max. 4 g daily; CHILD over 1 month, 20 mg/kg daily in 3 divided doses, doubled for severe infections, max. 1 g daily; *or* 1 month–1 year, 62.5 mg every 8 hours; 1–5 years, 125 mg; over 5 years, 250 mg; doses doubled for severe infections

Cefaclor (Non-proprietary) PoM

Capsules, cefaclor (as monohydrate) 250 mg, net price 21-cap pack = £5.09; 500 mg, 50-cap pack = £31.99. Label: 9

Brands include *Keftid®*

Suspension, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £8.33; 250 mg/5 mL, 100 mL = £6.97. Label: 9

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Brands include *Keftid®*

Distaclor® (Flynn) PoM

Capsules, cefaclor (as monohydrate) 500 mg (violet/grey), net price 21-cap pack = £18.19. Label: 9

Suspension, both pink, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £4.13; 250 mg/5 mL, 100 mL = £8.26. Label: 9

Distaclor MR® (Flynn) PoM

Tablets, m/r, both blue, cefaclor (as monohydrate) 375 mg. Net price 14-tab pack = £8.31. Label: 9, 21, 25

Dose 375 mg every 12 hours with food, dose doubled for pneumonia

Lower urinary-tract infections, 375 mg every 12 hours with food

CEFADROXIL

Indications see under Cefaclor; see also notes above

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment 1 g initially, then 500 mg every 12 hours if eGFR 26–50 mL/minute/1.73 m^2; 1 g initially, then 500 mg every 24 hours if eGFR 11–26 mL/minute/1.73 m^2; 1 g initially, then 500 mg every 36 hours if eGFR less than 11 mL/minute/1.73 m^2

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- 0.5–1 g twice daily; skin, soft-tissue, and uncomplicated urinary-tract infections, 1 g daily; CHILD 6–18 years, body-weight under 40 kg, 500 mg twice daily; body-weight over 40 kg, adult dose

Cefadroxil (Non-proprietary) PoM

Capsules, cefadroxil (as monohydrate) 500 mg, net price 20-cap pack = £4.83. Label: 9

CEFALEXIN
(Cephalexin)

Indications see under Cefaclor

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment max. 3 g daily if eGFR 40–50 mL/minute/1.73 m^2; max. 1.5 g daily if eGFR 10–40 mL/minute/1.73 m^2; max. 750 mg daily if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- 250 mg every 6 hours *or* 500 mg every 8–12 hours increased to 1–1.5 g every 6–8 hours for severe

infections; CHILD 25 mg/kg daily in divided doses, doubled for severe infections, max. 100 mg/kg daily; *or* under 1 year 125 mg every 12 hours, 1–5 years 125 mg every 8 hours, 5–12 years 250 mg every 8 hours

- Prophylaxis of recurrent urinary-tract infection, ADULT 125 mg at night

Cefalexin (Non-proprietary) PoM

Capsules, cefalexin 250 mg, net price 28-cap pack = £1.66; 500 mg, 21-cap pack = £2.09. Label: 9
Dental prescribing on NHS Cefalexin Capsules may be prescribed

Tablets, cefalexin 250 mg, net price 28-tab pack = £1.94; 500 mg, 21-tab pack = £2.39. Label: 9
Dental prescribing on NHS Cefalexin Tablets may be prescribed

Oral suspension, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.75; 250 mg/5 mL, 100 mL = £2.15. Label: 9
Dental prescribing on NHS Cefalexin Oral Suspension may be prescribed

Ceporex® (Co-Pharma) PoM

Capsules, both caramel/grey, cefalexin 250 mg, net price 28-cap pack = £4.02; 500 mg, 28-cap pack = £7.85. Label: 9

Tablets, all pink, f/c, cefalexin 250 mg, net price 28-tab pack = £4.02; 500 mg, 28-tab pack = £7.85. Label: 9

Syrup, all orange, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.43; 250 mg/5 mL, 100 mL = £2.87; 500 mg/5 mL, 100 mL = £5.57. Label: 9

Keflex® (Flynn) PoM

Capsules, cefalexin 250 mg (green/white), net price 28-cap pack = £1.46; 500 mg (pale green/dark green), 21-cap pack = £1.98. Label: 9

Tablets, both peach, cefalexin 250 mg, net price 28-tab pack = £1.60; 500 mg (scored), 21-tab pack = £2.08. Label: 9

Suspension, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = 84p; 250 mg/5 mL, 100 mL = £1.40. Label: 9

CEFIXIME

Indications see under Cefaclor (acute infections only); gonorrhoea [unlicensed indication] (Table 1, section 5.1)

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose if eGFR less than 20 mL/minute/1.73 m^2 (max. 200 mg once daily)

Pregnancy see under Cefaclor

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Cefaclor

Dose

- ADULT and CHILD over 10 years, 200–400 mg daily in 1–2 divided doses; CHILD over 6 months 8 mg/kg daily in 1–2 divided doses *or* 6 months–1 year 75 mg daily; 1–4 years 100 mg daily; 5–10 years 200 mg daily
- Uncomplicated gonorrhoea [unlicensed indication], 400 mg as a single dose

Suprax® (Sanofi-Aventis) PoM

Tablets, f/c, scored, cefixime 200 mg. Net price 7-tab pack = £13.23. Label: 9

Paediatric oral suspension, cefixime 100 mg/5 mL when reconstituted with water, net price 50 mL (with double-ended spoon for measuring 3.75 mL or 5 mL since dilution not recommended) = £10.53, 100 mL = £18.91. Label: 9

CEFOTAXIME

Indications see under Cefaclor; gonorrhoea; surgical prophylaxis; Haemophilus epiglottitis and meningitis (Table 1, section 5.1); see also notes above

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment if eGFR less than 5 mL/minute/1.73 m^2, initial dose of 1 g then use half normal dose

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor; rarely arrhythmias following rapid injection reported

Dose

- By intramuscular *or* intravenous injection *or* by intravenous infusion, 1 g every 12 hours increased in severe infections (e.g. meningitis) to 8 g daily in 4 divided doses; higher doses (up to 12 g daily in 3–4 divided doses) may be required; NEONATE 50 mg/kg daily in 2–4 divided doses increased to 150–200 mg/kg daily in severe infections; CHILD 100–150 mg/kg daily in 2–4 divided doses increased up to 200 mg/kg daily in very severe infections

  Uncomplicated gonorrhoea, 500 mg as a single dose
  Important. If meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) is suspected, and the patient cannot be given benzylpenicillin (e.g. because of an allergy), a single dose of cefotaxime can be given (if available) before urgent transfer to hospital, so long as this does not delay the transfer. If a patient with suspected bacterial meningitis without non-blanching rash cannot be transferred to hospital urgently and cannot be given benzylpenicillin, a single dose of cefotaxime can be given before transfer. Suitable doses of cefotaxime by intravenous injection (or by intramuscular injection) are ADULT and CHILD over 12 years 1 g; CHILD under 12 years 50 mg/kg; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins or cephalosporins

Cefotaxime (Non-proprietary) PoM

Injection, powder for reconstitution, cefotaxime (as sodium salt), net price 500-mg vial = £2.14; 1-g vial = £4.31; 2-g vial = £8.57

CEFPODOXIME

Indications see under Dose

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment increase dose interval to every 24 hours if eGFR 10–40 mL/minute/1.73 m^2; increase dose interval to every 48 hours if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- Upper respiratory-tract infections (but in pharyngitis and tonsillitis reserved for infections which are recurrent, chronic, or resistant to other antibacterials), 100 mg twice daily (200 mg twice daily in sinusitis); CHILD 15 days–6 months 4 mg/kg every 12 hours, 6

months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours

- Lower respiratory-tract infections (including bronchitis and pneumonia), 100–200 mg twice daily; CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Skin and soft-tissue infections, 200 mg twice daily; CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Uncomplicated urinary-tract infections, 100 mg twice daily (200 mg twice daily in uncomplicated upper urinary-tract infections); CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours

Orelox® (Sanofi-Aventis) PoM

Tablets, f/c, cefpodoxime 100 mg (as proxetil), net price 10-tab pack = £9.78. Label: 5, 9, 21

Oral suspension, cefpodoxime (as proxetil) for reconstitution with water, 40 mg/5 mL, net price 100 mL = £11.50. Label: 5, 9, 21

Excipients include aspartame (section 9.4.1)

CEFRADINE
(Cephradine)

Indications see under Cefaclor; surgical prophylaxis

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment use half normal dose if eGFR 5–20 mL/minute/1.73 m^2; use one-quarter normal dose if eGFR less than 5 mL/minute/1.73 m^2

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- 250–500 mg every 6 hours *or* 0.5–1 g every 12 hours; up to 1 g every 6 hours in severe infections; CHILD 7–12 years, 25–50 mg/kg daily in 2–4 divided doses

Cefradine (Non-proprietary) PoM

Capsules, cefradine 250 mg, net price 20-cap pack = £2.86; 500 mg, 20-cap pack = £4.50. Label: 9

Brands include *Nicef®*

Dental prescribing on NHS Cefradine Capsules may be prescribed

CEFTAZIDIME

Indications see under Cefaclor; see also notes above

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment reduce dose if eGFR less than 50 mL/minute/1.73 m^2—consult product literature

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- By deep intramuscular injection *or* intravenous injection *or* infusion, 1 g every 8 hours *or* 2 g every 12 hours; 2 g every 8–12 hours *or* 3 g every 12 hours in severe infections; single doses over 1 g intravenous route only; ELDERLY usual max. 3 g daily; CHILD, up to 2 months 25–60 mg/kg daily in 2 divided doses, over 2 months 30–100 mg/kg daily in 2–3 divided doses; up to 150 mg/kg daily (max. 6 g daily) in 3 divided doses if immunocompromised or meningitis; intravenous route recommended for children

  Urinary-tract and less serious infections, 0.5–1 g every 12 hours

  Pseudomonal lung infection in cystic fibrosis, ADULT 100–150 mg/kg daily in 3 divided doses; CHILD up to 150 mg/kg daily (max. 6 g daily) in 3 divided doses; intravenous route recommended for children

  Surgical prophylaxis, prostatic surgery, 1 g up to 30 minutes before the procedure, repeated if necessary when catheter removed

Ceftazidime (Non-proprietary) PoM

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 1-g vial = £8.50; 2-g vial = £17.90

Fortum® (GSK) PoM

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 250-mg vial = £2.20, 500-mg vial = £4.40, 1-g vial = £8.79, 2-g vial = £17.59, 3-g vial = £25.76; *Monovial*, 2 g vial (with transfer needle) = £17.59

Electrolytes Na^+ 2.3 mmol/g

Kefadim® (Flynn) PoM

Injection, powder for reconstitution, ceftazidime (as pentahydrate), with sodium carbonate, net price 1-g vial = £7.92; 2-g vial = £15.84

Electrolytes Na^+ 2.3 mmol/g

CEFTRIAXONE

Indications see under Cefaclor and notes above; surgical prophylaxis; prophylaxis of meningococcal meningitis [unlicensed indication] (Table 2, section 5.1)

Cautions see under Cefaclor; may displace bilirubin from serum albumin, administer over 60 minutes in neonates (see also Contra-indications); treatment longer than 14 days, renal failure, dehydration—risk of ceftriaxone precipitation in gall bladder; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor; neonates less than 41 weeks postmenstrual age; neonates over 41 weeks postmenstrual age with jaundice, hypoalbuminaemia, or acidosis; concomitant treatment with intravenous calcium (including total parenteral nutrition containing calcium) in neonates over 41 weeks postmenstrual age—risk of precipitation in urine and lungs

Hepatic impairment reduce dose and monitor plasma concentration if both hepatic and severe renal impairment

Renal impairment reduce dose if eGFR less than 10 mL/minute/1.73m^2 (max. 2 g daily); monitor plasma concentration if both hepatic and severe renal impairment

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis

Dose

- By deep intramuscular injection, *or* by intravenous injection over at least 2–4 minutes, *or* by intravenous infusion, 1 g daily; 2–4 g daily in severe infections; intramuscular doses over 1 g divided between more than one site; single intravenous doses above 1 g by intravenous infusion only

  NEONATE, by intravenous infusion over 60 minutes, 20–50 mg/kg daily (max. 50 mg/kg daily); INFANT and CHILD under 50 kg, by deep intramuscular injection, *or* by intravenous injection over 2–4 minutes, *or* by intravenous infusion, 20–50 mg/kg daily; up to 80 mg/kg daily in severe infections; doses of 50 mg/kg and over by intravenous infusion only; 50 kg and over, adult dose
- Endocarditis caused by haemophilus, actinobacillus, cardiobacterium, eikenella, and kingella species ('HACEK organisms') (in combination with another antibacterial, see Table 1, section 5.1; [unlicensed indication]), by intravenous infusion, 2–4 g daily
- Early syphilis [unlicensed indication], by deep intramuscular injection, 500 mg daily for 10 days
- Uncomplicated gonorrhoea, pelvic inflammatory disease (see also Table 1, section 5.1) by deep intramuscular injection, 250 mg as a single dose
- Surgical prophylaxis, by deep intramuscular injection *or* by intravenous injection over at least 2–4 minutes, 1 g up to 30 minutes before the procedure; colorectal surgery, by deep intramuscular injection *or* by intravenous infusion, 2 g up to 30 minutes before the procedure; intramuscular doses over 1 g divided between more than one site

Ceftriaxone (Non-proprietary) PoM

Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 1-g vial = £10.17; 2-g vial = £20.36

Rocephin® (Roche) PoM

Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 250-mg vial = £2.40; 1-g vial = £9.58; 2-g vial = £19.18

Electrolytes Na^+ 3.6 mmol /g

CEFUROXIME

Indications see under Cefaclor; surgical prophylaxis; more active against *Haemophilus influenzae*; Lyme disease

Cautions see under Cefaclor; **interactions:** Appendix 1 (cephalosporins)

Contra-indications see under Cefaclor

Renal impairment use parenteral dose of 750 mg twice daily if eGFR 10–20 mL/minute/1.73 m^2; use parenteral dose of 750 mg once daily if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy see under Cefaclor

Breast-feeding see under Cefaclor

Side-effects see under Cefaclor

Dose

- By mouth (as cefuroxime axetil), 250 mg twice daily in most infections including mild to moderate lower respiratory-tract infections (e.g. bronchitis); doubled for more severe lower respiratory-tract infections or if pneumonia suspected

  Urinary-tract infection, 125 mg twice daily, doubled in pyelonephritis

  CHILD over 3 months, 125 mg twice daily, if necessary doubled in child over 2 years with otitis media

  Lyme disease (see also section 5.1.1.3), ADULT and CHILD over 12 years, 500 mg twice daily for 14–21 days (for 28 days in Lyme arthritis) [unlicensed duration]
- By intramuscular injection *or* intravenous injection *or* infusion, 750 mg every 6–8 hours; 1.5 g every 6–8 hours in severe infections; single doses over 750 mg intravenous route only

  CHILD usual dose 60 mg/kg daily (range 30–100 mg/kg daily) in 3–4 divided doses (2–3 divided doses in neonates)
- Surgical prophylaxis, 1.5 g by intravenous injection up to 30 minutes before the procedure; up to 3 further doses of 750 mg may be given by intramuscular *or* intravenous injection every 8 hours for high-risk procedures

Cefuroxime (Non-proprietary) PoM

Tablets, cefuroxime (as axetil) 250 mg, net price 14-tab pack = £10.39. Label: 9, 21, 25

Injection, powder for reconstitution, cefuroxime (as sodium salt), net price 750-mg vial =£2.52; 1.5-g vial = £5.05

Zinacef® (GSK) PoM

Injection, powder for reconstitution, cefuroxime (as sodium salt). Net price 250-mg vial = 94p; 750-mg vial = £2.34; 1.5-g vial = £4.70

Electrolytes Na^+ 1.8 mmol/750-mg vial

Zinnat® (GSK) PoM

Tablets, both f/c, cefuroxime (as axetil) 125 mg, net price 14-tab pack = £4.56; 250 mg, 14-tab pack = £9.11. Label: 9, 21, 25

Suspension, cefuroxime (as axetil) 125 mg/5 mL when reconstituted with water, net price 70 mL (tutti-frutti-flavoured) = £5.20. Label: 9, 21

Excipients include aspartame (section 9.4.1), sucrose 3.1 g/5 mL

5.1.2.2 Carbapenems

The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; **imipenem**, **meropenem**, and **doripenem** have good activity against *Pseudomonas aeruginosa*. The carbapenems are not active against meticillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*.

Imipenem and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections including septicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary-tract infections. Doripenem is an alternative for hospital-acquired pneumonia, complicated intra-abdominal infections, and complicated urinary-tract infections.

Ertapenem is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. It is also licensed for treating foot infections of the skin and soft tissue in patients with diabetes. Unlike the other carbapenems, ertapenem is not active against *Pseudomonas* or against *Acinetobacter* spp.

Imipenem is partially inactivated in the kidney by enzymatic activity and is therefore administered in combination with **cilastatin**, a specific enzyme inhibitor, which blocks its renal metabolism. Meropenem, doripenem,

and ertapenem are stable to the renal enzyme which inactivates imipenem and therefore can be given without cilastatin.

Side-effects of imipenem with cilastatin are similar to those of other beta-lactam antibiotics; neurotoxicity has been observed at very high dosage, in renal failure, or in patients with CNS disease. Ertapenem has been associated with seizures uncommonly. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection.

DORIPENEM

Indications hospital-acquired pneumonia; complicated intra-abdominal infections; complicated urinary-tract infections

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 332); **interactions:** Appendix 1 (doripenem)

Renal impairment 250 mg every 8 hours if eGFR 30–50 mL/minute/1.73 m^2; 250 mg every 12 hours if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless essential—no information available

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—present in milk in *animal* studies

Side-effects nausea, diarrhoea; headache; phlebitis, pruritus, rash; *less commonly* antibiotic-associated colitis, thrombocytopenia, neutropenia; also reported, toxic epidermal necrolysis, and Stevens-Johnson syndrome

Dose

- By intravenous infusion, ADULT over 18 years, 500 mg every 8 hours; max. duration of treatment 14 days

Doribax® (Janssen-Cilag) ▼ PoM

Intravenous infusion, powder for reconstitution, doripenem (as monohydrate), net price 500-mg vial = £14.52

The *Scottish Medicines Consortium* (p. 4) has advised (February 2009) that doripenem (*Doribax®*) is not recommended for use within NHS Scotland for the treatment of complicated urinary-tract infections.

ERTAPENEM

Indications abdominal infections; acute gynaecological infections; community-acquired pneumonia; diabetic foot infections of the skin and soft-tissue; prophylaxis for colorectal surgery

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 332); elderly, CNS disorders—risk of seizures; **interactions:** Appendix 1 (ertapenem)

Renal impairment risk of seizures; max. 500 mg daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding present in milk—manufacturer advises avoid

Side-effects diarrhoea, nausea, vomiting, headache, injection-site reactions, rash (also reported with eosinophilia and systemic symptoms), pruritus, raised platelet count; *less commonly* dry mouth, taste disturbances, dyspepsia, abdominal pain, anorexia, constipation, melaena, antibiotic-associated colitis, bradycardia, hypotension, chest pain, oedema, pharyngeal discomfort, dyspnoea, dizziness, sleep disturbances, confusion, asthenia, seizures, raised glucose, petechiae; *rarely* dysphagia, cholecystitis, liver disorder (including jaundice), arrhythmia, increase in blood pressure, syncope, nasal congestion, cough, wheezing, anxiety, depression, agitation, tremor, pelvic peritonitis, renal impairment, muscle cramp, scleral disorder, blood disorders (including neutropenia, thrombocytopenia, haemorrhage), hypoglycaemia, electrolyte disturbances; also reported hallucinations, dyskinesia

Dose

- By intravenous infusion, ADULT and ADOLESCENT over 13 years, 1 g once daily; CHILD 3 months–13 years, 15 mg/kg every 12 hours (max. 1 g daily)

  Surgical prophylaxis, colorectal surgery, ADULT over 18 years, 1 g completed within 1 hour before surgery

Invanz® (MSD) PoM

Intravenous infusion, powder for reconstitution, ertapenem (as sodium salt), net price 1-g vial = £31.65

Electrolytes Na^+ 6 mmol/1-g vial

IMIPENEM WITH CILASTATIN

Indications aerobic and anaerobic Gram-positive and Gram-negative infections; surgical prophylaxis; hospital-acquired septicaemia (Table 1, section 5.1); not indicated for CNS infections

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 332); CNS disorders (e.g. epilepsy); **interactions:** Appendix 1 (imipenem with cilastatin)

Renal impairment risk of CNS side-effects; reduce dose if eGFR less than 70 mL/minute/1.73 m^2—consult product literature

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk (toxicity in *animal* studies)

Breast-feeding present in milk but unlikely to be absorbed (however, manufacturer advises avoid)

Side-effects nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), taste disturbances, tooth or tongue discoloration, hearing loss; blood disorders, positive Coombs' test; allergic reactions (with rash, pruritus, urticaria, Stevens-Johnson syndrome, fever, anaphylactic reactions, rarely toxic epidermal necrolysis, exfoliative dermatitis); myoclonic activity, convulsions, confusion and mental disturbances reported; slight increases in liver enzymes and bilirubin reported, rarely hepatitis; increases in serum creatinine and blood urea; red coloration of urine in children reported; local reactions: erythema, pain and induration, and thrombophlebitis

Dose

- By intravenous infusion, in terms of imipenem, 1–2 g daily (in 3–4 divided doses); less sensitive organisms, up to 50 mg/kg daily (max. 4 g daily) in 3–4 divided doses; CHILD 3 months and older, 60 mg/kg (max. 2 g) daily in 4 divided doses; over 40 kg, adult dose

  Surgical prophylaxis, 1 g up to 30 minutes before the procedure, repeated after 3 hours, supplemented in high risk (e.g. colorectal) surgery by doses of 500 mg 8 and 16 hours after initial dose

Primaxin® (MSD) PoM

Intravenous infusion, powder for reconstitution, imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg, net price per vial = £12.00

Electrolytes Na^+ 1.72 mmol/vial

MEROPENEM

Indications aerobic and anaerobic Gram-positive and Gram-negative infections (see notes above); hospital-acquired septicaemia (Table 1, section 5.1)

Cautions sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 332); **interactions:** Appendix 1 (meropenem)

Hepatic impairment monitor liver function

Renal impairment use normal dose every 12 hours if eGFR 26–50 mL/minute/1.73 m^2; use half normal dose every 12 hours if eGFR 10–25 mL/minute/1.73 m^2; use half normal dose every 24 hours if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding unlikely to be absorbed (however, manufacturer advises avoid unless potential benefit justifies potential risk)

Side-effects nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), abdominal pain, disturbances in liver function tests, headache, thrombocythaemia, rash, pruritus; *less commonly* paraesthesia, eosinophilia, thrombocytopenia, leucopenia; *rarely* convulsions; also reported haemolytic anaemia, positive Coombs' test, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dose

- By intravenous injection over 5 minutes *or* by intravenous infusion, 0.5–1 g every 8 hours; CHILD 3 months–12 years 10–20 mg/kg every 8 hours, body-weight over 50 kg, adult dose
- Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis, meningitis, by intravenous infusion, 2 g every 8 hours; CHILD 3 months–12 years 40 mg/kg every 8 hours, body-weight over 50 kg, adult dose

Meronem® (AstraZeneca) PoM

Injection, powder for reconstitution, meropenem (as trihydrate), net price 500-mg vial = £8.60; 1-g vial = £17.19

Electrolytes Na^+ 3.9 mmol/g

5.1.2.3 Other beta-lactam antibiotics

Aztreonam is a monocyclic beta-lactam ('monobactam') antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Neisseria meningitidis*, and *Haemophilus influenzae*; it should not be used alone for 'blind' treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection). Side-effects are similar to those of the other beta-lactams although aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients.

Aztreonam may be administered by nebuliser for the treatment of chronic *Ps. aeruginosa* infection in cystic fibrosis.

AZTREONAM

Indications Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*

Cautions hypersensitivity to beta-lactam antibiotics; **interactions:** Appendix 1 (aztreonam)

Specific cautions for inhaled treatment Other inhaled drugs should be administered before aztreonam; a bronchodilator should be administered before each dose

Contra-indications aztreonam hypersensitivity

Hepatic impairment use injection with caution and monitor liver function

Renal impairment if eGFR 10–30 mL/minute/1.73 m^2, usual initial dose of injection, then half normal dose; if eGFR less than 10 mL/minute/1.73 m^2, usual initial dose of injection, then one-quarter normal dose

Pregnancy no information available; manufacturer of injection advises avoid; manufacturer of powder for nebuliser solution advises avoid unless essential

Breast-feeding amount in milk probably too small to be harmful

Side-effects

Specific side-effects for parenteral treatment Nausea, vomiting, diarrhoea, abdominal cramps; mouth ulcers, altered taste; jaundice and hepatitis; flushing; hypersensitivity reactions; blood disorders (including thrombocytopenia and neutropenia); rashes, injection-site reactions; rarely hypotension, seizures, asthenia, confusion, dizziness, headache, halitosis, and breast tenderness; very rarely antibiotic-associated colitis, gastro-intestinal bleeding, and toxic epidermal necrolysis

Specific side-effects for inhaled treatment Wheezing, bronchospasm, cough; pyrexia; rash; rhinorrhoea, pharyngolaryngeal pain

Dose

- By deep intramuscular injection *or* by intravenous injection over 3–5 minutes *or* by intravenous infusion, 1 g every 8 hours *or* 2 g every 12 hours; 2 g every 6–8 hours for severe infections (including systemic *Pseudomonas aeruginosa* and lung infections in cystic fibrosis); single doses over 1 g intravenous route only

  Urinary-tract infections, 0.5–1 g every 8–12 hours
- CHILD over 1 week, by intravenous injection *or* infusion, 30 mg/kg every 6–8 hours increased in severe infections for child of 2 years or older to 50 mg/kg every 6–8 hours; max. 8 g daily
- Gonorrhoea, cystitis, by intramuscular injection, 1 g as a single dose
- Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis, by inhalation of nebulised solution, ADULT over 18 years, 75 mg 3 times daily (at least 4 hours apart) for 28 days; if additional courses required, a minimum of 28 days without aztreonam nebuliser solution recommended between courses

Parenteral

Azactam® (Squibb) PoM

Injection, powder for reconstitution, aztreonam, net price 1-g vial = £9.40; 2-g vial = £18.82

Inhalation

Cayston® (Gilead) ▼ PoM

Powder for nebuliser solution, aztreonam (as lysine), net price 84 × 75 mg vials (with solvent and nebuliser handset) = £2566.50

5.1.3 Tetracyclines

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. They remain, however, the treatment of choice

for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever), brucella (doxycycline with either streptomycin or rifampicin), and the spirochaete, *Borrelia burgdorferi* (Lyme disease—see section 5.1.1.3). They are also used in respiratory and genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against *Haemophilus influenzae*), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin).

For the role of tetracyclines in the management of meticillin-resistant *Staphylococcus aureus* (MRSA) infection, see p. 334.

Microbiologically, there is little to choose between the various tetracyclines, the only exception being **minocycline** which has a broader spectrum; it is active against *Neisseria meningitidis* and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo (see section 5.1, table 2 for current recommendations). Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

Oral infections In adults, tetracyclines can be effective against oral anaerobes but the development of resistance (especially by oral streptococci) has reduced their usefulness for the treatment of acute oral infections; they may still have a role in the treatment of destructive (refractory) forms of periodontal disease. Doxycycline has a longer duration of action than tetracycline or oxytetracycline and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

For the use of doxycycline in the treatment of recurrent aphthous ulceration, oral herpes, or as an adjunct to gingival scaling and root planing for periodontitis, see section 12.3.1 and section 12.3.2.

Cautions Tetracyclines may increase muscle weakness in patients with myasthenia gravis, and exacerbate systemic lupus erythematosus. Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces the absorption of demeclocycline, oxytetracycline, and tetracycline. Other **interactions:** Appendix 1 (tetracyclines).

Contra-indications Deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia, and they should **not** be given to children under 12 years, or to pregnant or breast-feeding women. However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given [unlicensed indication].Tetracyclines should not be given to patients with acute porphyria (section 9.8.2).

Hepatic impairment Tetracyclines should be avoided or used with caution in patients with hepatic impairment. Tetracyclines should also be used with caution in those receiving potentially hepatotoxic drugs.

Renal impairment With the exception of **doxycycline** and **minocycline**, the tetracyclines may exacerbate renal failure and should **not** be given to patients with renal impairment.

Pregnancy Tetracyclines should **not** be given to pregnant women. Effects on skeletal development have been documented when tetracyclines have been used in the first trimester of pregnancy in *animal* studies. Administration during the second or third trimester may cause discoloration of the child's teeth, and maternal hepatotoxicity has been reported with large parenteral doses.

Breast-feeding Tetracyclines should **not** be given to women who are breast-feeding (although absorption and therefore discoloration of teeth in the infant is probably usually prevented by chelation with calcium in milk).

Side-effects Side-effects of the tetracyclines include nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia, and oesophageal irritation. Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline), and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis). Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants.

TETRACYCLINE

Indications see notes above; acne vulgaris, rosacea (section 13.6)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above; max. 1 g daily in divided doses
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also acute renal failure, skin discoloration
Dose

- 250 mg every 6 hours, increased in severe infections to 500 mg every 6–8 hours
- Acne, see section 13.6.2
- Non-gonococcal urethritis, 500 mg every 6 hours for 7–14 days (21 days if failure or relapse after first course)

Counselling Tablets should be swallowed whole with plenty of fluid while sitting or standing

Tetracycline (Non-proprietary) PoM

Tablets, coated, tetracycline hydrochloride 250 mg, net price 28-tab pack = £13.67. Label: 7, 9, 23, counselling, posture

Dental prescribing on NHS Tetracycline Tablets may be prescribed

DEMECLOCYCLINE HYDROCHLORIDE

Indications see notes above; also inappropriate secretion of antidiuretic hormone, section 6.5.2
Cautions see notes above, but photosensitivity more common (avoid exposure to sunlight or sun lamps)
Contra-indications see notes above
Hepatic impairment see notes above; max. 1 g daily in divided doses
Renal impairment see notes above

Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also reversible nephrogenic diabetes insipidus, acute renal failure
Dose
- 150 mg every 6 hours *or* 300 mg every 12 hours

Ledermycin® (Goldshield) PoM
Capsules, red, demeclocycline hydrochloride 150 mg, net price 28-cap pack = £16.02. Label: 7, 9, 11, 23

DOXYCYCLINE

Indications see notes above; chronic prostatitis; sinusitis, syphilis, pelvic inflammatory disease (Table 1, section 5.1); treatment and prophylaxis of anthrax [unlicensed indication]; malaria treatment and prophylaxis (section 5.4.1); recurrent aphthous ulceration, adjunct to gingival scaling and root planing for periodontitis (section 12.3.1); oral herpes simplex (section 12.3.2); rosacea, acne vulgaris (section 13.6)
Cautions see notes above; alcohol dependence; photosensitivity reported (avoid exposure to sunlight or sun lamps)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment use with caution (avoid excessive doses)
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also anorexia, dry mouth, flushing, anxiety, and tinnitus
Dose
- 200 mg on first day, then 100 mg daily; severe infections (including refractory urinary-tract infections), 200 mg daily
- Early syphilis, 100 mg twice daily for 14 days; late latent syphilis, 100 mg twice daily for 28 days; neurosyphilis, 200 mg twice daily for 28 days
- Uncomplicated genital chlamydia, non-gonococcal urethritis, 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease, see also Table 1, section 5.1)
- Lyme disease (see also section 5.1.1.3), 100 mg twice daily for 10–14 days (28 days in Lyme arthritis)
- Anthrax (treatment or post-exposure prophylaxis; see also section 5.1.12), 100 mg twice daily; CHILD (only if alternative antibacterial cannot be given) [unlicensed dose] 5 mg/kg daily in 2 divided doses (max. 200 mg daily)

Counselling Capsules should be swallowed whole with plenty of fluid during meals while sitting or standing
Note Doxycycline doses in BNF may differ from those in product literature

Doxycycline (Non-proprietary) PoM
Capsules, doxycycline (as hyclate) 50 mg, net price 28-cap pack = £1.79; 100 mg, 8-cap pack = £1.16. Label: 6, 9, 11, 27, counselling, posture
Brands include *Doxylar®*
Dental prescribing on NHS Doxycycline Capsules 100 mg may be prescribed

Vibramycin-D® (Pfizer) PoM
Dispersible tablets, yellow, scored, doxycycline 100 mg, net price 8-tab pack = £4.91. Label: 6, 9, 11, 13
Dental prescribing on NHS May be prescribed as Dispersible Doxycycline Tablets

Modified-release

Efracea® (Galderma) PoM
Capsules, m/r, beige, doxycycline (as monohydrate) 40 mg, net price 56-cap pack = £29.78. Label: 6, 11, 27, counselling, posture
Dose papulopustular, facial rosacea (without ocular involvement), 40 mg daily in the morning for 16 weeks; consider discontinuing treatment if no response after 6 weeks

LYMECYCLINE

Indications see notes above
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- 408 mg every 12 hours, increased to 1.224–1.632 g daily in severe infections
- Acne, 408 mg daily for at least 8 weeks

Tetralysal 300® (Galderma) PoM
Capsules, red/yellow, lymecycline 408 mg (= tetracycline 300 mg), net price 28-cap pack = £7.77, 56-cap pack = £14.97. Label: 6, 9

MINOCYCLINE

Indications see notes above; meningococcal carrier state; acne vulgaris (section 13.6.2)
Cautions see notes above; if treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment use with caution (avoid excessive doses)
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also dizziness and vertigo (more common in women); *rarely* anorexia, tinnitus, impaired hearing, hyperaesthesia, paraesthesia, acute renal failure, pigmentation (sometimes irreversible), and alopecia; *very rarely* systemic lupus erythematosus, discoloration of conjunctiva, tears, and sweat
Dose
- 100 mg twice daily
- Acne, see section 13.6.2 and under preparations, below
- Prophylaxis of asymptomatic meningococcal carrier state (but no longer recommended, see notes above), 100 mg twice daily for 5 days usually followed by rifampicin

Counselling Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing

Minocycline (Non-proprietary) PoM
Capsules, minocycline (as hydrochloride) 50 mg, net price 56-cap pack = £15.27; 100 mg, 28-cap pack = £13.09. Label: 6, 9, counselling, posture
Brands include *Aknemin®*

Tablets, minocycline (as hydrochloride) 50 mg, net price 28-tab pack = £4.93, 100 mg, 28-tab pack = £9.52. Label: 6, 9, counselling, posture

Modified release

Minocycline m/r preparations PoM

Capsules, m/r, minocycline (as hydrochloride) 100 mg, net price 56-cap pack = £20.08. Label: 6, 25

Brands include *Acnamino®* MR, *Minocin MR®*, *Sebomin MR®*

Dose acne, 100 mg daily

OXYTETRACYCLINE

Indications see notes above; acne vulgaris, rosacea (section 13.6)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- 250–500 mg every 6 hours
- Acne, see section 13.6.2

Oxytetracycline (Non-proprietary) PoM

Tablets, coated, oxytetracycline dihydrate 250 mg, net price 28-tab pack = £1.28. Label: 7, 9, 23

Brands include *Oxymycin®*

Dental prescribing on NHS Oxtetracycline Tablets may be prescribed

Tigecycline

Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines; side-effects similar to those of the tetracyclines can potentially occur. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, but *Pseudomonas aeruginosa* and many strains of *Proteus spp* are resistant to tigecycline. Tigecycline should be reserved for the treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms; however, it is not recommended for the treatment of foot infections in patients with diabetes.

TIGECYCLINE

Indications complicated intra-abdominal infections; complicated skin and soft-tissue infections, but not diabetic foot infections

Cautions cholestasis; **interactions:** Appendix 1 (tigecycline)

Contra-indications hypersensitivity to tetracyclines

Hepatic impairment initially 100 mg then 25 mg every 12 hours in severe impairment

Pregnancy see under Tetracyclines, p. 347

Breast-feeding manufacturer advises caution—present in milk in *animal* studies

Side-effects see notes above; also nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, anorexia, bilirubinaemia, dizziness, headache, prolonged prothrombin time, prolonged activated partial thromboplastin time, rash, pruritus, and injection-site reactions; *less commonly* pancreatitis, cholestatic jaundice, and hypoproteinaemia; also reported, antibiotic-associated colitis, hepatic failure, and thrombocytopenia

Dose

- By intravenous infusion, ADULT over 18 years, initially 100 mg, then 50 mg every 12 hours for 5–14 days

Tygacil® (Wyeth) ▼ PoM

Intravenous infusion, powder for reconstitution, tigecycline, net price 50-mg vial = £32.31

5.1.4 Aminoglycosides

These include amikacin, gentamicin, neomycin, streptomycin, and tobramycin. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against *Pseudomonas aeruginosa*; streptomycin is active against *Mycobacterium tuberculosis* and is now almost entirely reserved for tuberculosis (section 5.1.9).

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections.

Most side-effects of this group of antibiotics are dose-related therefore care must be taken with dosage and whenever possible treatment should not exceed 7 days. The important side-effects are ototoxicity, and nephrotoxicity; they occur most commonly in the elderly and in patients with renal failure.

Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function.

Aminoglycosides should preferably not be given with potentially ototoxic diuretics (e.g. furosemide); if concurrent use is unavoidable administration of the aminoglycoside and of the diuretic should be separated by as long a period as practicable.

Renal impairment Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment. Ototoxicity and nephrotoxicity occur commonly in patients with renal failure. If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well. Serum-aminoglycoside concentrations **must** be monitored in patients with renal impairment, see Serum Concentrations below; renal, auditory, and vestibular function should also be monitored. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with a creatinine clearance less than 20 mL/minute.

Once daily dosage *Once daily administration* of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded *multiple daily dose regimens* (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside

should be avoided in patients with endocarditis, burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute.

Serum concentrations Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen; patients with renal impairment may require earlier and more frequent measurement of aminoglycoside concentration.

For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration ('peak' concentration) and also just before the next dose ('trough' concentration). If the pre-dose ('trough') concentration is high, the interval between doses must be increased. If the post-dose ('peak') concentration is high, the dose must be decreased. For once daily dose regimens, consult local guidelines on serum concentration monitoring.

Serum-aminoglycoside concentrations should be measured in all patients and **must** be determined in infants, in the elderly, in obesity, and in cystic fibrosis, *or* if high doses are being given, *or* if there is renal impairment.

Endocarditis **Gentamicin** is used in combination with other antibiotics for the treatment of bacterial endocarditis (Table 1, section 5.1). Serum-gentamicin concentration should be determined twice each week (more often in renal impairment). **Streptomycin** may be used as an alternative in gentamicin-resistant enterococcal endocarditis.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the 'blind' therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis (see above and Table 1, section 5.1).

Loading and maintenance doses of gentamicin may be calculated on the basis of the patient's weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate, in the patient with cystic fibrosis, or in the immunocompromised patient. Whenever possible treatment should not exceed 7 days.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is slightly more active against *Ps. aeruginosa* but shows less activity against certain other Gram-negative bacteria. Tobramycin may be administered by nebuliser on a cyclical basis (28 days of tobramycin followed by a 28–day tobramycin-free interval) for the treatment of chronic pulmonary *Ps. aeruginosa* infection in cystic fibrosis; however, resistance may develop and some patients do not respond to treatment.

Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin may be absorbed from the gut in patients with hepatic failure and, as these patients may also be uraemic, cumulation may occur with resultant ototoxicity.

Pregnancy There is a risk of auditory or vestibular nerve damage when aminoglycosides are used in the second and third trimesters of pregnancy. The risk is greatest with streptomycin (section 5.1.9). The risk is probably very small with gentamicin and tobramycin, but their use should be avoided unless essential (if given, serum-aminoglycoside concentration monitoring is essential).

GENTAMICIN

Indications septicaemia and neonatal sepsis; meningitis and other CNS infections; biliary-tract infection, acute pyelonephritis or prostatitis, endocarditis (see notes above); pneumonia in hospital patients, adjunct in listerial meningitis (Table 1, section 5.1); eye (section 11.3.1); ear (section 12.1.1)

Cautions neonates, infants and elderly (adjust dose and monitor renal, auditory and vestibular function together with serum gentamicin concentrations); avoid prolonged use; conditions characterised by muscular weakness; see also notes above; **interactions:** Appendix 1 (aminoglycosides)

Contra-indications myasthenia gravis

Renal impairment see notes above

Pregnancy see notes above

Side-effects vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis, stomatitis; also reported, nausea, vomiting, rash, blood disorders; see also notes above

Dose

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum-gentamicin concentration closely

- Multiple daily dose regimen, by intramuscular *or* by slow intravenous injection over at least 3 minutes *or* by intravenous infusion, 3–5 mg/kg daily (in divided doses every 8 hours), see also notes above; CHILD under 18 years see *BNF for Children*

  Endocarditis (in combination with other antibacterials, see Table 1, section 5.1), ADULT 1 mg/kg every 8 hours; CHILD under 18 years see BNF for Children
- Once daily dose regimen (see notes above and also consult local guidelines), by intravenous infusion, initially 5–7 mg/kg, then adjust according to serum-gentamicin concentration; CHILD under 18 years see BNF for Children
- By intrathecal injection, seek specialist advice, 1 mg daily (increased if necessary to 5 mg daily); only preservative-free, intrathecal preparation should be used; CHILD under 18 years see BNF for Children

Note For multiple daily dose regimen, one-hour ('peak') serum concentration should be 5–10 mg/litre (3–5 mg/litre for endocarditis); pre-dose ('trough') concentration should be less than 2 mg/litre (less than 1 mg/litre for endocarditis). For once-daily dose regimen, consult local guidelines on monitoring serum-gentamicin concentration

Gentamicin (Non-proprietary) PoM
Injection, gentamicin (as sulphate), net price 40 mg/mL, 1-mL amp = £1.40, 2-mL amp = £1.54, 2-mL vial = £1.48
Paediatric injection, gentamicin (as sulphate) 10 mg/mL, net price 2-mL vial = £1.80
Intrathecal injection, gentamicin (as sulphate) 5 mg/mL, net price 1-mL amp = 74p
Intravenous infusion, gentamicin (as sulphate) 1 mg/mL in sodium chloride intravenous infusion 0.9%, net price 80-mL (80 mg) bottle = £1.95; 3 mg/mL, 80-mL (240 mg) bottle = £5.95, 120-mL (360 mg) bottle = £8.45

Cidomycin® (Sanofi-Aventis) PoM
Injection, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp or vial = £1.48

Genticin® (Amdipharm) PoM
Injection, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp = £1.40

Isotonic Gentamicin Injection (Baxter) PoM
Intravenous infusion, gentamicin (as sulphate) 800 micrograms/mL in sodium chloride intravenous infusion 0.9%. Net price 100-mL (80-mg) *Viaflex®* bag = £1.61
Electrolytes Na^+ 15.4 mmol/100-mL bag

AMIKACIN

Indications serious Gram-negative infections resistant to gentamicin
Cautions see under Gentamicin; **interactions:** Appendix 1 (aminoglycosides)
Contra-indications see under Gentamicin
Renal impairment see notes above
Pregnancy see notes above
Side-effects see under Gentamicin
Dose

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and monitor serum-amikacin concentration closely

- By intramuscular *or* by slow intravenous injection *or* by infusion, 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses in severe infections; max. 1.5 g daily for up to 10 days (max. cumulative dose 15 g); CHILD under 18 years see *BNF for Children*
  Note One-hour ('peak') serum concentration should not exceed 30 mg/litre; pre-dose ('trough') concentration should be less than 10 mg/litre

Amikacin (Non-proprietary) PoM
Injection, amikacin (as sulphate) 250 mg/mL. Net price 2-mL vial = £10.14
Electrolytes Na^+ 0.56 mmol/500-mg vial

Amikin® (Bristol-Myers Squibb) PoM
Injection, amikacin (as sulphate) 50 mg/mL. Net price 2-mL vial = £2.07
Electrolytes $Na^+ < 0.5$ mmol/vial

NEOMYCIN SULPHATE

Indications bowel sterilisation before surgery, see also notes above
Cautions see under Gentamicin but too toxic for systemic use, see notes above; **interactions:** Appendix 1 (aminoglycosides)
Contra-indications see under Gentamicin; intestinal obstruction
Hepatic impairment absorbed from gastro-intestinal tract in liver disease—increased risk of ototoxicity
Renal impairment avoid; ototoxic; nephrotoxic
Pregnancy see notes above
Side-effects see under Gentamicin but poorly absorbed on oral administration; increased salivation, stomatitis, impaired intestinal absorption with steatorrhoea and diarrhoea
Dose

- By mouth, pre-operative bowel sterilisation, 1 g every hour for 4 hours, then 1 g every 4 hours for 2–3 days Hepatic coma, up to 4 g daily in divided doses usually for 5–7 days

Neomycin (Non-proprietary) PoM
Tablets, neomycin sulphate 500 mg. Net price 100= £20.65
Brands include *Nivemycin®*

TOBRAMYCIN

Indications see under Gentamicin and notes above
Cautions see under Gentamicin; **interactions:** Appendix 1 (aminoglycosides)
Specific cautions for inhaled treatment Other inhaled drugs should be administered before tobramycin; monitor for bronchospasm with initial dose, measure peak flow before and after nebulisation—if bronchospasm occurs, repeat test using bronchodilator; monitor renal function before treatment and then annually; severe haemoptysis
Contra-indications see under Gentamicin
Renal impairment see notes above
Pregnancy see notes above
Side-effects see under Gentamicin; *on inhalation*, mouth ulcers, taste disturbances, voice alteration, cough, bronchospasm (see Cautions)
Dose

To avoid excessive dosage in obese patients, use ideal weight for height to calculate parenteral dose and monitor serum-tobramycin concentration closely

- By intramuscular injection *or* by slow intravenous injection *or* by intravenous infusion, 3 mg/kg daily in divided doses every 8 hours, see also notes above; in severe infections up to 5 mg/kg daily in divided doses every 6–8 hours (reduced to 3 mg/kg as soon as clinically indicated); CHILD under 18 years see *BNF for Children*
- Urinary-tract infection, by intramuscular injection, 2–3 mg/kg daily as a single dose

Note One-hour ('peak') serum concentration should not exceed 10 mg/litre; pre-dose ('trough') concentration should be less than 2 mg/litre

- Chronic pulmonary *Pseudomonas aeruginosa* infection in patients with cystic fibrosis, by inhalation of nebulised solution, ADULT and CHILD over 6 years, 300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

Parenteral

Tobramycin (Non-proprietary) PoM
Injection, tobramycin (as sulphate) 40 mg/mL, net price 1-mL (40-mg) vial = £4.00, 2-mL (80-mg) vial = £4.16, 6-mL (240-mg) vial = £19.20

Inhalation

Bramitob® (Chiesi) PoM
Nebuliser solution, tobramycin 75 mg/mL, net price 56 × 4-mL (300-mg) unit = £1187.00

Tobi® (Novartis) PoM

Nebuliser solution, tobramycin 60 mg/mL, net price 56 × 5-mL (300-mg) unit = £1187.20

5.1.5 Macrolides

Erythromycin has an antibacterial spectrum that is similar but not identical to that of penicillin; it is thus an alternative in penicillin-allergic patients.

Indications for erythromycin include respiratory infections, whooping cough, legionnaires' disease, and campylobacter enteritis. It is active against many penicillin-resistant staphylococci but some are now also resistant to erythromycin; it has poor activity against *Haemophilus influenzae*. Erythromycin is also active against chlamydia and mycoplasmas.

Erythromycin causes nausea, vomiting, and diarrhoea in some patients; in mild to moderate infections this can be avoided by giving a lower dose (250 mg 4 times daily) but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed.

Azithromycin is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria but enhanced activity against some Gram-negative organisms including *H. influenzae*. Plasma concentrations are very low but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. Azithromycin is also used in the treatment of trachoma [unlicensed indication] (section 11.3.1).

Clarithromycin is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily.

For the role of erythromycin, azithromycin, and clarithromycin in the treatment of Lyme disease, see section 5.1.1.3

Spiramycin is also a macrolide (section 5.4.7).

Oral infections Clarithromycin or erythromycin is an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to macrolides or rapidly develop resistance; their use should therefore be limited to short courses. Metronidazole (section 5.1.11) may be preferred as an alternative to a penicillin.

Cautions Macrolides should be used with caution in patients with a predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval).

Side-effects Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side-effects of the macrolides, but they are mild and less frequent with azithromycin and clarithromycin than with erythromycin. Hepatotoxicity (including cholestatic jaundice) and rash occur less frequently. Other side-effects reported rarely or very rarely include pancreatitis, antibiotic-associated colitis, QT interval prolongation, arrhythmias, generally reversible hearing loss (sometimes with tinnitus) after large doses, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Intravenous infusion may cause local tenderness and phlebitis.

AZITHROMYCIN

Indications respiratory-tract infections; otitis media; skin and soft-tissue infections; uncomplicated genital chlamydial infections and non-gonococcal urethritis (Table 1, section 5.1); mild or moderate typhoid due to multiple-antibacterial-resistant organisms [unlicensed indication]; Lyme disease (see also section 5.1.1.3 [unlicensed indication]); prophylaxis of group A streptococcal infection (Table 2, section 5.1)

Cautions see notes above; **interactions:** Appendix 1 (macrolides)

Hepatic impairment manufacturers advise avoid in severe liver disease—no information available

Renal impairment use with caution if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy manufacturers advise use only if adequate alternatives not available

Breast-feeding present in milk; use only if no suitable alternatives

Side-effects see notes above; also anorexia, dyspepsia, flatulence, dizziness, headache, drowsiness, convulsions, arthralgia, and disturbances in taste and smell; *rarely* constipation, syncope, insomnia, agitation, anxiety, asthenia, paraesthesia, hyperactivity, thrombocytopenia, haemolytic anaemia, interstitial nephritis, acute renal failure, photosensitivity, tooth and tongue discoloration

Dose

- 500 mg once daily for 3 days *or* 500 mg on first day then 250 mg once daily for 4 days; CHILD over 6 months 10 mg/kg once daily for 3 days; *or* bodyweight 15–25 kg, 200 mg once daily for 3 days; bodyweight 26–35 kg, 300 mg once daily for 3 days; bodyweight 36–45 kg, 400 mg once daily for 3 days
- Uncomplicated genital chlamydial infections and non-gonococcal urethritis, 1 g as a single dose
- Lyme disease (see also section 5.1.1.3), typhoid [unlicensed indications], 500 mg once daily for 7–10 days (7 days in typhoid)

Azithromycin (Non-proprietary) PoM

Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £9.82, 6-cap pack = £14.73. Label: 5, 9, 23

Tablets, azithromycin (as monohydrate hemi-ethanolate) 250 mg, net price 4-tab pack = £9.83; 500 mg, 3-tab pack = £6.75. Label: 5, 9

Note Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic *Chlamydia trachomatis* genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to max. single dose of 1 g, max. daily dose 1 g, and a pack size of 1 g

Oral suspension, azithromycin (as monohydrate) 200 mg/5 mL when reconstituted with water, net price 15-mL pack = £5.86, 30-mL pack = £11.04. Label: 5, 9

Dental prescribing on NHS May be prescribed as Azithromycin Oral Suspension 200 mg/5 mL

Zithromax® (Pfizer) PoM

Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £7.16, 6-cap pack = £10.74. Label: 5, 9, 23

Oral suspension, cherry/banana-flavoured, azithromycin (as dihydrate) 200 mg/5 mL when reconstituted with water. Net price 15-mL pack = £4.06, 22.5-mL pack = £6.10, 30-mL pack = £11.04. Label: 5, 9

CLARITHROMYCIN

Indications respiratory-tract infections, mild to moderate skin and soft-tissue infections, otitis media; Lyme disease (see also section 5.1.1.3); *Helicobacter pylori* eradication (section 1.3)

Cautions see notes above; **interactions:** Appendix 1 (macrolides)

Hepatic impairment hepatic dysfunction including jaundice reported

Renal impairment use half normal dose if eGFR less than 30 mL/minute/1.73 m^2; avoid *Klaricid XL®* if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—present in milk

Side-effects see notes above; also tooth and tongue discoloration, smell and taste disturbances, stomatitis, glossitis, and headache; *less commonly* arthralgia and myalgia; *rarely* tinnitus; *very rarely* dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, interstitial nephritis, leucopenia, and thrombocytopenia

Dose

- By mouth, ADULT and CHILD over 12 years, 250 mg every 12 hours for 7 days, increased in pneumonia or severe infections to 500 mg every 12 hours for up to 14 days (see also Table 1, section 5.1); CHILD bodyweight under 8 kg, 7.5 mg/kg twice daily; 8–11 kg, 62.5 mg twice daily; 12–19 kg, 125 mg twice daily; 20–29 kg, 187.5 mg twice daily; 30–40 kg, 250 mg twice daily

  Lyme disease (see also section 5.1.1.3), ADULT and CHILD over 12 years, 500 mg every 12 hours for 14–21 days [unlicensed duration]; CHILD 1 month–12 years see *BNF for Children*
- By intravenous infusion into larger proximal vein, ADULT and CHILD over 12 years, 500 mg twice daily; CHILD 1 month–12 years see *BNF for Children*

Clarithromycin (Non-proprietary) PoM

Tablets, clarithromycin 250 mg, net price 14-tab pack = £3.17; 500 mg, 14-tab pack = £4.10. Label: 9
Dental prescribing on NHS Clarithromycin Tablets may be prescribed

Oral suspension, clarithromycin for reconstitution with water 125 mg/5 mL, net price 70 mL = £6.18; 250 mg/5 mL, 70 mL = £12.36. Label: 9
Dental prescribing on NHS Clarithromycin Oral Suspension may be prescribed

Intravenous infusion, powder for reconstitution, clarithromycin, net price 500-mg vial = £10.31

Klaricid® (Abbott) PoM

Tablets, both yellow, f/c, clarithromycin 250 mg, net price 14-tab pack = £6.30; 500 mg, 14-tab pack = £10.17, 20-tab pack = £14.54. Label: 9

Paediatric suspension, clarithromycin for reconstitution with water 125 mg/5 mL, net price 70 mL = £4.73, 100 mL = £8.14; 250 mg/5 mL, 70 mL = £9.46. Label: 9

Granules, clarithromycin 250 mg/sachet, net price 14-sachet pack = £11.68. Label: 9, 13

Intravenous infusion, powder for reconstitution, clarithromycin. Net price 500-mg vial = £9.45
Electrolytes $Na^+ < 0.5$ mmol/500-mg vial

Klaricid XL® (Abbott) PoM

Tablets, m/r, yellow, clarithromycin 500 mg, net price 7-tab pack = £6.46, 14-tab pack = £12.71. Label: 9, 21, 25

Dose 500 mg once daily (doubled in severe infections) for 7–14 days

ERYTHROMYCIN

Indications susceptible infections in patients with penicillin hypersensitivity; oral infections (see notes above); campylobacter enteritis, syphilis, non-gonococcal urethritis, respiratory-tract infections (including Legionella infection), skin infections (Table 1, section 5.1); chronic prostatitis; prophylaxis of diphtheria, group A streptococcal infection, and whooping cough (Table 2, section 5.1); acne vulgaris and rosacea (section 13.6)

Cautions see notes above; neonate under 2 weeks (risk of hypertrophic pyloric stenosis); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (macrolides)

Hepatic impairment may cause idiosyncratic hepatotoxicity

Renal impairment max. 1.5 g daily in severe renal impairment (ototoxicity)

Pregnancy not known to be harmful

Breast-feeding only small amounts in milk—not known to be harmful

Side-effects see notes above; also myasthenia-like syndrome

Dose

- By mouth, ADULT and CHILD over 8 years, 250–500 mg every 6 hours *or* 0.5–1 g every 12 hours (see notes above); up to 4 g daily in divided doses in severe infections; NEONATE 12.5 mg/kg every 6 hours; CHILD 1 month–2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours, doses doubled for severe infections

  Early syphilis, 500 mg 4 times daily for 14 days

  Uncomplicated genital chlamydia, non-gonococcal urethritis, 500 mg twice daily for 14 days

  Lyme disease (see also section 5.1.1.3), 500 mg 4 times daily for 14–21 days
- By intravenous infusion, ADULT and CHILD severe infections, 12.5 mg/kg every 6 hours; mild infections (when oral treatment not possible), 6.25 mg/kg every 6 hours; NEONATE see *BNF for Children*

Erythromycin (Non-proprietary) PoM

Capsules, enclosing e/c microgranules, erythromycin 250 mg, net price 28-cap pack = £15.00. Label: 5, 9, 25
Brands include *Tiloryth®*

Tablets, e/c, erythromycin 250 mg, net price 28 = £1.54. Label: 5, 9, 25
Dental prescribing on NHS Erythromycin Tablets e/c may be prescribed

Erythromycin Ethyl Succinate (Non-proprietary) PoM

Oral suspension, erythromycin (as ethyl succinate) for reconstitution with water 125 mg/5 mL, net price 100 mL = £1.99; 250 mg/5 mL, 100 mL = £2.64; 500 mg/5 mL, 100 mL = £4.31. Label: 9
Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription
Brands include *Primacine®*
Dental prescribing on NHS Erythromycin Ethyl Succinate Oral Suspension may be prescribed

Erythromycin Lactobionate (Non-proprietary) PoM
Intravenous infusion, powder for reconstitution, erythromycin (as lactobionate), net price 1-g vial = £9.98

Erymax® (Cephalon) PoM
Capsules, opaque orange/clear orange, enclosing orange and white e/c pellets, erythromycin 250 mg, net price 28-cap pack = £5.61, 112-cap pack = £22.44. Label: 5, 9, 25
Dose 1 capsule every 6 hours *or* 2 capsules every 12 hours; acne, 1 capsule twice daily for 1 month then 1 capsule daily

Erythrocin® (Amdipharm) PoM
Tablets, both f/c, erythromycin (as stearate), 250 mg, net price 100 = £18.20; 500 mg, 100 = £36.40. Label: 9
Dental prescribing on NHS May be prescribed as Erythromycin Stearate Tablets

Erythroped® (Amdipharm) PoM
Suspension SF, sugar-free, banana-flavoured, erythromycin (as ethyl succinate) for reconstitution with water, 125 mg/5 mL (*Suspension PI SF*), net price 140 mL = £3.06; 250 mg/5 mL, 140 mL = £5.95; 500 mg/5 mL (*Suspension SF Forte*), 140 mL = £10.56. Label: 9

Erythroped A® (Amdipharm) PoM
Tablets, yellow, f/c, erythromycin 500 mg (as ethyl succinate). Net price 28-tab pack = £10.78. Label: 9
Dental prescribing on NHS May be prescribed as Erythromycin Ethyl Succinate Tablets

Telithromycin

The ketolide **telithromycin** is a derivative of erythromycin. The antibacterial spectrum of telithromycin is similar to that of macrolides and it is also active against penicillin- and erythromycin-resistant *Streptococcus pneumoniae*. Telithromycin should only be used to treat beta-haemolytic streptococcal pharyngitis and tonsillitis, sinusitis, community-acquired pneumonia, and exacerbations of chronic bronchitis if caused by organisms resistant to beta-lactam antibacterials and other macrolides, or if conventional treatment is contra-indicated.

TELITHROMYCIN

Indications see notes above

Cautions coronary heart disease, ventricular arrhythmias, bradycardia, hypokalaemia, hypomagnesaemia—risk of QT interval prolongation; concomitant administration of drugs that prolong QT-interval; avoid in acute porphyria (section 9.8.2); **interactions**: Appendix 1 (telithromycin)
Hepatic disorders Patients should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, abdominal pain, jaundice, or dark urine develop
Driving Visual disturbances or transient loss of consciousness may affect performance of skilled tasks (e.g. driving); effects may occur after the first dose. Administration at bedtime may reduce these side-effects. Patients should be advised not to drive or operate machinery if affected

Contra-indications myasthenia gravis; history of telithromycin-associated hepatitis or jaundice; prolongation of QT interval; congenital or family history of QT interval prolongation (if not excluded by ECG)

Hepatic impairment manufacturer advises caution; see also Hepatic Disorders above

Renal impairment manufacturer advises avoid if possible if eGFR less than 30 mL/minute/1.73 m^2—if no alternative, use alternating daily doses of 800 mg and 400 mg, starting with 800 mg dose

Pregnancy toxicity in *animal* studies—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects diarrhoea, nausea, vomiting, flatulence, abdominal pain, taste disturbances; dizziness, headache; *less commonly* constipation, stomatitis, anorexia, hepatitis, flushing, palpitations, drowsiness, insomnia, nervousness, eosinophilia, blurred vision, rash, urticaria, and pruritus; *rarely* cholestatic jaundice, arrhythmias, hypotension, transient loss of consciousness, paraesthesia, and diplopia; *very rarely* antibiotic-associated colitis, altered sense of smell, muscle cramp, erythema multiforme; also reported pancreatitis, confusion, hallucinations and arthralgia

Dose

- 800 mg once daily for 5 days for sinusitis or exacerbation of chronic bronchitis *or* for 7–10 days in community-acquired pneumonia; CHILD under 18 years safety and efficacy not established
- Tonsillitis or pharyngitis caused by *Streptococcus pyogenes*, ADULT and CHILD over 12 years, 800 mg once daily for 5 days

Ketek® (Sanofi-Aventis) ▼ PoM
Tablets, orange, f/c, telithromycin 400 mg, net price 10-tab pack = £18.56. Label: 9, counselling , driving, hepatic disorders

5.1.6 Clindamycin

Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides fragilis*. It is well concentrated in bone and excreted in bile and urine.

Clindamycin is recommended for staphylococcal joint and bone infections such as osteomyelitis, and intra-abdominal sepsis; it is an alternative to macrolides for erysipelas or cellulitis in penicillin-allergic patients. Clindamycin can also be used for infections associated with meticillin-resistant *Staphylococcus aureus* (MRSA) in bronchiectasis, bone and joint infections, and skin and soft-tissue infections.

Clindamycin has been associated with antibiotic-associated colitis (section 1.5), which may be fatal; it is most common in middle-aged and elderly women, especially following an operation. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. Patients should therefore discontinue treatment immediately if diarrhoea develops.

Oral infections Clindamycin should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin-resistant bacteria. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

CLINDAMYCIN

Indications see notes above; staphylococcal bone and joint infections, peritonitis; falciparum malaria (section 5.4.1)

Cautions discontinue immediately if diarrhoea or colitis develops; monitor liver and renal function if treatment exceeds 10 days, and in neonates and infants; avoid rapid intravenous administration; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (clindamycin)

Contra-indications diarrhoeal states; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Pregnancy not known to be harmful

Breast-feeding amount probably too small to be harmful but bloody diarrhoea reported in 1 infant

Side-effects diarrhoea (discontinue treatment), abdominal discomfort, oesophagitis, oesophageal ulcers, taste disturbances, nausea, vomiting, antibiotic-associated colitis; jaundice; leucopenia, eosinophilia, and thrombocytopenia reported; polyarthritis reported; rash, pruritus, urticaria, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis reported; pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection

Dose

- By mouth, 150–300 mg every 6 hours; up to 450 mg every 6 hours in severe infections; CHILD, 3–6 mg/kg every 6 hours
  Counselling Patients should discontinue immediately and contact doctor if diarrhoea develops; capsules should be swallowed with a glass of water.
- By deep intramuscular injection *or* by intravenous infusion, 0.6–2.7 g daily (in 2–4 divided doses); life-threatening infection, up to 4.8 g daily; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; CHILD over 1 month, 15–40 mg/kg daily in 3–4 divided doses; severe infections, at least 300 mg daily regardless of weight

Clindamycin (Non-proprietary) PoM

Capsules, clindamycin (as hydrochloride) 150 mg, net price 24-cap pack = £11.75. Label: 9, 27, counselling, see above (diarrhoea)
Dental prescribing on NHS Clindamycin Capsules may be prescribed

Dalacin C® (Pharmacia) PoM

Capsules, clindamycin (as hydrochloride) 75 mg (green/white), net price 24-cap pack = £7.45; 150 mg, (white), 24-cap pack = £13.72. Label: 9, 27, counselling, see above (diarrhoea)
Dental prescribing on NHS May be prescribed as Clindamycin Capsules

Injection, clindamycin (as phosphate) 150 mg/mL, net price 2-mL amp = £6.20; 4-mL amp = £12.35
Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

5.1.7 Some other antibacterials

Antibacterials discussed in this section include chloramphenicol, fusidic acid, glycopeptide antibiotics (vancomycin and teicoplanin), linezolid, and the polymyxin, colistin.

Chloramphenicol

Chloramphenicol is a potent broad-spectrum antibiotic; however, it is associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections, particularly those caused by *Haemophilus influenzae*, and also for typhoid fever.

Chloramphenicol eye drops (section 11.3.1) and chloramphenicol ear drops (section 12.1.1) are also available.

CHLORAMPHENICOL

Indications see notes above

Cautions avoid repeated courses and prolonged treatment; blood counts required before and periodically during treatment; monitor plasma-chloramphenicol concentration in neonates (see below); **interactions:** Appendix 1 (chloramphenicol)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasma-chloramphenicol concentration

Renal impairment avoid in severe renal impairment unless no alternative; dose-related depression of haematopoiesis

Pregnancy manufacturer advises avoid; neonatal 'grey syndrome' if used in third trimester

Breast-feeding manufacturer advises avoid; use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'

Side-effects blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia), peripheral neuritis, optic neuritis, headache, depression, urticaria, erythema multiforme, nausea, vomiting, diarrhoea, stomatitis, glossitis, dry mouth; nocturnal haemoglobinuria reported; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism

Dose

- By mouth *or* by intravenous injection *or* infusion, 12.5 mg/kg every 6 hours (exceptionally, can be doubled for severe infections such as septicaemia and meningitis, providing high doses reduced as soon as clinically indicated); CHILD over 1 month, haemophilus epiglottitis and pyogenic meningitis, 12.5–25 mg/kg every 6 hours (high dosages decreased as soon as clinically indicated); NEONATE under 2 weeks, 12.5 mg/kg twice daily; 2 weeks–1 month, 12.5 mg/kg 2–4 times daily
  Note Plasma concentration monitoring required in neonates and preferred in those under 4 years of age, in the elderly, and in hepatic impairment; recommended peak plasma concentration (approx. 2 hours after administration by mouth, intravenous injection or infusion) 10–25 mg/litre; pre-dose ('trough') concentration should not exceed 15 mg/litre

Chloramphenicol (Non-proprietary) PoM

Capsules, chloramphenicol 250 mg. Net price 60 = £377.00

Kemicetine® (Pharmacia) PoM

Injection, powder for reconstitution, chloramphenicol (as sodium succinate). Net price 1-g vial = £1.39
Electrolytes Na^+ 3.14 mmol/g

Fusidic acid

Fusidic acid and its salts are narrow-spectrum antibiotics. The only indication for their use is in infections caused by penicillin-resistant staphylococci, especially osteomyelitis, as they are well concentrated in bone; they are also used for staphylococcal endocarditis. A second antistaphylococcal antibiotic is usually required to prevent emergence of resistance.

SODIUM FUSIDATE

Indications penicillin-resistant staphylococcal infection including osteomyelitis; staphylococcal endocarditis in combination with other antibacterials (Table 1, section 5.1)

Cautions monitor liver function with high doses or on prolonged therapy; elimination may be reduced in biliary disease or biliary obstruction; **interactions:** Appendix 1 (fusidic acid)

Hepatic impairment impaired biliary excretion; possibly increased risk of hepatotoxicity; avoid or reduce dose; monitor liver function

Pregnancy not known to be harmful; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding present in milk—manufacturer advises caution

Side-effects nausea, vomiting, reversible jaundice, especially after high dosage or rapid infusion (withdraw therapy if persistent); rarely hypersensitivity reactions, acute renal failure (usually with jaundice), blood disorders

Dose

- See under Preparations, below

Sodium fusidate (LEO) PoM

Intravenous infusion, powder for reconstitution, sodium fusidate 500 mg (= fusidic acid 480 mg), with buffer, net price per vial (with diluent) = £70.04

Electrolytes Na^+ 3.1 mmol/vial when reconstituted with buffer

Dose as sodium fusidate, by intravenous infusion, ADULT over 50 kg, 500 mg 3 times daily; ADULT under 50 kg and CHILD, 6–7 mg/kg 3 times daily

Fucidin® (LEO) PoM

Tablets, f/c, sodium fusidate 250 mg, net price 10-tab pack = £6.02. Label: 9

Dose as sodium fusidate, 500 mg every 8 hours, doubled for severe infections

Skin infection, as sodium fusidate, 250 mg every 12 hours for 5–10 days

Suspension, off-white, banana- and orange-flavoured, fusidic acid 250 mg/5 mL, net price 50 mL = £6.73. Label: 9, 21

Dose as fusidic acid, ADULT 750 mg every 8 hours; CHILD up to 1 year 50 mg/kg daily (in 3 divided doses), 1–5 years 250 mg every 8 hours, 5–12 years 500 mg every 8 hours

Note Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets

Vancomycin and teicoplanin

The glycopeptide antibiotics vancomycin and teicoplanin have bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci.

Vancomycin is used *by the intravenous route* in the treatment of endocarditis and other serious infections caused by Gram-positive cocci. It has a long duration of action and can therefore be given every 12 hours. Vancomycin (added to dialysis fluid) is also used in the treatment of peritonitis associated with peritoneal dialysis [unlicensed route] (Table 1 section 5.1).

Vancomycin given *by mouth* for 10–14 days is effective in the treatment of *Clostridium difficile* infection (see also section 1.5); low doses are considered adequate (higher dose may be considered if the infection fails to respond or it is life threatening). Vancomycin should **not** be given by mouth for systemic infections since it is not significantly absorbed.

Teicoplanin is similar to vancomycin but has a significantly longer duration of action allowing once-daily administration. Unlike vancomycin, teicoplanin can be given by intramuscular as well as by intravenous injection; it is not given by mouth.

VANCOMYCIN

Indications see notes above

Cautions avoid rapid infusion (risk of anaphylactoid reactions, see Side-effects); rotate infusion sites; elderly; avoid if history of deafness; all patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment), blood counts, urinalysis, and renal function tests; monitor auditory function in elderly or if renal impairment; teicoplanin sensitivity; systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses; **interactions:** Appendix 1 (vancomycin)

Renal impairment reduce dose—monitor plasma-vancomycin concentration and renal function regularly; see also Cautions above

Pregnancy manufacturer advises use only if potential benefit outweighs risk—plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity

Breast-feeding present in milk—significant absorption following oral administration unlikely

Side-effects after parenteral administration: nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders including neutropenia (usually after 1 week or cumulative dose of 25 g), rarely agranulocytosis and thrombocytopenia; nausea; chills, fever; eosinophilia, anaphylaxis, rashes (including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis); phlebitis (irritant to tissue); on rapid infusion, severe hypotension (including shock and cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body ('red man' syndrome), pain and muscle spasm of back and chest

Dose

- By mouth, *Clostridium difficile* infection, (see also notes above), ADULT and CHILD over 12 years, 125 mg every 6 hours for 10–14 days (increased up to 500 mg every 6 hours if infection fails to respond or is life-threatening); CHILD 1 month–5 years, 5 mg/kg every 6 hours for 10–14 days (increased up to 10 mg/kg every 6 hours if infection fails to respond or is life-threatening); 5–12 years, half adult dose

- By intravenous infusion, 1–1.5 g every 12 hours; ELDERLY over 65 years, 500 mg every 12 hours *or* 1 g once daily; CHILD over 1 month, 15 mg/kg every 8 hours (max. 2 g daily)

  Note Plasma concentration monitoring required (see Cautions above); pre-dose ('trough') concentration should be 10–15 mg/litre (15–20 mg/litre for less sensitive strains of meticillin-resistant *Staphylococcus aureus*)
- Surgical prophylaxis, by intravenous infusion, ADULT over 18 years, 1 g

Note Vancomycin doses in BNF may differ from those in product literature

Vancomycin (Non-proprietary) PoM

Capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £132.47; 250 mg, 28-cap pack = £132.47. Label: 9

Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £7.25; 1-g vial = £14.50

Note Can be used to prepare solution for oral administration

Vancocin® (Flynn) PoM

Matrigel capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £88.31. Label: 9

Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £8.05; 1-g vial = £16.11

Note Can be used to prepare solution for oral administration

TEICOPLANIN

Indications potentially serious Gram-positive infections including endocarditis, dialysis-associated peritonitis, and serious infections due to *Staphylococcus aureus*; prophylaxis in orthopaedic surgery at risk of infection with Gram-positive organisms

Cautions vancomycin sensitivity; blood counts and liver and kidney function tests required; monitor plasma-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis, renal impairment, in elderly, and in intravenous drug abusers; monitor renal and auditory function during prolonged treatment in renal impairment or if other nephrotoxic or neurotoxic drugs given; **interactions:** Appendix 1 (teicoplanin)

Renal impairment on day 4 use half normal dose if eGFR is 40–60 mL/minute/1.73 m^2 and use one-third normal dose if eGFR is less than 40 mL/minute/1.73 m^2; see also Cautions above

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding no information available

Side-effects rash, pruritus; *less commonly* nausea, vomiting, diarrhoea, bronchospasm, dizziness, headache, fever, leucopenia, thrombocytopenia, eosinophilia, tinnitus, mild hearing loss, vestibular disorders, thrombophlebitis; *also reported* renal failure, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dose

- By intravenous injection *or* infusion, ADULT body-weight under 70 kg, initially 400 mg every 12 hours for 3 doses, subsequently 400 mg once daily (subsequent doses can alternatively be given by intramuscular injection); body-weight over 70 kg, initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily; higher doses may be required in severe infection (including burns, septicaemia, septic arthritis, and osteomyelitis), consult product literature
- CHILD over 2 months by intravenous injection *or* infusion, initially 10 mg/kg (max. 400 mg) every 12 hours for 3 doses, subsequently 6 mg/kg (max. 200 mg) once daily (severe infections or in neutropenia, 10 mg/kg (max. 400 mg) once daily); subsequent doses can be given by intramuscular injection (but intravenous administration preferred in children); NEONATE by intravenous infusion, initially a single dose of 16 mg/kg, subsequently 8 mg/kg once daily
- Streptococcal endocarditis (in combination with another antibacterial if necessary, see Table 1, section 5.1), by intravenous injection *or* infusion, ADULT initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily
- Enterococcal endocarditis (in combination with another antibacterial, see Table 1, section 5.1), by intravenous injection *or* infusion, ADULT initially 10 mg/kg every 12 hours for 3 doses, then 10 mg/kg once daily
- Surgical prophylaxis, ADULT, by intravenous injection, 400 mg up to 30 minutes before the procedure; open fractures, by intravenous infusion, 800 mg up to 30 minutes before skeletal stabilisation and definitive soft-tissue closure

Note Plasma-teicoplanin concentration is not measured routinely because a relationship between plasma concentration and toxicity has not been established. However, the plasma-teicoplanin concentration can be used to optimise treatment in some patients (see Cautions). Pre-dose ('trough') concentrations should be greater than 10 mg/litre (greater than 15–20 mg/litre in endocarditis; greater than 20 mg/litre in deep-seated infection such as bone and joint infection), but less than 60 mg/litre. Teicoplanin doses in BNF may differ from those in product literature

Targocid® (Sanofi-Aventis) PoM

Injection, powder for reconstitution, teicoplanin, net price 200-mg vial (with diluent) = £3.57; 400-mg vial (with diluent) = £6.10

Electrolytes $Na^+ < 0.5$ mmol/200- and 400-mg vial

Daptomycin

Daptomycin is a lipopeptide antibacterial with a spectrum of activity similar to vancomycin but its efficacy against enterococci has not been established. Daptomycin should be reserved for complicated skin and soft-tissue infections caused by resistant Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA). It needs to be given with other antibacterials for mixed infections involving Gram-negative bacteria and some anaerobes.

The *Scottish Medicines Consortium* (p. 4) has advised (February 2008) that daptomycin (*Cubicin®*) is accepted for restricted use within NHS Scotland for the treatment of MRSA bacteraemia associated with right-sided endocarditis or with complicated skin and soft-tissue infections.

DAPTOMYCIN

Indications see under Dose

Cautions interference with assay for prothrombin time and INR—take blood sample immediately before daptomycin dose; **interactions:** Appendix 1 (daptomycin)

Muscle effects Myalgia, muscle weakness, and myositis may occur uncommonly; rhabdomyolysis is very rare. Monitor creatine kinase before treatment and then weekly during treatment (more frequently if creatine kinase elevated more than 5 times upper limit of normal before treatment, or if receiving another drug known to cause myopathy (preferably avoid concomitant use), or if eGFR less than 30 mL/

minute/1.73 m^2). If unexplained muscle pain, tenderness, weakness, or cramps develop during treatment, measure creatine kinase every 2 days; discontinue if unexplained muscular symptoms and creatine kinase elevated markedly

Hepatic impairment manufacturer advises caution in severe hepatic impairment—no information available

Renal impairment see Muscle Effects above; also monitor renal function if eGFR less than 80 mL/minute/1.73 m^2; use normal dose every 48 hours if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid

Side-effects nausea, vomiting, abdominal pain, flatulence, diarrhoea (antibiotic-associated colitis reported), constipation, hypertension, hypotension, headache, anxiety, insomnia, dizziness, asthenia, anaemia, arthralgia, rash, pruritus, injection-site reactions; *less commonly* dyspepsia, anorexia, taste disturbance, glossitis, flushing, arrhythmias, tremor, paraesthesia, hyperglycaemia, renal failure, eosinophilia, thrombocythaemia, electrolyte disturbances, muscle effects (see Cautions); *rarely* jaundice; also reported syncope, wheezing, pulmonary eosinophilia, peripheral neuropathy

Dose

- By slow intravenous injection over 2 minutes *or* by intravenous infusion, complicated skin and soft-tissue infections caused by Gram-positive bacteria, ADULT over 18 years, 4 mg/kg once daily; increased to 6 mg/kg once daily if associated with *Staphylococcus aureus* bacteraemia

  Right-sided endocarditis caused by *Staphylococcus aureus*, ADULT over 18 years, 6 mg/kg once daily

Cubicin® (Novartis) ▼ PoM

Intravenous infusion, powder for reconstitution, daptomycin, net price 350-mg vial = £62.00; 500-mg vial = £88.57

Linezolid

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is an option if a glycopeptide, such as vancomycin, cannot be used to treat pneumonia or severe skin and soft-tissue infections caused by MRSA. Linezolid is **not** active against Gram-negative organisms and must be given with other antibacterials if the infection also involves Gram-negative organisms (the combination should be used for mixed skin and soft tissue infections only when other treatments are not available). A higher incidence of blood disorders and optic neuropathy have been reported in patients receiving linezolid for more than the maximum recommended duration of 28 days.

LINEZOLID

Indications pneumonia, complicated skin and soft-tissue infections caused by Gram-positive bacteria (initiated under expert supervision)

Cautions monitor full blood count (including platelet count) weekly (see also Blood disorders below); history of seizures; unless close observation and blood-pressure monitoring possible, avoid in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states; **interactions:** Appendix 1 (MAOIs)

Blood disorders

Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

CHM advice (optic neuropathy)

Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:

- patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
- patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;
- visual function should be monitored regularly if treatment is required for longer than 28 days.

Monoamine oxidase inhibition Linezolid is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, $5HT_1$ agonists ('triptans'), tricyclic antidepressants, sympathomimetics, dopaminergics, buspirone, pethidine and possibly other opioid analgesics. For other interactions see Appendix 1 (MAOIs)

Contra-indications see Monoamine Oxidase Inhibition above

Hepatic impairment in severe hepatic impairment manufacturer advises use only if potential benefit outweighs risk

Renal impairment manufacturer advises metabolites may accumulate if eGFR less than 30 mL/minute/1.73 m^2; see also Blood Disorders, above

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects diarrhoea (antibiotic-associated colitis reported), nausea, vomiting, taste disturbances, headache; *less commonly* thirst, dry mouth, glossitis, stomatitis, tongue discoloration, abdominal pain, dyspepsia, gastritis, constipation, pancreatitis, hypertension, fever, fatigue, dizziness, insomnia, hypoaesthesia, paraesthesia, tinnitus, polyuria, leucopenia, thrombocytopenia, eosinophilia, electrolyte disturbances, blurred vision, rash, pruritus, diaphoresis, injection-site reactions; *rarely* tachycardia, transient ischaemic attacks, renal failure; also reported tooth discoloration, convulsions, lactic acidosis, pancytopenia, anaemia, Stevens-Johnson syndrome,

toxic epidermal necrolysis; peripheral and optic neuropathy reported on prolonged therapy (see also CHM advice above)

Dose

- By mouth, 600 mg every 12 hours usually for 10–14 days (max. duration of treatment 28 days); CHILD [unlicensed] 1 week–12 years, 10 mg/kg every 8 hours; 12–18 years, adult dose
- By intravenous infusion over 30–120 minutes, 600 mg every 12 hours; CHILD [unlicensed] 1 week–12 years, 10 mg/kg every 8 hours; 12–18 years, adult dose

Zyvox® (Pharmacia) ▼ PoM

Tablets, f/c, linezolid 600 mg, net price 10-tab pack = £445.00. Label: 9, 10, patient information leaflet

Suspension, yellow, linezolid 100 mg/5 mL when reconstituted with water, net price 150 mL (orange-flavoured) = £222.50. Label: 9, 10 patient information leaflet

Excipients include aspartame 20 mg/5 mL (section 9.4.1)

Intravenous infusion, linezolid 2 mg/mL, net price 300-mL *Excel*® bag = £44.50

Excipients include Na^+ 5 mmol/300-mL bag, glucose 13.71 g/300-mL bag

Polymyxins

The polymyxin antibiotic, **colistin**, is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Klebsiella pneumoniae*. It is **not** absorbed by mouth and thus needs to be given by injection for a systemic effect. Intravenous administration of colistin should be reserved for Gram-negative infections resistant to other antibacterials; its major adverse effects are dose-related neurotoxicity and nephrotoxicity.

Colistin is used by mouth in bowel sterilisation regimens in neutropenic patients (usually with nystatin); it is **not** recommended for gastro-intestinal infections. It is also given by inhalation of a nebulised solution as an adjunct to standard antibacterial therapy in patients with cystic fibrosis.

Both colistin and polymyxin B are included in some preparations for topical application.

COLISTIN

Indications see notes above

Cautions acute porphyria (section 9.8.2); risk of bronchospasm on inhalation—may be prevented or treated with a selective $beta_2$ agonist; **interactions:** Appendix 1 (polymyxins)

Contra-indications myasthenia gravis

Renal impairment monitor plasma-colistin concentration; reduce dose during parenteral treatment—consult product literature

Pregnancy avoid—possible risk of fetal toxicity especially in second and third trimesters

Breast-feeding present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk)

Side-effects neurotoxicity reported especially with excessive doses (including apnoea, perioral and peripheral paraesthesia, vertigo, headache, muscle weakness; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances); nephrotoxicity; hypersensitivity reactions including rash; injection-site reactions; inhalation may cause sore throat, sore mouth, cough, bronchospasm

Dose

- By mouth, bowel sterilisation, 1.5–3 million units every 8 hours
- By slow intravenous injection into a totally implantable venous access device, *or* by intravenous infusion (but see notes above), ADULT and CHILD body-weight under 60 kg, 50 000–75 000 units/kg daily in 3 divided doses; body-weight over 60 kg, 1–2 million units every 8 hours

  Note Plasma concentration monitoring required in renal impairment; recommended 'peak' plasma-colistin concentration (approx. 30 minutes after intravenous injection or infusion) 10–15 mg/litre (125–200 units/mL)
- By inhalation of nebulised solution, ADULT and CHILD over 2 years, 1–2 million units every 12 hours; CHILD under 2 years, 0.5–1 million units every 12 hours

Colomycin® (Forest) PoM

Tablets, scored, colistin sulphate 1.5 million units. Net price 50 = £58.28

Syrup, colistin sulphate 250 000 units/5 mL when reconstituted with water. Net price 80 mL = £3.48

Injection, powder for reconstitution, colistimethate sodium (colistin sulphomethate sodium). Net price 1 million-unit vial = £1.68; 2 million-unit vial = £3.09

Electrolytes (before reconstitution) $Na^+ < 0.5$ mmol/1 million-unit and 2 million-unit vial

Note *Colomycin*® Injection (dissolved in physiological saline) may be used for nebulisation

Promixin® (Profile) PoM

Powder for nebuliser solution, colistimethate sodium (colistin sulphomethate sodium), net price 1 million-unit vial = £4.60

Injection, powder for reconstitution, colistimethate sodium (colistin sulphomethate sodium), net price 1 million unit-vial = £2.30

Electrolytes (before reconstitution) $Na^+ < 0.5$ mmol/1 million-unit vial

5.1.8 Sulfonamides and trimethoprim

The importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

Sulfamethoxazole and trimethoprim are used in combination (as **co-trimoxazole**) because of their synergistic activity. However, co-trimoxazole is associated with rare but serious side-effects (e.g. Stevens-Johnson syndrome and blood dyscrasias, notably bone marrow depression and agranulocytosis) especially in the elderly (see Restrictions on the use of Co-trimoxazole below)

Restrictions on the use of co-trimoxazole

Co-trimoxazole should be limited to the role of drug of choice in *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia; it is also indicated for *toxoplasmosis* and *nocardiasis*. It should now only be considered for use in *acute exacerbations of chronic bronchitis* and *infections of the urinary tract* when there is good bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in *acute otitis media in children* when there is good reason to prefer it.

Trimethoprim can be used alone for urinary- and respiratory-tract infections and for prostatitis, shigellosis,

and invasive salmonella infections. Trimethoprim has side-effects similar to co-trimoxazole but they are less severe and occur less frequently.

For *topical preparations* of sulfonamides used in the treatment of burns see section 13.10.1.1.

CO-TRIMOXAZOLE

A mixture of trimethoprim and sulfamethoxazole (sulphamethoxazole) in the proportions of 1 part to 5 parts

Indications see restrictions above

Cautions maintain adequate fluid intake; avoid in blood disorders (unless under specialist supervision); monitor blood counts on prolonged treatment; discontinue immediately if blood disorders or rash develop; predisposition to folate deficiency or hyperkalaemia; elderly (see Restrictions on the use of Co-trimoxazole above); asthma; G6PD deficiency (section 9.1.5); avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia); **interactions:** Appendix 1 (trimethoprim, sulfamethoxazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment manufacturer advises avoid in severe liver disease

Renal impairment use half normal dose if eGFR 15–30 mL/minute/1.73 m^2; avoid if eGFR less than 15 mL/minute/1.73 m^2 and if plasma-sulfamethoxazole concentration cannot be monitored

Pregnancy teratogenic risk in first trimester (trimethoprim a folate antagonist). Neonatal haemolysis and methaemoglobinaemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole)

Side-effects nausea, diarrhoea; headache; hyperkalaemia; rash (very rarely including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity)—discontinue immediately; *less commonly* vomiting; *very rarely* glossitis, stomatitis, anorexia, liver damage (including jaundice and hepatic necrosis), pancreatitis, antibiotic-associated colitis, myocarditis, cough and shortness of breath, pulmonary infiltrates, aseptic meningitis, depression, convulsions, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycaemia, blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia), hyponatraemia, renal disorders including interstitial nephritis, arthralgia, myalgia, vasculitis, systemic lupus erythematosus and uveitis; rhabdomyolysis reported in HIV-infected patients

Dose

- By mouth, 960 mg every 12 hours; CHILD, every 12 hours, 6 weeks–5 months, 120 mg; 6 months–5 years, 240 mg; 6–12 years, 480 mg
- By intravenous infusion, 960 mg every 12 hours increased to 1.44 g every 12 hours in severe infections; CHILD 36 mg/kg daily in 2 divided doses increased to 54 mg/kg daily in severe infections
- Treatment of *Pneumocystis jirovecii* (*Pneumocystis carinii*) infections (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature), by mouth *or* by intravenous infusion, ADULT and CHILD over 4 weeks, 120 mg/kg daily in 2–4 divided doses for 14–21 days
- Prophylaxis of *Pneumocystis jirovecii* (*Pneumocystis carinii*) infections, by mouth, 960 mg once daily (may be reduced to 480 mg once daily to improve tolerance) *or* 960 mg on alternate days (3 times a week) *or* 960 mg twice daily on alternate days (3 times a week); CHILD 6 weeks–5 months, 120 mg twice daily on 3 consecutive or alternate days per week *or* on 7 days per week; 6 months–5 years, 240 mg; 6–12 years, 480 mg

  Note 480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg

Co-trimoxazole (Non-proprietary) PoM

Tablets, co-trimoxazole 480 mg, net price 28-tab pack = £18.99, 960 mg, 100 = £23.46. Label: 9

Brands include *Fectrim®*, *Fectrim® Forte*

Paediatric oral suspension, co-trimoxazole 240 mg/5 mL, net price 100 mL = £1.12. Label: 9

Oral suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL = £4.41. Label: 9

Septrin® (Aspen) PoM

Tablets, co-trimoxazole 480 mg, net price 100-tab pack= £15.52. Label: 9

Forte tablets, scored, co-trimoxazole 960 mg, net price 100-tab pack = £23.46. Label: 9

Adult suspension, co-trimoxazole 480 mg/5 mL, net price 100 mL (vanilla-flavoured) = £4.41. Label: 9

Paediatric suspension, sugar-free, co-trimoxazole 240 mg/5 mL, net price 100 mL (banana- and vanilla-flavoured) = £2.45. Label: 9

Intravenous infusion, co-trimoxazole 96 mg/mL. To be diluted before use. Net price 5-mL amp = £1.78

Electrolytes Na^+ 1.7 mmol/5 mL

Excipients include alcohol 13.2%, propylene glycol, sulphites

SULFADIAZINE

(Sulphadiazine)

Indications prevention of rheumatic fever recurrence, toxoplasmosis [unlicensed]—see section 5.4.7

Cautions see under Co-trimoxazole; **interactions:** Appendix 1 (sulfonamides)

Contra-indications see under Co-trimoxazole

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment

Renal impairment use with caution in mild to moderate impairment; avoid in severe impairment; high risk of crystalluria

Pregnancy neonatal haemolysis and methaemoglobinaemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants

Side-effects see under Co-trimoxazole; also hypothyroidism, benign intracranial hypertension, optic neuropathy

Dose

- Prevention of rheumatic fever, *by mouth*, 1 g daily (500 mg daily for patients less than 30 kg)

Sulfadiazine (Non-proprietary) PoM

Tablets, sulfadiazine 500 mg, net price 56-tab pack = £37.50. Label: 9, 27

TRIMETHOPRIM

Indications urinary-tract infections, acute and chronic bronchitis; pneumocystis pneumonia (section 5.4.8)

Cautions predisposition to folate deficiency; elderly; manufacturer recommends blood counts on long-

term therapy (but evidence of practical value unsatisfactory); neonates (specialist supervision required); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (trimethoprim)

Blood disorders On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop

Contra-indications blood dyscrasias

Renal impairment use half normal dose after 3 days if eGFR 15–30 mL/minute/1.73 m^2; use half normal dose if eGFR less than 15 mL/minute/1.73 m^2 (monitor plasma-trimethoprim concentration if eGFR less than 10 mL/minute/1.73 m^2)

Pregnancy teratogenic risk in first trimester (folate antagonist); manufacturers advise avoid

Breast-feeding present in milk—short-term use not known to be harmful

Side-effects gastro-intestinal disturbances including nausea and vomiting, pruritus, rashes, hyperkalaemia, depression of haematopoiesis; rarely erythema multiforme, toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis and uveitis reported

Dose

- Acute infections, 200 mg every 12 hours; CHILD 1 month–12 years, 4 mg/kg (max. 200 mg) every 12 hours; *or* 6 weeks–6 months 25 mg every 12 hours, 6 months–6 years 50 mg every 12 hours, 6–12 years 100 mg every 12 hours
- Prophylaxis, 100 mg at night; CHILD under 12 years, 2 mg/kg (max.100 mg) at night

Trimethoprim (Non-proprietary) PoM

Tablets, trimethoprim 100 mg, net price 28 = 94p; 200 mg, 14-tab pack = 91p. Label: 9

Brands include *Trimopan®*

Suspension, trimethoprim 50 mg/5 mL, net price 100 mL = £2.37. Label: 9

5.1.9 Antituberculosis drugs

Tuberculosis is treated in two phases—an *initial phase* using 4 drugs and a *continuation phase* using 2 drugs in fully sensitive cases. Treatment requires specialised knowledge, particularly where the disease involves resistant organisms or non-respiratory organs.

The regimens given below are recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen described below should be used; the two regimens should **not** be used concurrently.

Initial phase The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations unless one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of isoniazid, rifampicin, pyrazinamide and ethambutol. Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for 2 months. Where a positive culture for *M. tuberculosis* has been obtained, but susceptibility results are not available after 2 months, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.

Streptomycin is rarely used in the UK but it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced.

Continuation phase After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin (preferably given as a combination preparation). Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

Unsupervised treatment The following regimen should be used for patients who are likely to take antituberculous drugs reliably **without supervision**. Patients who are unlikely to comply with daily administration of antituberculous drugs should be treated with the regimen described under Supervised Treatment.

Recommended dosage for standard unsupervised 6-month treatment

Rifater® [rifampicin, isoniazid, and pyrazinamide] (for 2-month initial phase only)

ADULT body-weight under 40 kg 3 tablets daily; body-weight 40–49 kg 4 tablets daily; body-weight 50–64 kg 5 tablets daily; body-weight over 65 kg 6 tablets daily

Ethambutol (for 2-month initial phase only)

ADULT AND CHILD 15 mg/kg daily

Rifinah® [rifampicin and isoniazid] (for 4-month continuation phase following initial treatment with *Rifater®*)

ADULT body-weight under 50 kg 3 tablets daily of *Rifinah® 150/100*; body-weight 50 kg and over, 2 tablets daily of *Rifinah® 300/150*

or (if combination preparations not appropriate):

Isoniazid (for 2-month initial and 4-month continuation phases)

ADULT 300 mg daily; CHILD 10 mg/kg (max. 300 mg) daily

Rifampicin (for 2-month initial and 4-month continuation phases)

ADULT body-weight under 50 kg 450 mg daily; body-weight 50 kg and over, 600 mg daily; CHILD 10 mg/kg daily (max. 450 mg daily if body-weight under 50 kg; max. 600 mg daily if body-weight 50 kg and over)

Pyrazinamide (for 2-month initial phase only)

ADULT body-weight under 50 kg 1.5 g daily; body-weight 50 kg and over, 2 g daily; CHILD 35 mg/kg daily (max. 1.5 g daily if body-weight under 50 kg; max. 2 g daily if body-weight 50 kg and over)

Ethambutol (for 2-month initial phase only)

ADULT AND CHILD 15 mg/kg daily

Pregnancy The standard regimen (above) may be used during pregnancy. Streptomycin should not be given in pregnancy.

Breast-feeding The standard regimen (above) may be used during breast-feeding

Children Children are given isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and rifampicin during the next 4 months. However, care is needed in young children receiving ethambutol because of the difficulty in testing eyesight and in obtaining reports of visual symptoms (see below).

Supervised treatment Drug administration needs to be **fully supervised** (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) 3 times a week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times a week for a further 4 months.

Recommended dosage for intermittent supervised 6-month treatment

Isoniazid (for 2-month initial and 4-month continuation phases)

ADULT AND CHILD 15 mg/kg (max. 900 mg) 3 times a week

Rifampicin (for 2-month initial and 4-month continuation phases)

ADULT 600–900 mg 3 times a week; CHILD 15 mg/kg (max. 900 mg) 3 times a week

Pyrazinamide (for 2-month initial phase only)

ADULT body-weight under 50 kg 2 g 3 times a week; body-weight 50 kg and over, 2.5 g 3 times a week; CHILD 50 mg/kg 3 times a week (max. 2 g 3 times a week if body-weight under 50 kg; max. 2.5 g 3 times a week if body-weight 50 kg and over)

Ethambutol (for 2-month initial phase only)

ADULT AND CHILD 30 mg/kg 3 times a week

Immunocompromised patients Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed *M. tuberculosis* infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.

Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis in a HIV-positive individual; care is required in choosing the regimen and in avoiding potentially serious interactions. Starting antiretroviral treatment in the first 2 months of antituberculosis treatment increases the risk of immune reconstitution syndrome.

Infection may also be caused by other mycobacteria e.g. *M. avium* complex in which case specialist advice on management is needed.

Corticosteroids In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

Prevention of tuberculosis Some individuals may develop tuberculosis owing to reactivation of previously latent disease. Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with immunosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids). In these cases, chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months, see Table 2, section 5.1; longer chemoprophylaxis is not recommended.

For prevention of tuberculosis in susceptible close contacts or those who have become tuberculin-positive, see Table 2, section 5.1. For advice on immunisation against tuberculosis, see section 14.4

Monitoring Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity, *hepatic function* should be checked before treatment with these drugs. Those with pre-existing liver disease or alcohol dependence should have frequent checks particularly in the first 2 months. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. In view of the need to comply fully with antituberculous treatment on the one hand and to guard against serious liver damage on the other, patients and their carers should be informed carefully how to recognise signs of liver disorders and advised to discontinue treatment and seek **immediate** medical attention should symptoms of liver disease occur.

Renal function should be checked before treatment with antituberculous drugs and appropriate dosage adjustments made. Streptomycin or ethambutol should preferably be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasma-drug concentration monitored.

Visual acuity should be tested before ethambutol is used (see below).

Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the patient. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist physician.

Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication. Its only common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, malnutrition and HIV infection. In these circumstances pyridoxine 10 mg daily (or 20 mg daily if suitable product not available) (section 9.6.2) should be given prophylactically from the start of treatment. Other side-effects such as hepatitis (important: see Monitoring above) and psychosis are rare.

Rifampicin, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication.

During the first two months ('initial phase') of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease (important: see Monitoring above).

On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20 to 30% of patients.

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulfonylureas, and anticoagulants; **interactions:** Appendix 1 (rifamycins). **Important:** the effectiveness of hormonal contraceptives is

reduced and alternative family planning advice should be offered (section 7.3.1).

Rifabutin, another rifamycin, is indicated for *prophylaxis* against *M. avium* complex infections in patients with a low CD4 count; it is also licensed for the *treatment* of non-tuberculous mycobacterial disease and pulmonary tuberculosis. **Important:** as with rifampicin it induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced requiring alternative family planning methods.

Pyrazinamide [unlicensed] is a bactericidal drug only active against intracellular dividing forms of *Mycobacterium tuberculosis*; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against *M. bovis*. Serious liver toxicity may occasionally occur (important: see Monitoring above).

Ethambutol is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.

Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. These toxic effects are more common where excessive dosage is used or if the patient's renal function is impaired. The earliest features of ocular toxicity are subjective and patients should be advised to discontinue therapy immediately if they develop deterioration in vision and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Patients who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

Visual acuity should be tested by Snellen chart before treatment with ethambutol.

Streptomycin [unlicensed] is now rarely used in the UK except for resistant organisms. It is given intramuscularly in a dose of 15 mg/kg (max. 1 g) daily; the dose is reduced in those under 50 kg, those over 40 years or those with renal impairment. Plasma-drug concentration should be measured in patients with impaired renal function in whom streptomycin must be used with great care. Side-effects increase after a cumulative dose of 100 g, which should only be exceeded in exceptional circumstances.

Drug-resistant tuberculosis should be treated by a specialist physician with experience in such cases, and where appropriate facilities for infection-control exist. Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include amikacin, capreomycin, cycloserine, newer macrolides (e.g. azithromycin and clarithromycin), moxifloxacin and protionamide (prothionamide; no longer on UK market).

CAPREOMYCIN

Indications in combination with other drugs, tuberculosis resistant to first-line drugs

Cautions auditory impairment; monitor renal, hepatic, auditory, and vestibular function and electrolytes; **interactions:** Appendix 1 (capreomycin)

Hepatic impairment use with caution

Renal impairment reduce dose—consult product literature; nephrotoxic; ototoxic

Pregnancy manufacturer advises use only if potential benefit outweighs risk—teratogenic in *animal* studies

Breast-feeding manufacturer advises caution—no information available

Side-effects hypersensitivity reactions including urticaria and rashes; leucocytosis or leucopenia, rarely thrombocytopenia; changes in liver function tests; nephrotoxicity, electrolyte disturbances; hearing loss with tinnitus and vertigo; neuromuscular block after large doses, pain and induration at injection site

Dose

- By deep intramuscular injection, 1 g daily (not more than 20 mg/kg) for 2–4 months, then 1 g 2–3 times each week

Capreomycin (King) PoM

Injection, powder for reconstitution, capreomycin sulphate 1 million units (= capreomycin approx. 1 g). Net price per vial = £25.18

CYCLOSERINE

Indications in combination with other drugs, tuberculosis resistant to first-line drugs

Cautions monitor haematological, renal, and hepatic function; **interactions:** Appendix 1 (cycloserine)

Contra-indications epilepsy, depression, severe anxiety, psychotic states, alcohol dependence, acute porphyria (section 9.8.2)

Renal impairment reduce dose and monitor blood-cycloserine concentration; avoid in severe impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk—crosses the placenta

Breast-feeding amount too small to be harmful

Side-effects mainly neurological, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression (discontinue or reduce dose if symptoms of CNS toxicity); rashes, allergic dermatitis (discontinue or reduce dose); megaloblastic anaemia; changes in liver function tests; heart failure at high doses reported

Dose

- Initially 250 mg every 12 hours for 2 weeks increased according to blood concentration and response to max. 500 mg every 12 hours; CHILD 2–18 years see *BNF for Children*

  Note Blood concentration monitoring required especially in renal impairment or if dose exceeds 500 mg daily or if signs of toxicity; blood concentration should not exceed 30 mg/litre

Cycloserine (King) PoM

Capsules, red/grey cycloserine 250 mg, net price 100-cap pack = £333.80. Label: 2, 8

ETHAMBUTOL HYDROCHLORIDE

Indications tuberculosis, in combination with other drugs

Cautions elderly; test visual acuity before treatment and warn patients to report visual changes—see Monitoring in notes above; young children (see notes above)—routine ophthalmological monitoring recommended

Contra-indications optic neuritis, poor vision

Renal impairment reduce dose; if creatinine clearance less than 30 mL/minute, monitor plasma-ethambutol concentration; optic nerve damage

Pregnancy not known to be harmful; see also p. 361

Breast-feeding amount too small to be harmful; see also p. 361

Side-effects optic neuritis, red/green colour blindness, peripheral neuritis, rarely rash, pruritus, urticaria, thrombocytopenia

Dose

- See notes above

Note 'Peak' concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); 'trough' (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre); see Cautions above; for advice on laboratory assay of ethambutol contact the Poisons Unit at New Cross Hospital (Tel (020) 7771 5360)

Ethambutol (Non-proprietary) PoM

Tablets, ethambutol hydrochloride 100 mg, net price 56-tab pack = £12.00; 400 mg, 56-tab pack = £44.18. Label: 8

ISONIAZID

Indications tuberculosis, in combination with other drugs; prophylaxis—Table 2, section 5.1

Cautions see Monitoring in notes above; also slow acetylator status (increased risk of side-effects); epilepsy; history of psychosis; alcohol dependence, malnutrition, diabetes mellitus, HIV infection (risk of peripheral neuritis); acute porphyria (section 9.8.2); **interactions:** Appendix 1 (isoniazid)

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Contra-indications drug-induced liver disease

Hepatic impairment use with caution; monitor liver function regularly and particularly frequently in first 2 months; see also Hepatic Disorders above

Renal impairment max. 200 mg daily if eGFR less than 10 mL/minute/1.73 m^2; peripheral neuropathy

Pregnancy not known to be harmful; see also p. 361

Breast-feeding monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant; see also p. 361

Side-effects nausea, vomiting, constipation, dry mouth; peripheral neuritis with high doses (pyridoxine prophylaxis, see notes above), optic neuritis, convulsions, psychotic episodes, vertigo; hypersensitivity reactions including fever, Stevens-Johnson syndrome, purpura; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; hepatitis (especially over age of 35 years); pancreatitis; interstitial pneumonitis; systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia reported; hearing loss and tinnitus (in patients with end-stage renal impairment); when used with tyramine or histamine rich foods, tachycardia, palpitation, hypotension, flushing, headache, dizziness, and sweating also reported

Dose

- By mouth *or* by intramuscular *or* intravenous injection, see notes above

Isoniazid (Non-proprietary) PoM

Tablets, isoniazid 50 mg, net price 56-tab pack = £11.10; 100 mg, 28-tab pack = £11.30. Label: 8, 22

Elixir (BPC), isoniazid 50 mg, citric acid monohydrate 12.5 mg, sodium citrate 60 mg, concentrated anise water 0.05 mL, compound tartrazine solution 0.05 mL, glycerol 1 mL, double-strength chloroform water 2 mL, water to 5 mL. Label: 8, 22

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Injection, isoniazid 25 mg/mL, net price 2-mL amp = £11.04

PYRAZINAMIDE

Indications tuberculosis in combination with other drugs [unlicensed]

Cautions see Monitoring in notes above; also diabetes; gout (avoid in acute attack); **interactions:** Appendix 1 (pyrazinamide)

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment; see also Hepatic Disorders above

Pregnancy manufacturer advises use only if potential benefit outweighs risk; see also p. 361

Breast-feeding amount too small to be harmful; see also p. 361

Side-effects hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting, flushing, dysuria, arthralgia, sideroblastic anaemia, thrombocytopenia, rash and occasionally photosensitivity

Dose

- See notes above

Pyrazinamide (Non-proprietary) PoM

Tablets, scored, pyrazinamide 500 mg. Label: 8

Available from 'special order' manufacturers or specialist-importing companies, see p. 988

RIFABUTIN

Indications see under Dose

Cautions see under Rifampicin; acute porphyria (section 9.8.2)

Hepatic impairment reduce dose in severe impairment

Renal impairment use half normal dose if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting; leucopenia, thrombocytopenia, anaemia, rarely haemolysis; raised liver enzymes, jaundice, rarely hepatitis; uveitis following high doses or administration with drugs which raise plasma concentration—see also **interactions:** Appendix 1 (rifamycins); arthralgia, myalgia, influenza-like syndrome, dyspnoea; also hypersensitivity reactions including fever, rash, eosinophilia, bron-

chospasm, shock; skin, urine, saliva and other body secretions coloured orange-red; asymptomatic corneal opacities reported with long-term use

Dose

- Prophylaxis of *Mycobacterium avium* complex infections in immunosuppressed patients with low CD4 count (see product literature), 300 mg daily as a single dose
- Treatment of non-tuberculous mycobacterial disease, in combination with other drugs, 450–600 mg daily as a single dose for up to 6 months after cultures negative
- Treatment of pulmonary tuberculosis, in combination with other drugs, 150–450 mg daily as a single dose for at least 6 months
- CHILD not recommended

Mycobutin® (Pharmacia) PoM

Capsules, red-brown, rifabutin 150 mg. Net price 30-cap pack = £90.38. Label: 8, 14, counselling, lenses, see under Rifampicin

RIFAMPICIN

Indications see under Dose

Cautions see Monitoring in notes above; also liver function tests and blood counts in hepatic disorders, alcohol dependence, and on prolonged therapy, see also below); acute porphyria (section 9.8.2); **important:** advise patients on hormonal contraceptives to use additional means (see also section 7.3.1); discolours soft contact lenses; see also notes above; **interactions:** Appendix 1 (rifamycins)

Note If treatment interrupted re-introduce with low dosage and increase gradually; discontinue permanently if serious side-effects develop

Hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Contra-indications jaundice

Hepatic impairment impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily; see also Cautions above

Renal impairment use with caution if dose above 600 mg daily

Pregnancy manufacturers advise very high doses teratogenic in *animal* studies in first trimester; risk of neonatal bleeding may be increased in third trimester; see also p. 361

Breast-feeding amount too small to be harmful; see also p. 361

Side-effects gastro-intestinal symptoms including anorexia, nausea, vomiting, diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; those occurring mainly on intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation, and acute renal failure; alterations of liver function, jaundice; flushing, urticaria, and rashes; other side-effects reported include oedema, psychoses, adrenal insufficiency, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigoid reactions, leucopenia, eosinophilia, menstrual disturbances; urine, saliva, and other body secretions coloured orange-red; thrombophlebitis reported if infusion used for prolonged period

Dose

- Brucellosis, legionnaires' disease, endocarditis and serious staphylococcal infections, in combination with other drugs, by mouth *or* by intravenous infusion, 0.6–1.2 g daily (in 2–4 divided doses)
- Tuberculosis, in combination with other drugs, see notes above
- Leprosy, section 5.1.10
- Prophylaxis of meningococcal meningitis and *Haemophilus influenzae* (type b) infection, section 5.1, table 2

Rifampicin (Non-proprietary) PoM

Capsules, rifampicin 150 mg, net price 100 = £20.82; 300 mg, 100 = £46.21. Label: 8, 14, 22, counselling, see lenses above

Rifadin® (Sanofi-Aventis) PoM

Capsules, rifampicin 150 mg (blue/red), net price 100-cap pack= £18.32; 300 mg (red), 100-cap pack= £36.63. Label: 8, 14, 22, counselling, see lenses above

Syrup, red, rifampicin 100 mg/5 mL (raspberry-flavoured), net price 120 mL = £3.56. Label: 8, 14, 22, counselling, see lenses above

Intravenous infusion, powder for reconstitution, rifampicin, net price 600-mg vial (with solvent) = £7.67

Electrolytes $Na^+ < 0.5$ mmol/vial

Rimactane® (Sandoz) PoM

Capsules, rifampicin 150 mg (red), net price 60-cap pack = £11.35; 300 mg (red/brown), 60-cap pack = £22.69. Label: 8, 14, 22, counselling, see lenses above

Combined preparations

Rifater® (Sanofi-Aventis) PoM

Tablets, pink, s/c, rifampicin 120 mg, isoniazid 50 mg, pyrazinamide 300 mg, net price 100-tab pack= £21.95. Label: 8, 14, 22, counselling, see lenses above

Dose initial treatment of pulmonary tuberculosis, patients up to 40 kg 3 tablets daily preferably before breakfast, 40–49 kg 4 tablets daily, 50–64 kg 5 tablets daily, 65 kg or more, 6 tablets daily; not suitable for use in children

Rifinah® 150/100 (Sanofi-Aventis) PoM

Tablets, pink, s/c, rifampicin 150 mg, isoniazid 100 mg, net price 84-tab pack = £15.91. Label: 8, 14, 22, counselling, see lenses above

Dose ADULT under 50 kg, 3 tablets daily, preferably before breakfast

Note Some stock packaged as *Rifinah 150* or *Rifinah 100/150*

Rifinah® 300/150 (Sanofi-Aventis) PoM

Tablets, orange, s/c, rifampicin 300 mg, isoniazid 150 mg, net price 56-tab pack = £21.02. Label: 8, 14, 22, counselling, see lenses above

Dose ADULT 50 kg and over, 2 tablets daily, preferably before breakfast

Note Some stock packaged as *Rifinah 300* or *Rifinah 150/300*

STREPTOMYCIN

Indications tuberculosis, in combination with other drugs; adjunct to doxycycline in brucellosis; enterococcal endocarditis (Table 1, section 5.1)

Cautions see under Aminoglycosides, section 5.1.4; **interactions:** Appendix 1 (aminoglycosides)

Contra-indications see under Aminoglycosides, section 5.1.4

Renal impairment see under Aminoglycosides, section 5.1.4

Pregnancy see under Aminoglycosides, section 5.1.4

Side-effects see under Aminoglycosides, section 5.1.4; also hypersensitivity reactions, paraesthesia of mouth

Dose

- By deep intramuscular injection, tuberculosis [unlicensed], see notes above; brucellosis, expert advice essential

  Note One-hour ('peak') concentration should be 15–40 mg/litre; pre-dose ('trough') concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or in those over 50 years)

Streptomycin Sulphate (Non-proprietary) PoM

Injection, powder for reconstitution, streptomycin (as sulphate), net price 1-g vial = £8.25

Available as an unlicensed preparation from UCB Pharma

5.1.10 Antileprotic drugs

Advice from a member of the Panel of Leprosy Opinion is essential for the treatment of leprosy (Hansen's disease). Details of the Panel can be obtained from the Department of Health telephone (020) 7972 4480.

The World Health Organization has made recommendations to overcome the problem of dapsone resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are **dapsone**, **rifampicin** (section 5.1.9), and **clofazimine**. Other drugs with significant activity against *Mycobacterium leprae* include ofloxacin, minocycline and clarithromycin, but none of these are as active as rifampicin; at present they should be reserved as second-line drugs for leprosy.

A three-drug regimen is recommended for *multibacillary leprosy* (lepromatous, borderline-lepromatous, and borderline leprosy) and a two-drug regimen for *paucibacillary leprosy* (borderline-tuberculoid, tuberculoid, and indeterminate). The following regimens are widely used throughout the world (with minor local variations):

Multibacillary leprosy (3-drug regimen)

Rifampicin	600 mg once-monthly, supervised (450 mg for adults weighing less than 35 kg)
Dapsone	100 mg daily, self-administered (50 mg daily or 1–2 mg/kg daily for adults weighing less than 35 kg)
Clofazimine	300 mg once-monthly, supervised, *and* 50 mg daily (or 100 mg on alternate days), self-administered

Multibacillary leprosy should be treated for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum leprosum) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone (initially 40–60 mg daily) should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide [unlicensed] is also useful in men and post-menopausal women who have become corticosteroid dependent, but it should be used under **specialist supervision** and it should **never** be used in women of child-bearing potential (significant teratogenic risk—for CSM guidance on prescribing, see *Current Problems in Pharmacovigilance* 1994; **20**, 8). Increased doses of clofazimine 100 mg 3 times daily for the first month with subsequent reductions, are also useful but may take 4–6 weeks to attain full effect.

Paucibacillary leprosy (2-drug regimen)

Rifampicin	600 mg once-monthly, supervised (450 mg for those weighing less than 35 kg)
Dapsone	100 mg daily, self-administered (50 mg daily or 1–2 mg/kg daily for adults weighing less than 35 kg)

Paucibacillary leprosy should be treated for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

Neither the multibacillary nor the paucibacillary antileprosy regimen is sufficient to treat tuberculosis.

DAPSONE

Indications leprosy, dermatitis herpetiformis; *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia (section 5.4.8)

Cautions cardiac or pulmonary disease; anaemia (treat severe anaemia before starting); susceptibility to haemolysis including G6PD deficiency (section 9.1.5); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (dapsone)

Blood disorders On long-term treatment, patients and their carers should be told how to recognise signs of blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop

Pregnancy folic acid 5 mg daily should be given to mother throughout pregnancy; neonatal haemolysis and methaemoglobinaemia reported in third trimester

Breast-feeding haemolytic anaemia; although significant amount in milk, risk to infant very small unless infant is G6PD deficient

Side-effects (dose-related and uncommon at doses used for leprosy), haemolysis, methaemoglobinaemia, neuropathy, allergic dermatitis (rarely including toxic epidermal necrolysis and Stevens-Johnson syndrome), anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis, agranulocytosis; dapsone syndrome (rash with fever and eosinophilia)—discontinue immediately (may progress to exfoliative dermatitis, hepatitis, hypoalbuminaemia, psychosis and death)

Dose

- Leprosy, 1–2 mg/kg daily, see notes above
- Dermatitis herpetiformis, see specialist literature

Dapsone (Non-proprietary) PoM

Tablets, dapsone 50 mg, net price 28-tab pack = £32.53; 100 mg, 28-tab pack = £47.44 Label: 8

CLOFAZIMINE

Indications leprosy

Cautions may discolour soft contact lenses; avoid if persistent abdominal pain and diarrhoea

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy use with caution

Breast-feeding may alter colour of milk; skin discoloration of infant

Side-effects nausea, vomiting (hospitalise if persistent), abdominal pain; headache, tiredness; brownish-black discoloration of lesions and skin including areas exposed to light; reversible hair discoloration; dry skin; red discoloration of faeces, urine and other body fluids; also rash, pruritus, photosensitivity, acne-like eruptions, anorexia, eosinophilic enteropathy, bowel obstruction, dry eyes, dimmed vision, macular and subepithelial corneal pigmentation; elevation of blood sugar, weight loss, splenic infarction, lymphadenopathy

Dose

- Leprosy, see notes above
- Lepromatous lepra reactions, dosage increased to 300 mg daily for max. of 3 months

Clofazimine (Non-proprietary) PoM

Capsules, clofazimine 100 mg. Label: 8, 14, 21

Available on named-patient basis

5.1.11 Metronidazole and tinidazole

Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa; indications include trichomonal vaginitis (section 5.4.3), bacterial vaginosis (notably *Gardnerella vaginalis* infections), and *Entamoeba histolytica* and *Giardia lamblia* infections (section 5.4.2). It is also used for surgical and gynaecological sepsis in which its activity against colonic anaerobes, especially *Bacteroides fragilis*, is important. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible. Intravenous metronidazole is used for the treatment of established cases of tetanus; diazepam (section 10.2.2) and tetanus immunoglobulin (section 14.5.2) are also used.

Metronidazole by mouth is effective for the treatment of *Clostridium difficile* infection , see also section 1.5; it can be given by intravenous infusion if oral treatment is inappropriate.

Topical metronidazole (section 13.10.1.2) reduces the odour produced by anaerobic bacteria in fungating tumours; it is also used in the management of rosacea (section 13.6).

Tinidazole is similar to metronidazole but has a longer duration of action.

Oral infections Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes (Table 1, section 5.1). It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent's infection) and pericoronitis; suitable alternatives are amoxicillin (section 5.1.1.3) and erythromycin (section 5.1.5). For these purposes metronidazole in a dose of 200 mg 3 times daily for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole is licensed for the treatment of acute ulcerative gingivitis.

METRONIDAZOLE

Indications anaerobic infections (including dental), see under Dose below; protozoal infections (section 5.4.2); *Helicobacter pylori* eradication (section 1.3); skin (section 13.10.1.2)

Cautions disulfiram-like reaction with alcohol; avoid in acute porphyria (section 9.8.2); clinical and laboratory monitoring advised if treatment exceeds 10 days; **interactions:** Appendix 1 (metronidazole)

Hepatic impairment in severe liver disease reduce total daily dose to one-third, and give once daily; use with caution in hepatic encephalopathy

Pregnancy manufacturer advises avoidance of high-dose regimens

Breast-feeding significant amount in milk; manufacturer advises avoid large single doses

Side-effects gastro-intestinal disturbances (including nausea and vomiting), taste disturbances, furred tongue, oral mucositis, anorexia; *very rarely* hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, ataxia, psychotic disorders, darkening of urine, thrombocytopenia, pancytopenia, myalgia, arthralgia, visual disturbances, rash, pruritus, and erythema multiforme; on prolonged or intensive therapy peripheral neuropathy, transient epileptiform seizures, and leucopenia

Dose

- Anaerobic infections (usually treated for 7 days and for 10–14 days in *Clostridium difficile* infection), by mouth, *either* 400 mg every 8 hours *or* 500 mg every 8 hours, CHILD 1 month–12 years 7.5 mg/kg (max. 400 mg) every 8 hours; by rectum, 1 g every 8 hours for 3 days, then 1 g every 12 hours, CHILD every 8 hours for 3 days, then every 12 hours, 1 month–1 year 125 mg, 1–5 years 250 mg, 5–10 years 500 mg, over 10 years, adult dose; by intravenous infusion over 20 minutes, 500 mg every 8 hours; CHILD 7.5 mg/kg (max. 500 mg) every 8 hours
- Leg ulcers and pressure sores, by mouth, 400 mg every 8 hours for 7 days
- Bacterial vaginosis, by mouth, 400–500 mg twice daily for 5–7 days *or* 2 g as a single dose
- Pelvic inflammatory disease (see also Table 1, section 5.1), by mouth, 400 mg twice daily for 14 days
- Acute ulcerative gingivitis, by mouth, 200–250 mg every 8 hours for 3 days; CHILD 1–3 years 50 mg every 8 hours for 3 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours
- Acute oral infections, by mouth, 200 mg every 8 hours for 3–7 days (see also notes above); CHILD 1–3 years 50 mg every 8 hours for 3–7 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours
- Surgical prophylaxis, by mouth, 400–500 mg 2 hours before surgery; up to 3 further doses of 400–500 mg may be given every 8 hours for high-risk procedures; CHILD 1 month–12 years 7.5 mg/kg (max. 400 mg) 2 hours before surgery; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

  By rectum, 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures; CHILD 5–10 years 500 mg 2 hours before surgery; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures

  By intravenous infusion (if rectal administration inappropriate), 500 mg up to 30 minutes before the

procedure; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures; CHILD 7.5 mg/kg (max. 500 mg) up to 30 minutes before the procedure; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

Note Metronidazole doses in BNF may differ from those in product literature

Metronidazole (Non-proprietary) PoM

Tablets, metronidazole 200 mg, net price 21-tab pack = £1.36; 400 mg, 21-tab pack = £1.35. Label: 4, 9, 21, 25, 27

Brands include *Vaginyl*®

Dental prescribing on NHS Metronidazole Tablets may be prescribed

Tablets, metronidazole 500 mg, net price 21-tab pack = £29.84. Label: 4, 9, 21, 25, 27

Dental prescribing on NHS Metronidazole Tablets may be prescribed

Suspension, metronidazole (as benzoate) 200 mg/5 mL. Net price 100 mL = £11.43. Label: 4, 9

Brands include *Norzol*®

Dental prescribing on NHS Metronidazole Oral Suspension may be prescribed

Intravenous infusion, metronidazole 5 mg/mL. Net price 20-mL amp = £1.56, 100-mL container = £3.41

Flagyl® (Winthrop) PoM

Tablets, both f/c, ivory, metronidazole 200 mg, net price 21-tab pack = £4.49; 400 mg, 14-tab pack = £6.34. Label: 4, 9, 21, 25, 27

Suppositories, metronidazole 500 mg, net price 10 = £15.18; 1 g, 10 = £23.06. Label: 4, 9

Flagyl S® (Winthrop) PoM

Suspension, orange- and lemon-flavoured, metronidazole (as benzoate) 200 mg/5 mL. Net price 100 mL = £11.18. Label: 4, 9

Metrolyl® (Sandoz) PoM

Intravenous infusion, metronidazole 5 mg/mL, net price 100-mL Steriflex® bag = £1.22

Electrolytes Na^+ 14.53 mmol/100-mL bag

Suppositories, metronidazole 500 mg, net price 10 = £12.34; 1 g, 10 = £18.34. Label: 4, 9

TINIDAZOLE

Indications anaerobic infections, see under Dose below; protozoal infections (section 5.4.2); *Helicobacter pylori* eradication (section 1.3)

Cautions see under Metronidazole; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (tinidazole)

Pregnancy manufacturer advises avoid in first trimester

Breast-feeding present in milk—manufacturer advises avoid breast-feeding during and for 3 days after stopping treatment

Side-effects see under Metronidazole

Dose

- Anaerobic infections, 2 g initially, followed by 1 g daily *or* 500 mg twice daily, usually for 5–6 days
- Bacterial vaginosis and acute ulcerative gingivitis, a single 2-g dose
- Abdominal surgery prophylaxis, a single 2-g dose approximately 12 hours before surgery

Fasigyn® (Pfizer) PoM

Tablets, f/c, tinidazole 500 mg. Net price 16-tab pack = £11.04. Label: 4, 9, 21, 25

5.1.12 Quinolones

Nalidixic acid and **norfloxacin** are effective in uncomplicated urinary-tract infections.

Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis*; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

Ofloxacin is used for urinary-tract infections, lower respiratory-tract infections, gonorrhoea, and non-gonococcal urethritis and cervicitis.

Levofloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against pneumococci than ciprofloxacin. Levofloxacin is licensed for community-acquired pneumonia but it is considered to be **second-line treatment** for this indication.

Although ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are licensed for skin and soft-tissue infections, many staphylococci are resistant to the quinolones and their use should be avoided in MRSA infections.

Moxifloxacin should be reserved for the treatment of sinusitis, community-acquired pneumonia, exacerbations of chronic bronchitis, or complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials. It has been associated with life-threatening hepatotoxicity. Moxifloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against Gram-positive organisms, including pneumococci, than ciprofloxacin. Moxifloxacin is not active against *Pseudomonas aeruginosa* or meticillin-resistant *Staphylococcus aureus* (MRSA).

Anthrax *Inhalation* or *gastro-intestinal anthrax* should be treated initially with either **ciprofloxacin** [not licensed for gastro-intestinal anthrax] or **doxycycline** [unlicensed indication] (section 5.1.3) combined with one or two other antibacterials (such as amoxicillin, benzylpenicillin, chloramphenicol, clarithromycin, clindamycin, imipenem with cilastatin, rifampicin [unlicensed indication], and vancomycin). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed.

Cutaneous anthrax should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] (section 5.1.3) for 7 days. Treatment may be switched to amoxicillin (section 5.1.1.3) if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for *post-exposure prophylaxis*. If exposure is confirmed, anti-

bacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of *B. anthracis* is susceptible. Vaccination against anthrax (section 14.4) may allow the duration of antibacterial prophylaxis to be shortened.

Cautions Quinolones should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency (section 9.1.5), myasthenia gravis (risk of exacerbation), and in children or adolescents (arthropathy has developed in weight-bearing joints in young *animals*—see below). Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). The CSM has warned that quinolones may induce **convulsions** in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them. Other **interactions:** Appendix 1 (quinolones).

Use in children Quinolones cause arthropathy in the weight-bearing joints of immature *animals* and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of either ciprofloxacin or nalidixic acid may be justified in children. For further details see *BNF for Children*.

Tendon damage

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- patients over 60 years of age are more prone to tendon damage;
- the risk of tendon damage is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

Contra-indications quinolone hypersensitivity

Pregnancy Quinolones should be avoided in pregnancy because they have been shown to cause arthropathy in *animal* studies; safer alternatives are available

Side-effects Side-effects of the quinolones include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely antibiotic-associated colitis), headache, dizziness, rash (very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis). Less frequent side-effects include anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombocytopenia), arthralgia, myalgia, disturbances in vision and taste. Other side-effects reported rarely or very rarely include hepatic dysfunction (including jaundice and hepatitis), hypotension, vasculitis, dyspnoea (more frequent with moxifloxacin), convulsions, psychoses, paraesthesia, renal failure, interstitial nephritis, tendon inflammation and damage (see also Tendon Damage above), photosensitivity, disturbances in hearing and smell. The drug should be **discontinued** if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur.

CIPROFLOXACIN

Indications see notes above and under Dose; eye infections (section 11.3.1)

Cautions see notes above; avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); **interactions:** Appendix 1 (quinolones)

Driving May impair performance of skilled tasks (e.g. driving); effects enhanced by alcohol

Contra-indications see notes above

Renal impairment by mouth, 250–500 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m^2 (every 24 hours if eGFR less than 30 mL/minute/1.73 m^2); by intravenous infusion (200 mg over 30 minutes), 200–400 mg every 12 hours if eGFR 30–60 mL/minute/1.73 m^2 (every 24 hours if eGFR less than 30 mL/minute/1.73 m^2)

Pregnancy see notes above

Breast-feeding amount too small to be harmful but manufacturer advises avoid

Side-effects see notes above; also flatulence, pain and phlebitis at injection site; *rarely* dysphagia, pancreatitis, chest pain, tachycardia, syncope, oedema, hot flushes, abnormal dreams, sweating, hyperglycaemia, and erythema nodosum; *very rarely* movement disorders, tinnitus, and tenosynovitis

Dose

- By mouth, respiratory-tract infections, 500–750 mg twice daily (750 mg twice daily in pseudomonal lower respiratory-tract infection in cystic fibrosis)
  Urinary-tract infections, 250–750 mg twice daily (250 mg twice daily for 3 days usually adequate for acute uncomplicated cystitis in women)
  Acute or chronic prostatitis, 500 mg twice daily for 28 days
  Gonorrhoea, 500 mg as a single dose
  Most other infections, 500 mg twice daily (increased to 750 mg twice daily in severe or deep-seated infection)
  Surgical prophylaxis [unlicensed], 750 mg 60 minutes before procedure
  Prophylaxis of meningococcal meningitis, Table 2, section 5.1
- By intravenous infusion over 60 minutes, 400 mg every 8–12 hours
- Anthrax (treatment and post-exposure prophylaxis, see notes above), by mouth, 500 mg twice daily
  By intravenous infusion over 60 minutes, 400 mg every 12 hours
- CHILD under 18 years see *BNF for Children*

Ciprofloxacin (Non-proprietary) PoM

Tablets, ciprofloxacin (as hydrochloride) 100 mg, net price 6-tab pack = £1.42; 250 mg, 10-tab pack = 96p, 20-tab pack = £1.09; 500 mg, 10-tab pack = £1.06, 20-tab pack = £1.22; 750 mg, 10-tab pack = £6.15. Label: 7, 9, 25, counselling, driving

Intravenous infusion, ciprofloxacin (as lactate) 2 mg/mL, net price 50-mL bottle = £8.00, 100-mL bottle = £15.00, 200-mL bottle = £22.00

Ciproxin® (Bayer Schering) PoM

Tablets, all f/c, ciprofloxacin (as hydrochloride) 250 mg (scored), 10-tab pack = £6.59; 500 mg (scored), 10-tab pack = £12.49; 750 mg, 10-tab pack = £17.78. Label: 7, 9, 25, counselling, driving

Suspension, strawberry-flavoured, ciprofloxacin for reconstitution with diluent provided, 250 mg/5 mL,

net price 100 mL = £16.83. Label: 7, 9, 25, counselling, driving

Intravenous infusion, ciprofloxacin (as lactate) 2 mg/mL, in sodium chloride 0.9%, net price 50-mL bottle = £7.61, 100-mL bottle = £15.02, 200-mL bottle = £22.85

Electrolytes Na^+ 15.4 mmol/100-mL bottle

LEVOFLOXACIN

Indications see under Dose

Cautions see notes above; predisposition to QT interval prolongation (including cardiac disease, congenital long QT syndrome, electrolyte disturbances, concomitant use with other drugs known to prolong QT interval); history of psychiatric illness; **interactions:** Appendix 1 (quinolones)

Driving May impair performance of skilled tasks (e.g. driving)

Contra-indications see notes above

Renal impairment usual initial dose then use half normal dose if eGFR 20–50 mL/minute/1.73 m^2; consult product literature if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding manufacturer advises avoid

Side-effects see notes above; also flatulence, constipation; *rarely* tachycardia; *very rarely* pneumonitis, peripheral neuropathy, and hypoglycaemia; also reported, rhabdomyolysis and potentially life-threatening hepatic failure; local reactions and transient hypotension reported with infusion

Dose

- By mouth, acute sinusitis, 500 mg daily for 10–14 days

  Exacerbation of chronic bronchitis, 250–500 mg daily for 7–10 days

  Community-acquired pneumonia, 500 mg once or twice daily for 7–14 days

  Urinary-tract infections, 250 mg daily for 7–10 days (for 3 days in uncomplicated infection)

  Chronic prostatitis, 500 mg once daily for 28 days

  Skin and soft tissue infections, 250 mg daily *or* 500 mg once or twice daily for 7–14 days

- By intravenous infusion (over at least 60 minutes for 500 mg), community-acquired pneumonia, 500 mg once or twice daily

  Complicated urinary-tract infections, 250 mg daily, increased in severe infections

  Skin and soft tissue infections, 500 mg twice daily

Tavanic® (Sanofi-Aventis) PoM

Tablets, yellow-red, f/c, scored, levofloxacin 250 mg, net price 5-tab pack = £7.23, 10-tab pack = £14.45; 500 mg, 5-tab pack = £12.93, 10-tab pack = £25.85. Label: 6, 9, 25, counselling, driving

Intravenous infusion, levofloxacin 5 mg/mL, net price 100-mL bottle = £26.40

Electrolytes Na^+ 15.4 mmol/100-mL bottle

MOXIFLOXACIN

Indications sinusitis, community-acquired pneumonia, exacerbations of chronic bronchitis, or complicated skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials

Cautions see notes above; conditions pre-disposing to arrhythmias, including myocardial ischaemia; **interactions:** Appendix 1 (quinolones)

Driving May impair performance of skilled tasks (e.g. driving)

Contra-indications see notes above; history of QT-interval prolongation, bradycardia, history of symptomatic arrhythmias, heart failure with reduced left ventricular ejection fraction, electrolyte disturbances, concomitant use with other drugs known to prolong QT-interval

Hepatic impairment manufacturer advises avoid in severe impairment

Pregnancy see notes above

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects see notes above; also gastritis, flatulence, constipation, arrhythmias, palpitation, angina, vasodilatation, hyperlipidaemia, and sweating; *rarely* oedema, hypertension, syncope, dysphagia, abnormal dreams, incoordination, amnesia, hyperglycaemia, hyperuricaemia, and stomatitis; *very rarely* rhabdomyolysis and potentially life-threatening hepatic failure; *on intravenous infusion*, pain and phlebitis at injection site

Dose

- By mouth, 400 mg once daily
- By intravenous infusion over 60 minutes, community-acquired pneumonia, complicated skin and soft-tissue infections, 400 mg once daily

Note Recommended duration of treatment is 7–14 days for community-acquired pneumonia, 5–10 days in exacerbations of chronic bronchitis, 7 days in sinusitis, 7–21 days for complicated skin and soft-tissue infections

Avelox® (Bayer Schering) ▼ PoM

Tablets, red, f/c, moxifloxacin (as hydrochloride) 400 mg, net price 5-tab pack = £12.43. Label: 6, 9, counselling, driving

Intravenous infusion, moxifloxacin (as hydrochloride) 1.6 mg/mL, net price 250-mL bottle (400 mg) = £39.95

Electrolytes Na^+ 34 mmol/250-mL bottle

NALIDIXIC ACID

Indications urinary-tract infections

Cautions see notes above; avoid in acute porphyria (section 9.8.2); false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; **interactions:** Appendix 1 (quinolones)

Contra-indications see notes above

Hepatic impairment manufacturer advises caution in liver disease

Renal impairment use with caution; avoid if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding risk to infant very small but one case of haemolytic anaemia reported

Side-effects see notes above; also reported toxic psychosis, increased intracranial pressure, cranial nerve palsy, peripheral neuropathy, and metabolic acidosis

Dose

- 900 mg every 6 hours for 7 days, reduced in chronic infections to 600 mg every 6 hours; CHILD 3 months–18 years see *BNF for Children*

Nalidixic Acid (Rosemont) PoM

Suspension, pink, nalidixic acid 300 mg/5 mL, net price 150 mL (raspberry- and strawberry-flavoured) = £12.50. Label: 9, 11

Excipients include sucrose 450 mg/5 mL

NORFLOXACIN

Indications see under Dose

Cautions see notes above; **interactions:** Appendix 1 (quinolones)

Driving May impair performance of skilled tasks (e.g. driving)

Contra-indications see notes above

Renal impairment use 400 mg once daily if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding no information available—manufacturer advises avoid

Side-effects see notes above; also tinnitus, epiphora; *rarely* pancreatitis; *very rarely* arrhythmias; also reported, polyneuropathy and exfoliative dermatitis

Dose

- 'Lower' urinary-tract infections, 400 mg twice daily for 7–10 days (for 3 days for uncomplicated infections in women)
- Chronic relapsing 'lower' urinary-tract infections, 400 mg twice daily for up to 12 weeks; may be reduced to 400 mg once daily if adequate suppression within first 4 weeks
- Chronic prostatitis, 400 mg twice daily for 28 days

Norfloxacin (Non-proprietary) PoM

Tablets, norfloxacin 400 mg, net price 6-tab pack = £2.30, 14-tab pack = £6.20. Label: 7, 9, 23, counselling, driving

Utinor® (MSD) PoM

Tablets, scored, norfloxacin 400 mg. Net price 7-tab pack = £2.56, 14-tab pack = £5.11. Label: 7, 9, 23, counselling, driving

OFLOXACIN

Indications see under Dose

Cautions see notes above; history of psychiatric illness; **interactions:** Appendix 1 (quinolones)

Driving May affect performance of skilled tasks (e.g. driving); effects enhanced by alcohol

Contra-indications see notes above

Hepatic impairment use with caution; elimination may be reduced in severe impairment

Renal impairment usual initial dose, then use half normal dose if eGFR 20–50 mL/minute/1.73 m^2; 100 mg every 24 hours if eGFR less than 20 mL/minute/1.73 m^2

Pregnancy see notes above

Breast-feeding amount probably too small to be harmful but manufacturer advises avoid

Side-effects see notes above; also eye irritation; *rarely* arrhythmias, abnormal dreams, hot flushes, hyperhidrosis; *very rarely* neuropathy, extrapyramidal symptoms; also reported pneumonitis, changes in blood sugar, myopathy, rhabdomyolysis; on intravenous infusion, hypotension and local reactions (including thrombophlebitis)

Dose

- By mouth, urinary-tract infections, 200–400 mg daily preferably in the morning, increased if necessary in upper urinary-tract infections to 400 mg twice daily
  Acute or chronic prostatitis, 200 mg twice daily for 28 days
  Lower respiratory-tract infections, 400 mg daily preferably in the morning, increased if necessary to 400 mg twice daily
  Skin and soft-tissue infections, 400 mg twice daily
  Uncomplicated gonorrhoea, 400 mg as a single dose
  Uncomplicated genital chlamydial infection, non-gonococcal urethritis, 400 mg daily in single or divided doses for 7 days
  Pelvic inflammatory disease (see also section 5.1, table 1), 400 mg twice daily for 14 days
- By intravenous infusion (over at least 30 minutes for each 200 mg), complicated urinary-tract infection, 200 mg daily
  Lower respiratory-tract infection, 200 mg twice daily
  Septicaemia, 200 mg twice daily
  Skin and soft-tissue infections, 400 mg twice daily
  Severe or complicated infections, dose may be increased to 400 mg twice daily

Ofloxacin (Non-proprietary) PoM

Tablets, ofloxacin 200 mg, net price 10-tab pack = £8.29; 400 mg, 5-tab pack = £5.71, 10-tab pack = £5.52. Label: 6, 9, 11, counselling, driving

Tarivid® (Sanofi-Aventis) PoM

Tablets, f/c, scored, ofloxacin 200 mg, net price 10-tab pack = £7.53, 20-tab pack = £15.05; 400 mg (yellow), 5-tab pack = £7.52, 10-tab pack = £14.99. Label: 6, 9, 11, counselling, driving

Intravenous infusion, ofloxacin (as hydrochloride) 2 mg/mL, net price 100-mL bottle = £16.16 (hosp. only)

5.1.13 Urinary-tract infections

Urinary-tract infection is more common in women than in men; when it occurs in men there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.

Escherichia coli is the most common cause of urinary-tract infection; *Staphylococcus saprophyticus* is also common in sexually active young women. Less common causes include Proteus and Klebsiella spp. *Pseudomonas aeruginosa* infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. *Staphylococcus epidermidis* and *Enterococcus faecalis* infection may complicate catheterisation or instrumentation.

A specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy;

- in men;
- in pregnant women;
- in children under 3 years of age;
- in patients with suspected upper urinary-tract infection, complicated infection, or recurrent infection;
- if resistant organisms are suspected;
- if urine dipstick testing gives a single positive result for leucocyte esterase or nitrite;
- if clinical symptoms are not consistent with results of dipstick testing.

Treatment should not be delayed while waiting for results. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.

Uncomplicated lower urinary-tract infections often respond to trimethoprim, nitrofurantoin, amoxicillin, or nalidixic acid given for 7 days (3 days may be

adequate for infections in women; see also Table 1, section 5.1); those caused by fully sensitive bacteria respond to two 3-g doses of amoxicillin (section 5.1.1.3). Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav (amoxicillin with clavulanic acid), an oral cephalosporin, pivmecillinam, or a quinolone.

Long-term low dose therapy may be required in selected patients to prevent *recurrence of infection*; indications include frequent relapses and significant kidney damage. Trimethoprim, nitrofurantoin and cefalexin have been recommended for long-term therapy.

Methenamine (hexamine) should **not** generally be used because it requires an acidic urine for its antimicrobial activity and it is ineffective for upper urinary-tract infections; it may, however, have a role in the prophylaxis and treatment of chronic or recurrent uncomplicated lower urinary-tract infections.

Acute pyelonephritis can lead to septicaemia and is treated initially by injection of a broad-spectrum antibacterial such as cefuroxime or a quinolone if the patient is severely ill; gentamicin can also be used.

Prostatitis can be difficult to cure and requires treatment for several weeks with an antibacterial which penetrates prostatic tissue such as trimethoprim, or some quinolones.

Where infection is localised and associated with an indwelling *catheter* a bladder instillation is often effective (section 7.4.4).

Pregnancy Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulfonamides, quinolones, and tetracyclines should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

Renal impairment In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methenamine, and nitrofurantoin should be avoided altogether.

Children Urinary-tract infections in children require prompt antibacterial treatment to minimise the risk of renal scarring. Uncomplicated 'lower' urinary-tract infections in *children over 3 months of age* can be treated with trimethoprim, nitrofurantoin, a first generation cephalosporin (e.g. cefalexin), or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment. Amoxicillin should only be used if the organism causing the infection is sensitive to it.

Acute pyelonephritis in children over 3 months of age can be treated with a first generation cephalosporin or co-amoxiclav for 7–10 days. If the patient is severely ill, then the infection is best treated initially by injection of a broad-spectrum antibacterial such as cefotaxime or co-amoxiclav; gentamicin is an alternative.

Children under 3 months of age should be transferred to hospital and treated initially with intravenous antibacterial drugs such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

Recurrent episodes of infection are an indication for imaging tests. *Antibacterial prophylaxis* with low doses of trimethoprim or nitrofurantoin may be considered for children with recurrent infection, significant urinary-tract anomalies, or significant kidney damage.

NITROFURANTOIN

Indications urinary-tract infections

Cautions anaemia; diabetes mellitus; electrolyte imbalance; vitamin B and folate deficiency; pulmonary disease; on long-term therapy, monitor liver function and monitor for pulmonary symptoms, especially in the elderly (discontinue if deterioration in lung function); susceptibility to peripheral neuropathy; false positive urinary glucose (if tested for reducing substances); urine may be coloured yellow or brown; **interactions:** Appendix 1 (nitrofurantoin)

Contra-indications infants less than 3 months old, G6PD deficiency (section 9.1.5); acute porphyria (section 9.8.2)

Hepatic impairment use with caution; cholestatic jaundice and chronic active hepatitis reported

Renal impairment avoid if eGFR less than 60 mL/minute/1.73 m^2; risk of peripheral neuropathy; ineffective because of inadequate urine concentrations

Pregnancy avoid at term—may produce neonatal haemolysis

Breast-feeding avoid; only small amounts in milk but could be enough to produce haemolysis in G6PD-deficient infants (section 9.1.5)

Side-effects anorexia, nausea, vomiting, and diarrhoea; acute and chronic pulmonary reactions (pulmonary fibrosis reported; possible association with lupus erythematosus-like syndrome); peripheral neuropathy; also reported, hypersensitivity reactions (including angioedema, anaphylaxis, sialadenitis, urticaria, rash and pruritus); rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis, erythema multiforme, pancreatitis, arthralgia, blood disorders (including agranulocytosis, thrombocytopenia, and aplastic anaemia), benign intracranial hypertension, and transient alopecia

Dose

- Acute uncomplicated infection, 50 mg every 6 hours with food for 7 days (3 days usually adequate in women); CHILD over 3 months, 3 mg/kg daily in 4 divided doses
- Severe chronic recurrent infection, 100 mg every 6 hours with food for 7 days (dose reduced or discontinued if severe nausea)
- Prophylaxis (but see Cautions), 50–100 mg at night; CHILD over 3 months, 1 mg/kg at night

Nitrofurantoin (Non-proprietary) PoM

Tablets, nitrofurantoin 50 mg, net price 28-tab pack = £1.84; 100 mg, 28-tab pack = £4.43. Label: 9, 14, 21

Oral suspension, nitrofurantoin 25 mg/5 mL, net price 300 mL = £99.05. Label: 9, 14, 21

Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Furadantin® (Goldshield) PoM
Tablets, all yellow, scored, nitrofurantoin 50 mg, net price 100-tab pack = £9.79; 100 mg, 100-tab pack = £18.11. Label: 9, 14, 21

Macrodantin® (Goldshield) PoM
Capsules, yellow/white, nitrofurantoin 50 mg (as macrocrystals), net price 30-cap pack = £2.49; 100 mg (yellow/white), 30-cap pack = £4.81. Label: 9, 14, 21

Modified release

Macrobid® (Goldshield) PoM
Capsules, m/r, blue/yellow, nitrofurantoin 100 mg (as nitrofurantoin macrocrystals and nitrofurantoin monohydrate), net price 14-cap pack = £4.89. Label: 9, 14, 21, 25
Dose uncomplicated urinary-tract infection, 1 capsule twice daily with food
Genito-urinary surgical prophylaxis, 1 capsule twice daily on day of procedure and for 3 days after

METHENAMINE HIPPURATE
(Hexamine hippurate)

Indications prophylaxis and long-term treatment of chronic or recurrent lower urinary-tract infections
Cautions avoid concurrent administration with sulfonamides (risk of crystalluria) or urinary alkalinising agents; **interactions:** Appendix 1 (methenamine)
Contra-indications severe dehydration, gout, metabolic acidosis
Hepatic impairment avoid
Renal impairment avoid if eGFR less than 10 mL/minute/1.73 m^2—risk of hippurate crystalluria
Pregnancy use with caution
Breast-feeding amount too small to be harmful
Side-effects gastro-intestinal disturbances, bladder irritation, rash
Dose
- 1 g every 12 hours (may be increased in patients with catheters to 1 g every 8 hours); CHILD 6–12 years 500 mg every 12 hours

Hiprex® (Meda)
Tablets, scored, methenamine hippurate 1 g, net price 60-tab pack = £6.58. Label: 9

5.2 Antifungal drugs

Treatment of fungal infections

The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. For local treatment of fungal infections, see section 7.2.2 (genital), section 7.4.4 (bladder), section 11.3.2 (eye), section 12.1.1 (ear), section 12.3.2 (oropharynx), and section 13.10.2 (skin).

Aspergillosis Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the heart, brain, and skin. **Voriconazole** (section 5.2.1) is the treatment of choice for aspergillosis; **liposomal amphotericin** (section 5.2.3) is an alternative first-line treatment when voriconazole cannot be used. **Caspofungin** (section 5.2.4), **itraconazole** (section 5.2.1), or **posaconazole** (section 5.2.1) can be used in patients who are refractory to, or intolerant of voriconazole and liposomal amphotericin. Itraconazole is also used for the treatment of chronic pulmonary aspergillosis or as an adjunct in the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication].

Candidiasis Many superficial candidal infections including infections of the skin (section 13.10.2) are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis (section 7.2.2) may be treated with locally acting antifungals or with fluconazole (section 5.2.1) given by mouth; for resistant organisms, itraconazole (section 5.2.1) can be given by mouth.

Oropharyngeal candidiasis generally responds to topical therapy (section 12.3.2); fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for fluconazole-resistant infections. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

For *invasive or disseminated candidiasis*, an **echinocandin** (section 5.2.4) can be used. **Fluconazole** (section 5.2.1) is an alternative for *Candida albicans* infection in clinically stable patients who have not received an azole antifungal recently. **Amphotericin** (section 5.2.3) is an alternative when an echinocandin or fluconazole cannot be used, however, amphotericin should be considered for the initial treatment of CNS candidiasis. **Voriconazole** (section 5.2.1) can be used for infections caused by fluconazole-resistant *Candida* spp. when oral therapy is required, or in patients intolerant of amphotericin or an echinocandin. In refractory cases, **flucytosine** (section 5.2.5) can be used with intravenous amphotericin.

Cryptococcosis Cryptococcosis is uncommon but infection in the immunocompromised, especially in HIV-positive patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is **amphotericin** (section 5.2.3) by intravenous infusion and **flucytosine** (section 5.2.5) by intravenous infusion for 2 weeks, followed by **fluconazole** (section 5.2.1) by mouth for 8 weeks or until cultures are negative. In cryptococcosis, **fluconazole** is sometimes given alone as an alternative in HIV-positive patients with mild, localised infections or in those who cannot tolerate amphotericin. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

Histoplasmosis Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons. **Itraconazole** (section 5.2.1) can be used for the treatment of immunocompetent patients with indolent non-meningeal infection, including chronic pulmonary histoplasmosis. **Amphotericin** (section 5.2.3) by intravenous infusion is preferred in patients with fulminant or severe infections. Following successful treatment, itraconazole can be used for prophylaxis against relapse until immunity recovers.

Skin and nail infections Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy (section

13.10.2). Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Oral imidazole or triazole antifungals (particularly **itraconazole**) and **terbinafine** are used more frequently than griseofulvin because they have a broader spectrum of activity and require a shorter duration of treatment.

Tinea capitis is treated systemically; additional topical application of an antifungal (section 13.10.2) may reduce transmission. **Griseofulvin** (section 5.2.5) is used for tinea capitis in adults and children; it is effective against infections caused by *Trichophyton tonsurans* and *Microsporum* spp. **Terbinafine** (section 5.2.5) is used for tinea capitis caused by *T. tonsurans* [unlicensed indication]. The role of terbinafine in the management of *Microsporum* infections is uncertain.

Pityriasis versicolor (section 13.10.2) may be treated with **itraconazole** (section 5.2.1) by mouth if topical therapy is ineffective; **fluconazole** (section 5.2.1) by mouth is an alternative. Oral **terbinafine** is **not** effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. **Terbinafine** (section 5.2.5) and **itraconazole** (section 5.2.1) have largely replaced griseofulvin for the systemic treatment of *onychomycosis*, particularly of the toenail; terbinafine is considered to be the drug of choice. Itraconazole can be administered as intermittent 'pulse' therapy. For the role of topical antifungals in the treatment of onychomycosis, see section 13.10.2.

Immunocompromised patients Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral triazole antifungals are the drugs of choice for prophylaxis. **Fluconazole** (section 5.2.1) is more reliably absorbed than **itraconazole** (section 5.2.1), but fluconazole is not effective against *Aspergillus* spp. Itraconazole is preferred in patients at risk of invasive aspergillosis. **Posaconazole** (section 5.2.1) can be used for prophylaxis in patients who are undergoing haematopoietic stem cell transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome, if they are intolerant of fluconazole or itraconazole. **Micafungin** (section 5.2.4) can be used for prophylaxis of candidiasis in patients undergoing haematopoietic stem cell transplantation when fluconazole, itraconazole or posaconazole cannot be used.

Amphotericin (section 5.2.3) by intravenous infusion or **caspofungin** (section 5.2.4) is used for the empirical *treatment* of serious fungal infections; caspofungin is not effective against fungal infections of the CNS.

5.2.1 Triazole antifungals

For the role of triazole antifungal drugs in the prevention and systemic treatment of fungal infections, see p. 373.

Fluconazole is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis. Fluconazole is excreted largely unchanged in the urine and can be used to treat candiduria.

Itraconazole is active against a wide range of dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption.

Itraconazole has been associated with liver damage and should be avoided or used with caution in patients with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Posaconazole is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment.

Voriconazole is a broad-spectrum antifungal drug which is licensed for use in life-threatening infections.

FLUCONAZOLE

Indications see under Dose

Cautions concomitant use with hepatotoxic drugs, monitor liver function with high doses or extended courses—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis); susceptibility to QT interval prolongation; **interactions:** Appendix 1 (antifungals, triazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment toxicity with related drugs

Renal impairment usual initial dose then halve subsequent doses if eGFR less than 50 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses

Breast-feeding present in milk but amount probably too small to be harmful

Side-effects nausea, abdominal discomfort, diarrhoea, flatulence, headache, rash (discontinue treatment or monitor closely if infection invasive or systemic); less frequently dyspepsia, vomiting, taste disturbance, hepatic disorders, hypersensitivity reactions, anaphylaxis, dizziness, seizures, alopecia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome (severe cutaneous reactions more likely in AIDS patients), hyperlipidaemia, leucopenia, thrombocytopenia, and hypokalaemia reported

Dose

- Vaginal candidiasis (see also Recurrent Vulvovaginal Candidiasis, section 7.2.2) and candidal balanitis, ADULT and CHILD over 16 years, by mouth, a single dose of 150 mg
- Mucosal candidiasis (except genital), by mouth, 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); CHILD by mouth *or* by intravenous infusion, 3–6 mg/kg on first day then 3 mg/kg daily (every 72 hours in NEONATE up to 2 weeks old, every 48 hours in neonate 2–4 weeks old)
- Tinea pedis, corporis, cruris, pityriasis versicolor, and dermal candidiasis, by mouth, 50 mg daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks
- Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal

infections (including meningitis), by mouth *or* intravenous infusion, 400 mg on first day then 200–400 mg daily; max. 800 mg daily in severe infections [unlicensed dose]; treatment continued according to response (at least 8 weeks for cryptococcal meningitis); CHILD 6–12 mg/kg daily (every 72 hours in NEONATE up to 2 weeks old, every 48 hours in NEONATE 2–4 weeks old); max. 800 mg daily [unlicensed dose]

- Prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy, by mouth *or* by intravenous infusion, 200 mg daily
- Prevention of fungal infections in immunocompromised patients, by mouth *or* by intravenous infusion, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range; CHILD according to extent and duration of neutropenia, 3–12 mg/kg daily (every 72 hours in NEONATE up to 2 weeks old, every 48 hours in NEONATE 2–4 weeks old); max. 400 mg daily

Fluconazole (Non-proprietary) PoM

[1] Capsules, fluconazole 50 mg, net price 7-cap pack = £1.14; 150 mg, single-capsule pack = 98p; 200 mg, 7-cap pack = £5.04. Label: 9, (50 and 200 mg)

Dental prescribing on NHS Fluconazole Capsules 50 mg may be prescribed

Intravenous infusion, fluconazole 2 mg/mL, net price 25-mL bottle = £7.31; 100-mL bottle = £29.27; 100-mL infusion bag = £27.82

Diflucan® (Pfizer) PoM

[1] Capsules, fluconazole 50 mg (blue/white), net price 7-cap pack = £16.61; 150 mg (blue), single-capsule pack = £7.12; 200 mg (purple/white), 7-cap pack = £66.42. Label: 9, (50 and 200 mg)

Oral suspension, orange-flavoured, fluconazole for reconstitution with water, 50 mg/5 mL, net price 35 mL = £16.61; 200 mg/5 mL, 35 mL = £66.42. Label: 9

Dental prescribing on NHS May be prescribed as Fluconazole Oral Suspension 50 mg/5 mL

Intravenous infusion, fluconazole 2 mg/mL in sodium chloride intravenous infusion 0.9%, net price 25-mL bottle = £7.32; 100-mL bottle = £29.28

Electrolytes Na^+ 15 mmol/100-mL bottle

ITRACONAZOLE

Indications see under Dose

Cautions absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary); susceptibility to congestive heart failure (see also Heart Failure, below); **interactions:** Appendix 1 (antifungals, triazole)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported very rarely—discontinue if signs of hepatitis develop. Avoid or use with caution if history of hepatotoxicity with other drugs or in active liver disease. Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment

Counselling Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop

1. Capsules can be sold to the public for vaginal candidiasis and associated candidal balanitis in those aged 16–60 years, in a container or packaging containing not more than 150 mg and labelled to show a max. dose of 150 mg

Heart failure

Following reports of heart failure, caution is advised when prescribing itraconazole to patients at high risk of heart failure. Those at risk include:

- patients receiving high doses and longer treatment courses;
- older patients and those with cardiac disease;
- patients receiving treatment with negative inotropic drugs, e.g. calcium channel blockers.

Itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure unless the infection is serious.

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment use only if potential benefit outweighs risk of hepatotoxicity (see Hepatotoxicity above); dose reduction may be necessary

Renal impairment risk of congestive heart failure; bioavailability of oral formulations possibly reduced; use intravenous infusion with caution if eGFR 30–80 mL/minute/1.73 m^2; avoid intravenous infusion if eGFR less than 30 mL/minute/1.73m^2

Pregnancy manufacturer advises use only in life-threatening situations (toxicity at high doses in *animal* studies); ensure effective contraception during treatment and until the next menstrual period following end of treatment

Breast-feeding small amounts present in milk—may accumulate; manufacturer advises avoid

Side-effects nausea, abdominal pain, rash; *less commonly* vomiting, dyspepsia, taste disturbances, flatulence, diarrhoea, constipation, oedema, headache, dizziness, paraesthesia (discontinue treatment if neuropathy), menstrual disorder, and alopecia; *rarely* pancreatitis, hypoaesthesia, urinary frequency, leucopenia, visual disturbances, and tinnitus; also reported, heart failure (see Cautions above), hypertriglyceridaemia, hepatitis (see Hepatotoxicity above), erectile dysfunction, thrombocytopenia, hypokalaemia, myalgia, arthralgia, photosensitivity, toxic epidermal necrolysis, and Stevens–Johnson syndrome; *with intravenous injection* hypertension and hyperglycaemia

Dose

- By mouth, oropharyngeal candidiasis, see under *Sporanox®* oral liquid below

Vulvovaginal candidiasis, (see also Recurrent Vulvovaginal Candidiasis, section 7.2.2) 200 mg twice daily for 1 day

Pityriasis versicolor, 200 mg once daily for 7 days

Tinea corporis and tinea cruris, *either* 100 mg once daily for 15 days *or* 200 mg once daily for 7 days

Tinea pedis and tinea manuum, *either* 100 mg once daily for 30 days *or* 200 mg twice daily for 7 days

Onychomycosis, *either* 200 mg once daily for 3 months *or* course ('pulse') of 200 mg twice daily for 7 days, subsequent courses repeated after 21-day interval; fingernails 2 courses, toenails 3 courses

Histoplasmosis, 200 mg 3 times daily for 3 days, then 200 mg once or twice daily

Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective, 200 mg once daily (candidiasis 100–200 mg once daily) increased in invasive or disseminated disease and in cryptococcal meningitis to 200 mg twice daily

Maintenance in HIV-infected patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate, 200 mg once daily, increased to 200 mg twice daily if low plasma-itraconazole concentration (see Cautions)

Prophylaxis in patients with haematological malignancy or undergoing bone-marrow transplant, see under *Sporanox®* oral liquid below

- By intravenous infusion, systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective, histoplasmosis, 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days
- CHILD under 18 years see *BNF for Children*

Note Itraconazole doses in BNF may differ from those in product literature

Itraconazole (Non-proprietary) PoM

Capsules, enclosing coated beads, itraconazole 100 mg, net price 15-cap pack = £7.21. Label: 5, 9, 21, 25, counselling, hepatotoxicity

Sporanox® (Janssen-Cilag) PoM

Capsules, blue/pink, enclosing coated beads, itraconazole 100 mg, net price 4-cap pack = £3.67; 15-cap pack = £13.77; 28-cap pack (*Sporanox®-Pulse*) = £25.72; 60-cap pack = £55.10. Label: 5, 9, 21, 25, counselling, hepatotoxicity

Oral liquid, sugar-free, cherry-flavoured, itraconazole 10 mg/mL, net price 150 mL (with 10-mL measuring cup) = £45.80. Label: 9, 23, counselling, administration, hepatotoxicity

Dose oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients, 20 mL (2 measuring cups) daily in 1–2 divided doses for 1 week (continue for another week if no response)

Fluconazole-resistant oral or oesophageal candidiasis, 10–20 mL (1–2 measuring cups) twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)

Prophylaxis of deep fungal infections (when standard therapy is inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic, 5 mg/kg daily in 2 divided doses; starting before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers; CHILD and ELDERLY safety and efficacy not established

Counselling Do not take with food; swish around mouth and swallow, do not rinse afterwards

Concentrate for intravenous infusion, itraconazole 10 mg/mL. For dilution before use. Net price 25-mL amp (with infusion bag and filter) = £62.58

Excipients include propylene glycol

POSACONAZOLE

Indications invasive aspergillosis (see notes above); fusariosis either unresponsive to, or in patients intolerant of, amphotericin; chromoblastomycosis and mycetoma either unresponsive to, or in patients intolerant of, itraconazole; coccidioidomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole; see also under Dose

Cautions cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation, concomitant use with other drugs known to cause QT-interval prolongation; monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy, monitor liver function; **interactions:** Appendix 1 (antifungals, triazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment monitor liver function; manufacturer advises caution

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk and recommends effective contraception during treatment; toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, and flatulence); dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia; blood disorders (including anaemia, neutropenia, and thrombocytopenia), electrolyte disturbances; dry mouth; rash; *less commonly* pancreatitis, hepatic disorders, arrhythmias, palpitation, changes in blood pressure, oedema, convulsions, neuropathy, tremor, hyperglycaemia, menstrual disorders, renal failure, musculoskeletal pain, visual disturbances, mouth ulcers, and alopecia; *rarely* ileus, cardiac failure, myocardial infarction, stroke, thrombosis, syncope, pneumonitis, psychosis, depression, encephalopathy, adrenal insufficiency, breast pain, hearing impairment, and Stevens-Johnson syndrome

Dose

- 400 mg twice daily with food *or* if food not tolerated, 200 mg 4 times daily
- Oropharyngeal candidiasis (severe infection or in immunocompromised patients only), 200 mg with food on first day, then 100 mg once daily with food for 13 days
- Prophylaxis of invasive fungal infections in patients undergoing bone-marrow transplantation or receiving chemotherapy for acute myeloid leukaemia and myelodysplastic syndrome who are expected to become neutropenic, and who are intolerant of fluconazole or itraconazole, 200 mg 3 times daily with food, starting before transplantation or before chemotherapy and continued until neutrophil count recovers
- CHILD under 18 years not recommended

Noxafil® (Schering-Plough) ▼ PoM

Suspension, posaconazole 200 mg/5 mL, net price 105 mL (cherry-flavoured) = £491.20. Label: 3, 9, 21

VORICONAZOLE

Indications invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

Cautions electrolyte disturbances, cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation, concomitant use with other drugs that prolong QT interval; avoid exposure to sunlight; patients at risk of pancreatitis; monitor liver function before treatment and during treatment; haematological malignancy (increased risk of hepatic reactions); monitor renal function; **interactions:** Appendix 1 (antifungals, triazole)

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment in mild to moderate hepatic cirrhosis use usual initial dose then halve subsequent

doses; no information available for severe hepatic cirrhosis—manufacturer advises use only if potential benefit outweighs risk

Renal impairment intravenous vehicle may accumulate if eGFR less than 50 mL/minute/1.73 m^2—use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required)

Pregnancy toxicity in *animal* studies—manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, abdominal pain, diarrhoea, jaundice, oedema, hypotension, chest pain, respiratory distress syndrome, sinusitis, headache, dizziness, asthenia, anxiety, depression, confusion, agitation, hallucinations, paraesthesia, tremor, influenza-like symptoms, hypoglycaemia, haematuria, blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia, visual disturbances (including altered perception, blurred vision, and photophobia), rash, pruritus, photosensitivity, alopecia, cheilitis, injection-site reactions; *less commonly* dyspepsia, duodenitis, cholecystitis, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, Stevens-Johnson syndrome; *rarely* pseudomembranous colitis, taste disturbances (more common with oral suspension), convulsions, insomnia, tinnitus, hearing disturbances, extrapyramidal effects, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, pseudoporphyria, retinal haemorrhage, optic atrophy; also reported squamous cell carcinoma of skin (particularly in presence of phototoxicity or in the immunosuppressed)

Dose

- By mouth, ADULT and CHILD over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours; CHILD 2–12 years, (oral suspension recommended) 200 mg every 12 hours
- By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months; CHILD 2–18 years see *BNF for Children*

Vfend® (Pfizer) PoM

Tablets, f/c, voriconazole 50 mg, net price 28-tablet pack = £275.68; 200 mg, 28-tab pack = £1102.74. Label: 9, 11, 23

Oral suspension, voriconazole 200 mg/5 mL when reconstituted with water, net price 75 mL (orange-flavoured) = £551.37. Label: 9, 11, 23

Intravenous infusion, powder for reconstitution, voriconazole, net price 200-mg vial = £77.14

Excipients include sulphobutylether beta cyclodextrin sodium (risk of accumulation in renal impairment)

Electrolytes Na^+ 9.47 mmol/vial

5.2.2 Imidazole antifungals

The imidazole antifungals include clotrimazole, econazole, ketoconazole, and tioconazole. They are used for the local treatment of vaginal candidiasis (section 7.2.2) and for dermatophyte infections (section 13.10.2).

Ketoconazole is better absorbed by mouth than other imidazoles. However, its use is restricted because it is associated with fatal hepatotoxicity (see below).

Miconazole (section 12.3.2) can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.

KETOCONAZOLE

Indications dermatophytoses and *Malassezia* folliculitis *either* resistant to fluconazole, terbinafine, or itraconazole *or* in patients intolerant of these antifungals; chronic mucocutaneous, cutaneous, and oropharyngeal candidiasis *either* resistant to fluconazole or itraconazole *or* in patients intolerant of these antifungals

Cautions predisposition to adrenocortical insufficiency; **interactions:** Appendix 1 (antifungals, imidazole)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported very rarely; risk of hepatotoxicity greater if given for longer than 10 days. Monitor liver function before treatment, then on weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests (avoid in active liver disease) or if history of hepatotoxicity with other drugs.

Counselling Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, or dark urine develop

Contra-indications acute porphyria (section 9.8.2)

Hepatic impairment avoid; see also Hepatotoxicity above

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk (teratogenicity in *animal* studies)

Breast-feeding manufacturer advises avoid

Side-effects nausea, vomiting, abdominal pain; pruritus; *less commonly* diarrhoea, headache, dizziness, drowsiness, and rash; also reported fatal liver damage (see Hepatotoxicity above), dyspepsia, raised intracranial pressure, paraesthesia, adrenocortical insufficiency, erectile dysfunction, menstrual disorders, azoospermia (with high doses), gynaecomastia, thrombocytopenia, photophobia, photosensitivity, and alopecia

Dose

- 200 mg once daily, increased if response inadequate to 400 mg once daily; continued until symptoms have cleared and cultures negative, but see Cautions (max. duration of treatment 4 weeks for *Malassezia* infection); CHILD body-weight 15–30 kg, 100 mg once daily; body-weight over 30 kg, adult dose

Nizoral® (Janssen-Cilag) PoM

Tablets, scored, ketoconazole 200 mg. Net price 30-tab pack = £14.02. Label: 5, 9, 21, counselling, hepatotoxicity

5.2.3 Polyene antifungals

The polyene antifungals include amphotericin and nystatin; neither drug is absorbed when given by mouth. Nystatin is used for oral, oropharyngeal, and perioral infections by local application in the mouth (section 12.3.2). Nystatin is also used for *Candida albicans* infection of the skin (section 13.10.2).

Amphotericin by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (*Abelcet®* and *AmBisome®*) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; lipid formulations are more expensive. For the role of amphotericin in the systemic treatment of fungal infections, see p. 373.

AMPHOTERICIN
(Amphotericin B)

Indications See under Dose

Cautions when given parenterally, toxicity common (close supervision necessary and test dose required; see Anaphylaxis below); hepatic and renal function tests, blood counts, and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required; corticosteroids (avoid except to control reactions); avoid rapid infusion (risk of arrhythmias); **interactions:** Appendix 1 (amphotericin)

Anaphylaxis Anaphylaxis occurs rarely with any intravenous amphotericin product and a test dose is advisable before the first infusion; the patient should be carefully observed for at least 30 minutes after the test dose. Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential)

Renal impairment use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation

Pregnancy not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk

Breast-feeding no information available

Side-effects when given parenterally, anorexia, nausea and vomiting, diarrhoea, epigastric pain; febrile reactions, headache, muscle and joint pain; anaemia; disturbances in renal function (including hypokalaemia and hypomagnesaemia) and renal toxicity; also cardiovascular toxicity (including arrhythmias, blood pressure changes), blood disorders, neurological disorders (including hearing loss, diplopia, convulsions, peripheral neuropathy, encephalopathy), abnormal liver function (discontinue treatment), rash, anaphylactoid reactions (see Anaphylaxis, above); pain and thrombophlebitis at injection site

Dose

- By intravenous infusion, see preparations

Note Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should **not** be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.

Fungizone® (Squibb) PoM

Intravenous infusion, powder for reconstitution, amphotericin (as sodium deoxycholate complex), net price 50-mg vial = £3.88

Electrolytes $Na^+ < 0.5$ mmol/vial

Dose by intravenous infusion, systemic fungal infections, initial test dose of 1 mg over 20–30 minutes then 250 micrograms/kg daily, gradually increased over 2–4 days, if tolerated, to 1 mg/kg daily; max. (severe infection) 1.5 mg/kg daily or on alternate days; CHILD under 18 years see *BNF for Children*

Note Prolonged treatment usually necessary; if interrupted for longer than 7 days recommence at 250 micrograms/kg daily and increase gradually

Lipid formulations

Abelcet® (Cephalon) PoM

Intravenous infusion, amphotericin 5 mg/mL as lipid complex with L-α-dimyristoylphosphatidylcholine and L-α-dimyristoylphosphatidylglycerol, net price 20-mL vial = £77.43 (hosp. only)

Electrolytes Na^+ 3.12 mmol/vial

Dose by intravenous infusion, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, initial test dose 1 mg over 15 minutes then 5 mg/kg once daily for at least 14 days; CHILD under 18 years see *BNF for Children*

AmBisome® (Gilead) PoM

Intravenous infusion, powder for reconstitution, amphotericin 50 mg encapsulated in liposomes, net price 50-mg vial = £96.69

Electrolytes $Na^+ < 0.5$ mmol/vial

Excipients include sucrose 900 mg/vial

Dose by intravenous infusion, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin, aspergillosis, initial test dose 1 mg over 10 minutes then 3 mg/kg once daily; max. 5 mg/kg once daily [unlicensed dose]; CHILD under 18 years see *BNF for Children*

Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials, initial test dose 1 mg over 10 minutes then 3 mg/kg once daily until afebrile for 3 consecutive days; max. period of treatment 42 days; max. 5 mg/kg once daily [unlicensed dose]; CHILD under 18 years see *BNF for Children*

Visceral leishmaniasis, see section 5.4.5 and product literature

5.2.4 Echinocandin antifungals

The echinocandin antifungals include **anidulafungin**, **caspofungin** and **micafungin**. They are only active against *Aspergillus* spp. and *Candida* spp.; however, anidulafungin and micafungin are not used for the treatment of aspergillosis. Echinocandins are not effective against fungal infections of the CNS. For the role of echinocandin antifungals in the prevention and systemic treatment of fungal infections, see p. 373.

ANIDULAFUNGIN

Indications invasive candidiasis (see notes above)

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—present in milk in *animal* studies

Side-effects diarrhoea, nausea, vomiting, flushing, convulsion, headache, coagulopathy, hypokalaemia, raised serum creatinine, rash, pruritus; *less commonly* abdominal pain, cholestasis, hypertension, hyper-

glycaemia, urticaria, injection-site pain; also reported, hypotension, dyspnoea, bronchospasm, hepatitis

Dose

- By intravenous infusion, ADULT over 18 years, 200 mg on first day then 100 mg once daily

Ecalta® (Pfizer) ▼ PoM

Intravenous infusion, powder for reconstitution, anidulafungin, net-price 100-mg vial = £299.99

CASPOFUNGIN

Indications invasive aspergillosis (see notes above); invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

Cautions **interactions:** Appendix 1 (caspofungin)

Hepatic impairment 70 mg on first day then 35 mg once daily in moderate impairment; no information available for severe impairment

Pregnancy manufacturer advises avoid unless essential—toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies—manufacturer advises avoid

Side-effects nausea, diarrhoea, vomiting; dyspnoea; headache; hypokalaemia; arthralgia; rash, pruritus, sweating, injection-site reactions; *less commonly* abdominal pain, dyspepsia, dry mouth, dysphagia, taste disturbances, anorexia, constipation, flatulence, cholestasis, hepatic dysfunction, ascites, palpitation, arrhythmia, chest pain, heart failure, thrombophlebitis, flushing, hypotension, hypertension, bronchospasm, cough, dizziness, fatigue, paraesthesia, hypoaesthesia, sleep disturbances, tremor, anxiety, disorientation, hyperglycaemia, renal failure, hypomagnesaemia, hypocalcaemia, metabolic acidosis, anaemia, thrombocytopenia, leucopenia, myalgia, muscular weakness, blurred vision, and erythema multiforme; also reported, adult respiratory distress syndrome and anaphylaxis

Dose

- By intravenous infusion, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg); CHILD under 18 years see *BNF for Children*

Cancidas® (MSD) ▼ PoM

Intravenous infusion, powder for reconstitution, caspofungin (as acetate), net price 50-mg vial = £327.67; 70-mg vial = £416.78

MICAFUNGIN

Indications see under Dose

Cautions monitor renal function; **interactions:** Appendix 1 (micafungin)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported. Monitor liver function—discontinue if significant and persistent abnormalities in liver function tests develop. Use with caution in hepatic impairment (avoid if severe) or if receiving other hepatotoxic drugs. Risk of hepatic side-effects greater in children under 1 year of age

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment; see also Hepatotoxicity above

Renal impairment use with caution; renal function may deteriorate

Pregnancy manufacturer advises avoid unless essential—toxicity in *animal* studies

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—present in milk in *animal* studies

Side-effects nausea, vomiting, diarrhoea, abdominal pain; headache, fever; hypokalaemia, hypomagnesaemia, hypocalcaemia, leucopenia, anaemia; rash, phlebitis; *less commonly* dyspepsia, constipation, hepatomegaly, hepatitis and cholestasis (see also Hepatotoxicity above), taste disturbances, anorexia, tachycardia, palpitation, bradycardia, blood pressure changes, flushing, dyspnoea, sleep disturbances, anxiety, confusion, dizziness, tremor, pancytopenia, thrombocytopenia, eosinophilia, hyponatraemia, hypophosphataemia, hyperkalaemia, hyperhidrosis, and pruritus; *rarely* haemolytic anaemia; also reported renal failure (more frequent in children)

Dose

- By intravenous infusion, invasive candidiasis, ADULT body-weight over 40 kg, 100 mg once daily (increased to 200 mg daily if inadequate response) for at least 14 days; body-weight under 40 kg, 2 mg/kg once daily (increased to 4 mg/kg daily if inadequate response) for at least 14 days; CHILD under 18 years see *BNF for Children*

  Oesophageal candidiasis, ADULT body-weight over 40 kg, 150 mg once daily; body-weight under 40 kg, 3 mg/kg once daily; CHILD 16–18 years see *BNF for Children*

  Prophylaxis of candidiasis in patients undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days, ADULT body-weight over 40 kg, 50 mg once daily; body-weight under 40 kg, 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range; CHILD under 18 years see *BNF for Children*

Mycamine® (Astellas) ▼ PoM

Intravenous infusion, powder for reconstitution, micafungin (as sodium), net price 50-mg vial = £196.08; 100-mg vial = £341.00

5.2.5 Other antifungals

Flucytosine is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in AIDS patients; weekly blood counts are necessary during prolonged therapy. Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment. For the role of flucytosine in the treatment of systemic candidiasis and cryptococcal meningitis, see p. 373.

Griseofulvin is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophyton infections in children. Duration of therapy is dependent on the site of the infection and may extend to a number of months. For the role of griseofulvin in the treatment of tinea capitis, see p. 373.

Terbinafine is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate (see p. 373).

FLUCYTOSINE

Indications systemic yeast and fungal infections; adjunct to amphotericin in cryptococcal meningitis (see Cryptococcosis, p. 373), adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections

Cautions elderly; blood disorders; liver- and kidney-function tests and blood counts required (weekly in blood disorders); **interactions:** Appendix 1 (flucytosine)

Renal impairment liver- and kidney-function tests and blood counts required weekly; use 50 mg/kg every 12 hours if creatinine clearance 20–40 mL/minute; use 50 mg/kg every 24 hours if creatinine clearance 10–20 mL/minute; use initial dose of 50 mg/kg if creatinine clearance less than 10 mL/minute and then adjust dose according to plasma-flucytosine concentration

Pregnancy teratogenic in *animal* studies; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid

Side-effects nausea, vomiting, diarrhoea, rashes; less frequently cardiotoxicity, confusion, hallucinations, convulsions, headache, sedation, vertigo, alterations in liver function tests (hepatitis and hepatic necrosis reported), and toxic epidermal necrolysis; blood disorders including thrombocytopenia, leucopenia, and aplastic anaemia reported

Dose

- By intravenous infusion over 20–40 minutes, 200 mg/kg daily in 4 divided doses usually for not more than 7 days; extremely sensitive organisms, 100–150 mg/kg daily may be sufficient; CHILD under 18 years see *BNF for Children*

  Cryptococcal meningitis (adjunct to amphotericin, see Cryptococcosis, p. 373) 100 mg/kg daily in 4 divided doses for 2 weeks [unlicensed duration]; CHILD under 18 years see *BNF for Children*

  Note For plasma concentration monitoring, blood should be taken shortly before starting the next infusion; plasma concentration for optimum response 25–50 mg/litre (200–400 micromol/litre)—should not be allowed to exceed 80 mg/litre (620 micromol/litre)

Ancotil® (Meda) PoM

Intravenous infusion, flucytosine 10 mg/mL, net price 250-mL infusion bottle = £30.33 (hosp. only)
Electrolytes Na^+ 34.5 mmol/250-mL bottle

Note Flucytosine tablets [unlicensed] may be available from 'special-order' manufacturers or specialist-importing companies, see p. 988

GRISEOFULVIN

Indications dermatophyte infections of the skin, scalp, hair and nails where topical therapy has failed or is inappropriate

Cautions **interactions:** Appendix 1 (griseofulvin)

Driving May impair performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications severe liver disease; systemic lupus erythematosus (risk of exacerbation); acute porphyria (section 9.8.2)

Hepatic impairment avoid in severe liver disease

Pregnancy avoid (fetotoxicity and teratogenicity in *animals*); effective contraception required during and for at least 1 month after administration to women (**important:** effectiveness of oral contraceptives may be reduced, additional contraceptive precautions e.g. barrier method, required); also men should avoid fathering a child during and for at least 6 months after administration

Breast-feeding avoid—no information available

Side-effects nausea, vomiting, diarrhoea; headache; also reported, abdominal pain, dyspepsia, hepatotoxicity, glossitis, taste disturbances, sleep disturbances, dizziness, fatigue, confusion, agitation, depression, impaired coordination and hearing, peripheral neuropathy, menstrual disturbances, renal failure, leucopenia, systemic lupus erythematosus, rash (including rarely erythema multiforme, toxic epidermal necrolysis), and photosensitivity

Dose

- Dermatophyte infections, 500 mg once daily or in divided doses; in severe infection dose may be doubled, reducing when response occurs; CHILD under 50 kg, 10 mg/kg once daily or in divided doses
- Tinea capitis caused by *Trichophyton tonsurans*, 1 g once daily or in divided doses; CHILD under 50 kg, 15–20 mg/kg once daily or in divided doses

Note Griseofulvin doses in BNF may differ from those in product literature

Griseofulvin (Non-proprietary) PoM

Tablets, griseofulvin 125 mg, net price 100 = £34.86; 500 mg, 100= £90.34. Label: 9, 21, counselling, driving

Fulsovin® (Kappin) PoM

Oral suspension, griseofulvin 125 mg/5 mL, net price 100 mL (peppermint-flavoured) = £59.90. Label: 9, 21, counselling,, driving

TERBINAFINE

Indications dermatophyte infections of the nails, ringworm infections (including tinea pedis, cruris, and corporis) where oral therapy appropriate (due to site, severity or extent)

Cautions psoriasis (risk of exacerbation); autoimmune disease (risk of lupus-erythematosus-like effect); **interactions:** Appendix 1 (terbinafine)

Hepatic impairment manufacturer advises avoid—elimination reduced

Renal impairment use half normal dose if eGFR less than 50 mL/minute/1.73 m^2 and no suitable alternative available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding avoid—present in milk

Side-effects abdominal discomfort, anorexia, nausea, diarrhoea; headache; rash and urticaria occasionally with arthralgia or myalgia; *less commonly* taste disturbance; *rarely* liver toxicity (including jaundice, cholestasis and hepatitis)—discontinue treatment, angioedema, dizziness, malaise, paraesthesia, hypoaesthesia, photosensitivity, serious skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)—discontinue treatment if progressive skin rash; *very rarely* psychiatric disturbances, blood disorders (including leucopenia and thrombocytopenia), lupus erythematosus-like effect, and exacerbation of psoriasis

Dose

- By mouth, 250 mg daily usually for 2–6 weeks in tinea pedis, 2–4 weeks in tinea cruris, 4 weeks in tinea corporis, 6 weeks–3 months in nail infections (occa-

sionally longer in toenail infections); CHILD [unlicensed] usually for 4 weeks, tinea capitis, over 1 year, body-weight 10–20 kg, 62.5 mg once daily; body-weight 20–40 kg, 125 mg once daily; body-weight over 40 kg, 250 mg once daily

Terbinafine (Non-proprietary) PoM
Tablets, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £2.33, 28-tab pack = £3.02. Label: 9

Lamisil® (Novartis) PoM
Tablets, off-white, scored, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £21.30, 28-tab pack = £41.09. Label: 9

5.3 Antiviral drugs

5.3.1 HIV infection
5.3.2 Herpesvirus infections
5.3.3 Viral hepatitis
5.3.4 Influenza
5.3.5 Respiratory syncytial virus

The majority of virus infections resolve spontaneously in immunocompetent subjects. A number of specific treatments for viral infections are available, particularly for the immunocompromised. This section includes notes on herpes simplex and varicella-zoster, human immunodeficiency virus, cytomegalovirus, respiratory syncytial virus, viral hepatitis and influenza.

5.3.1 HIV infection

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection (antiretrovirals) may be associated with serious side-effects. Although antiretrovirals increase life expectancy considerably and decrease the risk of complications associated with premature ageing, mortality and morbidity remain slightly higher than in uninfected individuals. Treatment should be undertaken only by those experienced in their use.

Principles of treatment Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the risk of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and patient tolerance. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.

Initiation of treatment The optimum time for initiating antiretroviral treatment depends primarily on the CD4 cell count; the plasma viral load and clinical symptoms may also help. The timing and choice of treatment should also take account of the possible effects of antiretroviral drugs on factors such as the risk of cardiovascular events. Treatment includes a combination of drugs known as 'highly active antiretroviral therapy'. Treatment is initiated with 2 nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor; the regimens of choice contain *either* tenofovir, emtricitabine, and efavirenz *or* abacavir, lamivudine, and efavirenz. Regimens containing 2 nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor are reserved for patients with resistance to first-line regimens, women wishing to become pregnant, or patients with psychiatric illness. Patients who require treatment for both HIV and chronic hepatitis B should be treated with antivirals active against both diseases (section 5.3.3).

Switching therapy Deterioration of the condition (including clinical and virological changes) may require a change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

Pregnancy Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral drugs is unknown), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. **All treatment options require careful assessment by a specialist**. Zidovudine monotherapy reduces transmission of infection to the neonate. However, combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother. Combination antiretroviral therapy may be associated with a greater risk of preterm delivery.

Breast-feeding Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

Children HIV disease in children has a different natural progression to adults. Children infected with HIV should be managed within a formal paediatric HIV clinical network by specialists with access to guidelines and information on antiretroviral drugs for children.

Post-exposure prophylaxis Prophylaxis with antiretroviral drugs [unlicensed indication] may be appropriate following exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer's Expert Advisory Group on AIDS, www.dh.gov.uk) and local ones may also be available. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Prompt prophylaxis with antiretroviral drugs [unlicensed indication] is also appropriate following potential sexual exposure to HIV; recommendations have been developed by the British Association for Sexual Health and HIV, www.bashh.org

Drugs for HIV infection **Zidovudine**, a nucleoside reverse transcriptase inhibitor (or 'nucleoside analogue'), was the first anti-HIV drug to be introduced.

Other nucleoside reverse transcriptase inhibitors include **abacavir**, **didanosine**, **emtricitabine**, **lamivudine**, **stavudine**, and **tenofovir**.

The protease inhibitors include **atazanavir**, **darunavir**, **fosamprenavir** (a pro-drug of amprenavir), **indinavir**, **lopinavir**, **nelfinavir**, **ritonavir**, **saquinavir**, and **tipranavir**. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. A combination of lopinavir with low-dose ritonavir is available. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below).

The non-nucleoside reverse transcriptase inhibitors **efavirenz**, **etravirine**, and **nevirapine** are active against the subtype HIV-1 but not HIV-2, a subtype that is rare in the UK. These drugs may interact with a number of drugs metabolised in the liver. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz. CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz has also been associated with an increased plasma cholesterol concentration. Etravirine is used in regimens containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide, which inhibits the fusion of HIV to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.

Maraviroc is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV. The *Scottish Medicines Consortium* (p. 4) has advised (March 2008) that maraviroc (*Celsentri*®) is **not** recommended for use within NHS Scotland.

Raltegravir is an inhibitor of HIV integrase. It is licensed for the treatment of HIV infection in combination with other antiretroviral drugs. The *Scottish Medicines Consortium* (p. 4) has advised (April 2010) that raltegravir (*Isentress*®) is accepted for restricted use within NHS Scotland for the treatment of HIV infection when non-nucleoside reverse transcriptase inhibitors or protease inhibitors cannot be used because of intolerance, drug interactions, or resistance.

Immune reconstitution syndrome Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms.

Lipodystrophy syndrome Metabolic effects associated with antiretroviral treatment include *fat redistribution*, *insulin resistance*, and *dyslipidaemia*; collectively these have been termed *lipodystrophy syndrome*. The usual risk factors for cardiovascular disease should be taken into account before starting antiretroviral therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk. Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then annually.

Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, 'buffalo hump' and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors. Stavudine (especially in combination with didanosine), and to a lesser extent zidovudine, are associated with a higher risk of lipoatrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia is associated with antiretroviral treatment, particularly with protease inhibitors. Protease inhibitors and some nucleoside reverse transcriptase inhibitors are associated with insulin resistance and hyperglycaemia. Of the protease inhibitors, atazanavir and darunavir may be less likely to cause dyslipidaemia, while saquinavir and atazanavir may be less likely to impair glucose tolerance.

Osteonecrosis Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

Nucleoside reverse transcriptase inhibitors

Cautions

Lactic acidosis Life-threatening lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with nucleoside reverse transcriptase inhibitors. They should be used with caution in patients (particularly obese women) with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver-enzyme abnormalities and with other risk factors for liver disease and hepatic steatosis (including alcohol abuse). Treatment with the nucleoside reverse transcriptase inhibitor should be **discontinued** in case of symptomatic hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function. Stavudine, especially with didanosine, is associated with a higher risk of lactic acidosis and should be used only if alternative regimens are not suitable.

Hepatic impairment Nucleoside reverse transcriptase inhibitors should be used with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects); see also Lactic acidosis above.

Pregnancy see p. 381

Breast-feeding see p. 381

Side-effects Side-effects of the nucleoside reverse transcriptase inhibitors include gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea), anorexia, pancreatitis, liver damage (see also Lactic Acidosis, above), dyspnoea, cough, headache, insomnia, dizziness, fatigue, blood disorders (including anaemia, neutropenia, and thrombocytopenia), myalgia, arthralgia, rash, urticaria, and fever. See notes above for metabolic effects and lipodystrophy (Lipodystrophy Syndrome), and Osteonecrosis.

ABACAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also test for HLA-B*5701 allele before treatment or if restarting treatment and HLA-B*5701 status not known—increased risk of hypersensitivity reaction in presence of HLA-B*5701 allele; HIV load greater than 100 000 copies/mL; patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%); **interactions:** Appendix 1 (abacavir)

Hypersensitivity reactions Life-threatening hypersensitivity reactions reported—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia; less frequently mouth ulceration, oedema, hypotension, sore throat, acute respiratory distress syndrome, anaphylaxis, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and renal failure; rarely myolysis; laboratory abnormalities may include raised liver function tests (see Lactic Acidosis p. 382) and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks for 2 months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity

Counselling Patients should be told the importance of regular dosing (intermittent therapy may increase the risk of sensitisation), how to recognise signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment; patients should be advised to keep Alert Card with them at all times

Hepatic impairment see notes above; also avoid in moderate impairment unless essential; avoid in severe impairment

Renal impairment manufacturer advises avoid in end-stage renal disease; avoid *Kivexa*® or *Trizivir*® if eGFR less than 50 mL/minute/1.73 m^2 (consult product literature)

Pregnancy manufacturer advises avoid (toxicity in *animal* studies); see also p. 381

Breast-feeding see p. 381

Side-effects see notes above; also hypersensitivity reactions (see above); *very rarely* Stevens-Johnson syndrome and toxic epidermal necrolysis; rash and gastro-intestinal disturbances more common in children

Dose

- 600 mg daily in 1–2 divided doses; CHILD 3 months–12 years, 8 mg/kg every 12 hours (max. 600 mg daily) *or* body-weight 14–21 kg, 150 mg every 12 hours; body-weight 21–30 kg, 150 mg in the morning and 300 mg in the evening; body-weight over 30 kg, 300 mg every 12 hours

Ziagen® (ViiV) PoM

Tablets, yellow, f/c, scored, abacavir (as sulphate) 300 mg, net price 60-tab pack = £208.95. Counselling, hypersensitivity reactions

Oral solution, sugar-free, banana and strawberry flavoured, abacavir (as sulphate) 20 mg/mL, net price 240-mL = £55.72. Counselling, hypersensitivity reactions

With lamivudine

For **cautions**, **contra-indications** and **side-effects** see under individual drugs

Kivexa® (ViiV) PoM

Tablets, orange, f/c, abacavir (as sulphate) 600 mg, lamivudine 300 mg, net price 30-tab pack = £352.25. Counselling, hypersensitivity reactions

Dose ADULT and CHILD over 12 years, body-weight over 40 kg, 1 tablet once daily

With lamivudine and zidovudine

Note For patients stabilised (for 6–8 weeks) on the individual components in the same proportions. For **cautions**, **contra-indications** and **side-effects** see under individual drugs

Trizivir® (ViiV) PoM

Tablets, blue-green, f/c, abacavir (as sulphate) 300 mg, lamivudine 150 mg, zidovudine 300 mg, net price 60-tab pack = £509.06. Counselling, hypersensitivity reactions

Dose ADULT over 18 years, 1 tablet twice daily

DIDANOSINE

(ddI, DDI)

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Side-effects); ophthalmological examination (including visual acuity, colour vision, and dilated fundus examination) recommended annually or if visual changes occur; **interactions:** Appendix 1 (didanosine)

Pancreatitis Suspend treatment if serum lipase raised (even if asymptomatic) or if symptoms of pancreatitis develop; discontinue if pancreatitis confirmed. Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated

Hepatic impairment see notes above; also insufficient information but monitor for toxicity

Renal impairment reduce dose if eGFR less than 60 mL/minute/1.73 m^2; consult product literature

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; also pancreatitis (see also under Cautions), liver failure, anaphylactic reactions, peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), diabetes mellitus, hypoglycaemia, acute renal failure, rhabdomyolysis, dry eyes, retinal and optic nerve changes, dry mouth, parotid gland enlargement, sialadenitis, alopecia, hyperuricaemia (suspend if raised significantly)

Dose

- ADULT under 60 kg 250 mg daily in 1–2 divided doses, 60 kg and over 400 mg daily in 1–2 divided doses; CHILD over 3 months (under 6 years *Videx*® tablets only), 240 mg/m^2 daily (180 mg/m^2 daily in combination with zidovudine) in 1–2 divided doses

Videx® (Bristol-Myers Squibb) PoM

Tablets, with calcium and magnesium antacids, didanosine 25 mg, net price 60-tab pack = £25.06. Label: 23, counselling, administration, see below

Excipients include aspartame equivalent to phenylalanine 36.5 mg per tablet (section 9.4.1)

Note Antacids in formulation may affect absorption of other drugs—see **interactions:** Appendix 1 (antacids)

Counselling To ensure sufficient antacid, each dose to be taken as at least 2 tablets (CHILD under 1 year 1 tablet) chewed thoroughly, crushed or dispersed in water; clear apple juice may be added for flavouring; tablets to be taken 2 hours after lopinavir with ritonavir capsules and oral solution or atazanavir with ritonavir

Videx® EC capsules, enclosing e/c granules, didanosine 125 mg, net price 30-cap pack = £48.18; 200 mg, 30-cap pack = £77.09; 250 mg, 30-cap pack = £96.37; 400 mg, 30-cap pack = £154.19. Label: 25, counselling, administration, see below

Counselling Capsules to be taken at least 2 hours before or 2 hours after food

EMTRICITABINE
(FTC)

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); **interactions:** Appendix 1 (emtricitabine)

Hepatic impairment see notes above and Cautions above

Renal impairment reduce dose if eGFR less than 50 mL/minute/1.73 m^2; consult product literature

Pregnancy no information available—manufacturer advises use only if essential

Breast-feeding see p. 381

Side-effects see notes above; also abnormal dreams, pruritus, and hyperpigmentation

Dose

- See preparations

Emtriva® (Gilead) PoM

Capsules, white/blue, emtricitabine 200 mg, net price 30-cap pack = £163.50

Dose ADULT and CHILD body-weight over 33 kg, 200 mg once daily

Oral solution, orange, emtricitabine 10 mg/mL, net price 170-mL pack (candy-flavoured) = £46.50

Dose ADULT and CHILD body-weight over 33 kg, 240 mg once daily; CHILD 4 months–18 years, body-weight under 33 kg, 6 mg/kg once daily

Electrolytes Na^+ 460 micromol/mL

Note 240 mg oral solution ≡ 200 mg capsule; where appropriate the capsule may be used instead of the oral solution

With tenofovir

See under Tenofovir

With efavirenz and tenofovir

See under Tenofovir

LAMIVUDINE
(3TC)

Indications see preparations below

Cautions see notes above; **interactions:** Appendix 1 (lamivudine)

Chronic Hepatitis B Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine. When treating chronic hepatitis B with lamivudine, monitor liver function tests every 3 months, and viral and serological markers of hepatitis B every 3–6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue for at least 1 year after discontinuation)

Hepatic impairment see notes above and Cautions above

Renal impairment reduce dose if eGFR less than 50 mL/minute/1.73 m^2; consult product literature

Pregnancy see p. 381

Breast-feeding can be used with caution in women infected with chronic hepatitis B alone, providing adequate measures are taken to prevent hepatitis B infection in infants; for women infected with HIV, see p. 381

Side-effects see notes above; also peripheral neuropathy, muscle disorders including rhabdomyolysis, nasal symptoms, alopecia

Dose

- See preparations below

Epivir® (ViiV) PoM

Tablets, f/c, lamivudine 150 mg (scored, white), net price 60-tab pack = £143.32; 300 mg (grey), 30-tab pack = £157.51

Oral solution, banana- and strawberry-flavoured, lamivudine 50 mg/5 mL, net price 240-mL pack = £39.01

Excipients include sucrose 1 g/5 mL

Dose HIV infection in combination with other antiretroviral drugs, 150 mg every 12 hours *or* 300 mg once daily; CHILD 3 months–12 years, 4 mg/kg (max. 150 mg) every 12 hours *or* body-weight 14–21 kg, 75 mg twice daily; body-weight 21–30 kg, 75 mg in the morning and 150 mg in the evening; body-weight over 30 kg, 150 mg twice daily

Zeffix® (ViiV) PoM

Tablets, brown, f/c, lamivudine 100 mg, net price 28-tab pack = £78.09

Oral solution, banana and strawberry flavoured, lamivudine 25 mg/5 mL, net price 240-mL pack = £22.79

Excipients include sucrose 1 g/5 mL

Dose chronic hepatitis B infection *either* with compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis) when first-line treatments cannot be used, *or* (in combination with another antiviral drug without cross-resistance to lamivudine) with decompensated liver disease, 100 mg daily; CHILD [unlicensed indication] 2–11 years, 3 mg/kg once daily (max. 100 mg daily); 12–17 years, adult dose

Note Patients receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection

With abacavir

See under Abacavir

With zidovudine

See under Zidovudine

With abacavir and zidovudine

See under Abacavir

STAVUDINE
(d4T)

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also history of peripheral neuropathy (see under Side-effects); history of pan-

creatitis or concomitant use with other drugs associated with pancreatitis; **interactions:** Appendix 1 (stavudine)

Hepatic impairment see notes above

Renal impairment use half normal dose every 12 hours if eGFR 25–50 mL/minute/1.73 m^2; use half normal dose every 24 hours if eGFR less than 25 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; also peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), abnormal dreams, cognitive dysfunction, drowsiness, depression, pruritus; *less commonly* anxiety, gynaecomastia

Dose

- ADULT under 60 kg, 30 mg every 12 hours preferably at least 1 hour before food; 60 kg and over, 40 mg every 12 hours; NEONATE under 2 weeks, 500 micrograms/kg every 12 hours; CHILD over 2 weeks, body-weight under 30 kg, 1 mg/kg every 12 hours; body-weight 30 kg and over, adult dose

Zerit® (Bristol-Myers Squibb) PoM

Capsules, stavudine 20 mg (brown), net price 56-cap pack = £139.46; 30 mg (light orange/dark orange), 56-cap pack = £146.25; 40 mg (dark orange), 56-cap pack = £150.66 (all hosp. only)

Oral solution, cherry-flavoured, stavudine for reconstitution with water, 1 mg/mL, net price 200 mL = £22.94

TENOFOVIR DISOPROXIL

Indications HIV infection in combination with other antiretroviral drugs; chronic hepatitis B infection with *either* compensated liver disease (with evidence of viral replication, and histologically documented active liver inflammation or fibrosis) *or* decompensated liver disease

Cautions see notes above; also test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases; concomitant or recent use of nephrotoxic drugs; on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); **interactions:** Appendix 1 (tenofovir)

Hepatic impairment see notes above and Cautions above

Renal impairment monitor renal function—interrupt treatment if further deterioration; 245 mg every 2 days if eGFR 30–50 mL/minute/1.73 m^2; 245 mg every 3–4 days if eGFR 10–30 mL/minute/1.73 m^2; avoid *Atripla®* if eGFR less than 50 mL/minute/1.73 m^2; use normal dose of *Truvuda®* every 2 days if eGFR 30–50 mL/minute/1.73 m^2; avoid *Truvada®* if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy no information available—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; hypophosphataemia; *rarely* renal failure, proximal renal tubulopathy, nephrogenic diabetes insipidus; also reported reduced bone density

Dose

- ADULT over 18 years, 245 mg once daily

Viread® (Gilead) ▼ PoM

Tablets, f/c, blue, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £255.00. Label: 21, counselling, administration

Counselling Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

With emtricitabine

For **cautions**, **contra-indications**, and **side-effects** see under individual drugs

Truvada® (Gilead) PoM

Tablets, blue, f/c, tenofovir disoproxil (as fumarate) 245 mg, emtricitabine 200 mg, net price 30-tab pack = £418.50. Label: 21, counselling, administration

Counselling Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

Dose HIV infection in combination with other antiretroviral drugs, ADULT over 18 years, 1 tablet once daily

With efavirenz and emtricitabine

For **cautions**, **contra-indications**, and **side-effects** see under individual drugs

Atripla® (Gilead) PoM

Tablets, pink, f/c, efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £626.90. Label: 23, 25

Dose HIV infection stabilised on antiretroviral therapy for more than 3 months, ADULT over 18 years, 1 tablet once daily

ZIDOVUDINE

(Azidothymidine, AZT)

Note The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug

Indications HIV infection in combination with other antiretroviral drugs; prevention of maternal-fetal HIV transmission (see notes above under Pregnancy and Breast-feeding)

Cautions see notes above; also haematological toxicity particularly with high dose and advanced disease—monitor full blood count after 4 weeks of treatment, then every 3 months; vitamin B_{12} deficiency (increased risk of neutropenia); if anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment; elderly; **interactions:** Appendix 1 (zidovudine)

Contra-indications abnormally low neutrophil counts or haemoglobin concentration (consult product literature); neonates with hyperbilirubinaemia requiring treatment other than phototherapy, or with raised transaminase (consult product literature); acute porphyria (section 9.8.2)

Hepatic impairment see notes above; also accumulation may occur

Renal impairment reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if eGFR is less than 10 mL/minute/1.73 m^2; avoid *Combivir®* if eGFR less than 50 mL/minute/1.73m^2 (consult product literature)

Pregnancy limited information available; manufacturer advises use only if clearly indicated; see also p. 381

Breast-feeding see p. 381

Side-effects see notes above; also anaemia (may require transfusion), taste disturbance, chest pain, influenza-like symptoms, paraesthesia, neuropathy, convulsions, dizziness, drowsiness, anxiety, depression, loss of mental acuity, myopathy, gynaecomastia, urinary frequency, sweating, pruritus, pigmentation of nails, skin and oral mucosa

Dose

- By mouth, ADULT and CHILD body-weight over 30 kg, 250–300 mg twice daily; CHILD body-weight 4–9 kg, 12 mg/kg twice daily; body-weight 9–30 kg, 9 mg/kg twice daily *or* body-weight 8–14 kg, 100 mg twice daily; body-weight 14–21 kg, 100 mg in the morning and 200 mg in the evening; body-weight 21–28 kg, 200 mg twice daily; body-weight 28–30 kg, 200–250 mg twice daily
- Prevention of maternal-fetal HIV transmission, seek specialist advice (combination therapy preferred)
- Patients temporarily unable to take zidovudine by mouth, by intravenous infusion over 1 hour, 0.8–1 mg/kg every 4 hours (approximating to 1.2–1.5 mg/kg every 4 hours by mouth) usually for not more than 2 weeks; CHILD 3 months–12 years, 60–80 mg/m^2 every 6 hours (approximating to 9–12 mg/kg twice daily by mouth)

Zidovudine (Non-proprietary) PoM

Capsules, zidovudine 100 mg, net price 60-cap pack = £50.17; 250 mg, 60-cap pack = £125.44

Retrovir® (ViiV) PoM

Capsules, zidovudine 100 mg (white/blue band), net price 100-cap pack = £104.54; 250 mg (blue/white/dark blue band), 40-cap pack = £104.54

Oral solution, sugar-free, strawberry-flavoured, zidovudine 50 mg/5 mL, net price 200-mL pack with 10-mL oral syringe = £20.91

Injection, zidovudine 10 mg/mL. For dilution and use as an intravenous infusion. Net price 20-mL vial = £10.50

With lamivudine

For **cautions**, **contra-indications**, and **side-effects** see under individual drugs

Combivir® (ViiV) PoM

Tablets, f/c, scored, zidovudine 300 mg, lamivudine 150 mg, net price 60-tab pack = £300.12

Dose ADULT and CHILD body-weight over 30 kg, 1 tablet twice daily; CHILD body-weight 14–21 kg, half a tablet twice daily; body-weight 21–30 kg, half a tablet in the morning and one tablet in the evening

Note Tablets may be crushed and mixed with semi-solid food or liquid just before administration

With abacavir and lamivudine

See under Abacavir

Protease inhibitors

Cautions Protease inhibitors are associated with hyperglycaemia and should be used with caution in diabetes (see Lipodystrophy Syndrome, p. 382). Caution is also needed in patients with haemophilia who may be at increased risk of bleeding.

Contra-indications Protease inhibitors should not be given to patients with acute porphyria (but see section 9.8.2).

Hepatic impairment Protease inhibitors should be used with caution in patients with chronic hepatitis B or C (increased risk of hepatic side-effects)

Pregnancy See p. 381

Breast-feeding See p. 381

Side-effects Side-effects of the protease inhibitors include gastro-intestinal disturbances (including diarrhoea, nausea, vomiting, abdominal pain, flatulence), anorexia, hepatic dysfunction, pancreatitis; blood disorders including anaemia, neutropenia, and thrombocytopenia; sleep disturbances, fatigue, headache, dizziness, paraesthesia, myalgia, myositis, rhabdomyolysis; taste disturbances; rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis; see also notes above for lipodystrophy and metabolic effects (Lipodystrophy Syndrome), and Osteonecrosis.

ATAZANAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also concomitant use with drugs that prolong PR interval; cardiac conduction disorders; predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); **interactions:** Appendix 1 (atazanavir)

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild impairment; avoid in moderate to severe impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia in neonate if used as term

Breast-feeding see p. 381

Side-effects see notes above; also AV block (in children); *less commonly* mouth ulcers, dry mouth, hypertension, syncope, chest pain, dyspnoea, peripheral neuropathy, abnormal dreams, amnesia, disorientation, depression, anxiety, weight changes, increased appetite, gynaecomastia, nephrolithiasis, urinary frequency, haematuria, proteinuria, arthralgia, and alopecia; *rarely* hepatosplenomegaly, oedema, palpitation, and abnormal gait; also reported, cholelithiasis, cholecystitis, and torsade de pointes

Dose

- With low-dose ritonavir, 300 mg once daily; CHILD over 6 years, body-weight 15–20 kg, 150 mg once daily; body-weight 20–40 kg, 200 mg once daily; body-weight over 40 kg, adult dose

Reyataz® (Bristol-Myers Squibb) ▼ PoM

Capsules, atazanavir (as sulphate) 150 mg (dark blue/light blue), net price 60-cap pack = £303.38; 200 mg (dark blue), 60-cap pack = £303.38; 300 mg (red/blue), 30-cap pack = £303.38. Label: 5, 21

DARUNAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also sulfonamide sensitivity; monitor liver function before and during treatment; **interactions:** Appendix 1 (darunavir)

Rash Mild to moderate rash occurs commonly, usually within the first 4 weeks of therapy and resolves without

stopping treatment. Severe skin rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) occurs less frequently and may be accompanied by fever, malaise, arthralgia, myalgia, oral lesions, conjunctivitis, hepatitis, or eosinophilia; treatment should be stopped if severe rash develops

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild to moderate impairment; avoid in severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding see p. 381

Side-effects see notes above; also haematemesis, myocardial infarction, angina, QT interval prolongation, syncope, bradycardia, tachycardia, palpitation, hypertension, flushing, peripheral oedema, dyspnoea, cough, peripheral neuropathy, anxiety, confusion, memory impairment, depression, abnormal dreams, convulsions, increased appetite, weight changes, pyrexia, hypothyroidism, osteoporosis, gynaecomastia, erectile dysfunction, reduced libido, dysuria, polyuria, nephrolithiasis, renal failure, arthralgia, visual disturbances, dry eyes, conjunctival hyperaemia, rhinorrheoa, throat irritation, dry mouth, stomatisis, nail discoloration, acne, seborrhoeic dermatitis, eczema, increased sweating, alopecia

Dose

- With low-dose ritonavir, ADULT and CHILD over 6 years, body-weight over 40 kg, previously treated with antiretroviral therapy, 600 mg twice daily; CHILD over 6 years, previously treated with antiretroviral therapy, body-weight 20–30 kg, 375 mg twice daily; body-weight 30–40 kg, 450 mg twice daily
- With low-dose ritonavir, ADULT over 18 years not previously treated with antiretroviral therapy, 800 mg once daily

Missed dose If a dose is more than 6 hours late on the twice daily regimen (or more than 12 hours late on the once daily regimen), the missed dose should not be taken and the next dose should be taken at the normal time

Prezista® (Janssen-Cilag) ▼ PoM

Tablets, f/c, darunavir (as ethanolate) 75 mg (white), net price 480-tab pack = £446.70; 150 mg (white), 240-tab pack = £446.70; 400 mg (light orange), 60-tab pack = £297.80; 600 mg (orange), 60-tab pack = £446.70. Label: 21

FOSAMPRENAVIR

Note Fosamprenavir is a pro-drug of amprenavir

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; **interactions:** Appendix 1 (fosamprenavir)

Rash Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—usually resolves within 2 weeks and may respond to antihistamines

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild impairment; reduce dose to 450 mg twice daily in moderate impairment; reduce dose to 300 mg twice daily in severe impairment

Pregnancy toxicity in *animal* studies; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; also reported, rash including rarely Stevens-Johnson syndrome (see also Rash above)

Dose

- With low-dose ritonavir, ADULT and CHILD over 6 years, body-weight over 39 kg, 700 mg twice daily; CHILD over 6 years, body-weight 25–39 kg, 18 mg/kg twice daily

Note 700 mg fosamprenavir is equivalent to approx. 600 mg amprenavir

Telzir® (ViiV) PoM

Tablets, f/c, pink, fosamprenavir (as calcium) 700 mg, net price 60-tab pack = £258.97

Oral suspension, fosamprenavir (as calcium) 50 mg/mL, net price 225-mL pack (grape-bubblegum-and peppermint-flavoured) (with 10-mL oral syringe) = £69.06. Counselling, administration

Counselling In adults, oral suspension should be taken on an empty stomach; in children under 18 years, oral suspension should be taken with food

INDINAVIR

Indications HIV infection in combination with nucleoside reverse transcriptase inhibitors

Cautions see notes above; also ensure adequate hydration (risk of nephrolithiasis especially in children); patients at risk of nephrolithiasis (monitor for nephrolithiasis); patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%); **interactions:** Appendix 1 (indinavir)

Contra-indications see notes above

Hepatic impairment see notes above; also increased risk of nephrolithiasis; reduce dose in mild to moderate impairment; not studied in severe impairment

Renal impairment use with caution; monitor for nephrolithiasis

Pregnancy toxicity in *animal* studies; manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia and renal stones in neonate if used at term

Breast-feeding see p. 381

Side-effects see notes above; also reported, dry mouth, hypoaesthesia, dry skin, hyperpigmentation, alopecia, paronychia, interstitial nephritis (with medullary calcification and cortical atrophy in asymptomatic severe leucocyturia), nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children), pyelonephritis; haemolytic anaemia

Dose

- ADULT over 18 years, seek specialist advice

Crixivan® (MSD) PoM

Capsules, indinavir (as sulphate), 200 mg, net price 360-cap pack = £226.28; 400 mg, 180-cap pack = £226.28. Label: 27, counselling, administration

Counselling Administer 1 hour before or 2 hours after a meal; may be administered with a low-fat light meal; in combination with didanosine tablets, allow 1 hour between each drug (antacids in didanosine tablets reduce absorption of indinavir); in combination with low-dose ritonavir, give with food

Note Dispense in original container (contains desiccant)

LOPINAVIR WITH RITONAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; concomitant use with drugs that prolong QT or PR interval; cardiac conduction disorders, structural heart disease; patients at high risk of cardiovascular disease (especially if 10-year cardiovascular risk greater than 20%); pancreatitis (see below); **interactions:** Appendix 1 (lopinavir, ritonavir)

Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

Contra-indications see notes above

Hepatic impairment see notes above; also avoid oral solution due to propylene glycol content; manufacturer advises avoid capsules and tablets in severe impairment

Renal impairment avoid oral solution due to propylene glycol content; use tablets with caution in severe impairment

Pregnancy avoid oral solution due to high propylene glycol content; manufacturer advises use capsules and tablets only if potential benefit outweighs risk (toxicity in *animal* studies)

Breast-feeding see p. 381

Side-effects see notes above; also electrolyte disturbances in children; *less commonly* haemorrhagic colitis, weight changes, chest pain, oedema, anxiety, depression, abnormal dreams, peripheral neuropathy, pyrexia, Cushing's syndrome, sexual dysfunction, dehydration, arthralgia, tinnitus, dry mouth, acne, alopecia, and sweating; *rarely* cholecystitis, gastric ulcer, rectal bleeding, myocardial infarction, hypertension, palpitation, AV block, deep vein thrombosis, thromobophlebitis, vasculitis, dyspnoea, cough, appetite changes, agitation, confusion, amnesia, ataxia, hypertonia, extrapyramidal effects, influenza-like symptoms, hypothyroidism, amenorrhoea, menorrhagia, gynaecomastia, nephrolithiasis, nephritis, albuminuria, haematuria, hypercalciuria, hypophosphataemia, lactic acidosis, hyperuricaemia, visual disturbances, otitis media, dysphagia, mouth ulceration, stomatitis, periodontitis, sialadenitis, eczema, skin discoloration, and nail disorders

Dose

- See preparations below

Kaletra® (Abbott) PoM

Tablets, pale yellow, f/c, lopinavir 100 mg, ritonavir 25 mg, net price 60-tab pack = £76.85. Label: 25

Dose CHILD over 2 years with body-weight under 40 kg and body surface area 0.5–0.9 m^2, 2 tablets twice daily; body surface area 0.9–1.4 m^2, 3 tablets twice daily

Tablets, yellow, f/c, lopinavir 200 mg, ritonavir 50 mg, net price 120-tab pack = £307.39. Label: 25

Dose ADULT and CHILD with body surface area greater than 1.4 m^2 or body-weight 40 kg and over, 2 tablets twice daily

Note Alternatively, in adults with a HIV strain that has less than 3 mutations to protease inhibitors, 4 tablets may be taken once daily

Oral solution, lopinavir 400 mg, ritonavir 100 mg/5 mL, net price 5×60-mL packs = £307.39. Label: 21

Excipients include propylene glycol 153 mg/mL (see Excipients, p. 2), alcohol 42%

Dose 5 mL twice daily with food; CHILD 2–12 years 2.9 mL/m^2 twice daily with food, max. 5 mL twice daily

NELFINAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; **interactions:** Appendix 1 (nelfinavir)

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy no information available—manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; also reported, fever

Dose

- 1.25 g twice daily *or* 750 mg 3 times daily; CHILD 3–13 years, initially 50–55 mg/kg twice daily (max. 1.25 g twice daily) *or* 25–30 mg/kg 3 times daily (max. 750 mg 3 times daily)

Viracept® (Roche) PoM

Tablets, blue, f/c, nelfinavir (as mesilate) 250 mg, net price 300-tab pack = £257.32. Label: 21

RITONAVIR

Indications HIV infection in combination with other antiretroviral drugs; low doses used to increase effect of some protease inhibitors

Cautions see notes above; concomitant use with drugs that prolong PR interval; cardiac conduction disorders, structural heart disease; pancreatitis (see below); **interactions:** Appendix 1 (ritonavir)

Pancreatitis Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

Contra-indications see notes above

Hepatic impairment see notes above; also avoid in decompensated liver disease; in severe impairment without decompensation, use 'booster' doses with caution (avoid treatment doses)

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Breast-feeding see p. 381

Side-effects see notes and Cautions above; also diarrhoea (may impair absorption—close monitoring required), vasodilatation, cough, throat irritation, anxiety, perioral and peripheral paraesthesia, hyperaesthesia, fever, decreased blood thyroxine concentration, electrolyte disturbances, raised uric acid, dry mouth, mouth ulcers, and sweating; *less commonly* increased prothrombin time and dehydration; syncope, postural hypotension, seizures, menorrhagia, and renal failure also reported

Dose

- Initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days to 600 mg every 12 hours; CHILD over 2 years initially 250 mg/m^2 every 12 hours, increased by 50 mg/m^2 at intervals of 2–3 days to 350 mg/m^2 every 12 hours (max. 600 mg every 12 hours)
- Low-dose booster to increase effect of other protease inhibitors, 100–200 mg once or twice daily

Norvir® (Abbott) PoM

Tablets, f/c, ritonavir 100 mg, net price 30-tab pack = £33.70. Label: 21, 25

Oral solution, sugar-free, ritonavir 400 mg/5 mL, net price 5 × 90-mL packs (with measuring cup) = £403.20. Label: 21, counselling, administration

Counselling Oral solution contains 43% alcohol; bitter taste can be masked by mixing with chocolate milk; do not mix with water, measuring cup must be dry

With lopinavir

See under Lopinavir with Ritonavir

SAQUINAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; monitor ECG before starting treatment and then on day 3 or 4 of treatment—discontinue if QT interval over 480 milliseconds, if QT interval more than 20 milliseconds above baseline, or if prolongation of PR interval; concomitant use of garlic (avoid garlic capsules—reduces plasma-saquinavir concentration); **interactions:** Appendix 1 (saquinavir)

Counselling Patients should be told how to recognise signs of arrhythmia and advised to seek medical attention if symptoms such as palpitation or syncope develop

Contra-indications see notes above; predisposition to cardiac arrhythmias (including congenital QT prolongation, bradycardia, history of symptomatic arrhythmias, heart failure with reduced left ventricular ejection fraction, electrolyte disturbances, concomitant use of drugs that prolong QT or PR interval); concomitant use of drugs that increase plasma-saquinavir concentration (avoid unless no alternative treatment available)

Hepatic impairment see notes above; also manufacturer advises caution in moderate impairment; avoid in decompensated liver disease

Renal impairment use with caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects see notes above; also dyspnoea, increased appetite, peripheral neuropathy, convulsions, changes in libido, renal impairment, dry mouth, and alopecia

Dose

- With low-dose ritonavir, ADULT and ADOLESCENT over 16 years previously treated with antiretroviral therapy, 1 g every 12 hours
- With low-dose ritonavir, ADULT and ADOLESCENT over 16 years not previously treated with antiretroviral therapy, 500 mg every 12 hours for 7 days then 1 g every 12 hours

Invirase® (Roche) PoM

Capsules, brown/green, saquinavir (as mesilate) 200 mg, net price 270-cap pack = £226.14. Label: 21, counselling, arrhythmias

Tablets, orange, f/c, saquinavir (as mesilate) 500 mg, net price 120-tab pack = £251.26. Label: 21, counselling, arrhythmias

TIPRANAVIR

Indications HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

Cautions see notes above; also patients at risk of increased bleeding from trauma, surgery or other pathological conditions; concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (tipranavir)

Hepatotoxicity Potentially life-threatening hepatotoxicity reported; monitor liver function before treatment then every 2 weeks for 1 month, then every 3 months. Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature)

Contra-indications see notes above

Hepatic impairment see notes above; also manufacturer advises caution in mild impairment; avoid in moderate or severe impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in *animal* studies

Breast-feeding see p. 381

Side-effects see notes above; also dyspnoea, anorexia, peripheral neuropathy, influenza-like symptoms, renal impairment and photosensitivity; *rarely* dehydration

Dose

- See preparations

Aptivus® (Boehringer Ingelheim) ▼ PoM

Capsules, pink, tipranavir 250 mg, net price 120–cap pack = £441.00. Label: 5, 21

Excipients include ethanol 100 mg per capsule

Dose with low-dose ritonavir, ADULT and CHILD over 12 years, 500 mg twice daily

Oral Solution, toffee-and mint-flavoured, tipranavir 100 mg/mL, net price 95–mL pack = £129.65. Label: 5, 21, counselling, crystallisation

Excipients include vitamin E 78 mg/mL

Dose with low-dose ritonavir, CHILD 2–12 years, 375 mg/m^2 twice daily

Note The bioavailability of *Aptivus®* oral solution is higher than that of the capsules; the oral solution is **not** interchangeable with the capsules on a milligram-for-milligram basis

Counselling Patients should be told to observe the oral solution for crystallisation; the bottle should be replaced if more than a thin layer of crystals form (doses should continue to be taken at the normal time until the bottle is replaced)

Non-nucleoside reverse transcriptase inhibitors

EFAVIRENZ

Indications HIV infection in combination with other antiretroviral drugs

Cautions elderly; history of mental illness or seizures; monitor liver function if receiving other hepatotoxic drugs; **interactions:** Appendix 1 (efavirenz)

Rash Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—usually resolves within 1 month

Psychiatric disorders Patients or their carers should be advised to seek immediate medical attention if symptoms such as severe depression, psychosis or suicidal ideation occur

Contra-indications acute porphyria (but see section 9.8.2)

Hepatic impairment in mild liver disease, monitor for dose related side-effects (e.g. CNS effects) and monitor liver function; avoid in moderate to severe impairment; greater risk of hepatic side-effects in chronic hepatitis B or C

Renal impairment manufacturer advises caution in severe renal failure—no information available

Pregnancy manufacturer advises avoid (effective contraception required during treatment and for 12 weeks after treatment); use efavirenz only if no alternative available

Breast-feeding see p. 381

Side-effects rash including Stevens-Johnson syndrome (see Rash above); abdominal pain, diarrhoea, nausea, vomiting; anxiety, depression, sleep disturbances, abnormal dreams, dizziness, headache, fatigue, impaired concentration (administration at bedtime especially in first 2–4 weeks reduces CNS effects); pruritus; *less commonly* pancreatitis, hepatitis, flushing, psychosis, mania, suicidal ideation, amnesia, ataxia, tremor, convulsions, gynaecomastia, blurred vision, tinnitus; *rarely* hepatic failure, photosensitivity; also reported raised serum cholesterol (see Lipodystrophy Syndrome, p. 382); see also Osteonecrosis, p. 382

Dose

- See preparations below

Sustiva® (Bristol-Myers Squibb) PoM

Capsules, efavirenz 50 mg (yellow/white), net price 30-cap pack = £16.73; 100 mg (white), 30-cap pack = £33.41; 200 mg (yellow), 90-cap pack = £200.27. Label: 23

Dose ADULT and CHILD over 3 years, body-weight 13–15 kg, 200 mg once daily; body-weight 15–20 kg, 250 mg once daily; body-weight 20–25 kg, 300 mg once daily; body-weight 25–32.5 kg, 350 mg once daily; body-weight 32.5–40 kg, 400 mg once daily; body-weight 40 kg and over, 600 mg once daily

Tablets, f/c, yellow, efavirenz 600 mg, net price 30-tab pack = £200.27. Label: 23

Dose ADULT and CHILD, body-weight over 40 kg, 600 mg once daily

Oral solution, sugar-free, strawberry and mint flavour, efavirenz 30 mg/mL, net price 180-mL pack = £53.84

Dose ADULT and CHILD over 5 years, body-weight 13–15 kg, 270 mg once daily; body-weight 15–20 kg, 300 mg once daily; body-weight 20–25 kg, 360 mg once daily; body-weight 25–32.5 kg, 450 mg once daily; body-weight 32.5–40 kg, 510 mg once daily; body-weight 40 kg and over, 720 mg once daily; CHILD 3–5 years, body-weight 13–15 kg, 360 mg once daily; body-weight 15–20 kg, 390 mg once daily; body-weight 20–25 kg, 450 mg once daily; body-weight 25–32.5 kg, 510 mg once daily

Note The bioavailability of *Sustiva®* oral solution is lower than that of the capsules and tablets; the oral solution is **not** interchangeable with either capsules or tablets on a milligram-for-milligram basis

With emtricitabine and tenofovir

See under Tenofovir

ETRAVIRINE

Indications in combination with other antiretroviral drugs (including a boosted protease inhibitor) for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors

Cautions **interactions:** Appendix 1 (etravirine)

Hypersensitivity reactions Rash, usually in the second week, is the most common side-effect and appears more frequently in women. Life-threatening hypersensitivity reactions reported usually during week 3–6 of treatment and characterised by rash, eosinophilia, and systemic symptoms (including fever, general malaise, myalgia, arthralgia, blistering, oral lesions, conjunctivitis, and hepatitis). Discontinue permanently if hypersensitivity reaction or severe rash develop. If rash mild or moderate (without signs of hypersensitivity reaction), may continue without interruption—usually resolves within 2 weeks

Counselling Patients should be told how to recognise hypersensitivity reactions and advised to seek immediate medical attention if hypersensitivity reaction or severe rash develop

Contra-indications acute porphyria (but see section 9.8.2)

Hepatic impairment manufacturer advises caution in moderate impairment; avoid in severe impairment—no information available; greater risk of hepatic side-effects in chronic hepatitis B or C

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects rash (including Stevens-Johnson syndrome rarely and toxic epidermal necrolysis very rarely; see also Hypersensitivity Reactions above); gastro-oesophageal reflux, nausea, abdominal pain, flatulence, gastritis; myocardial infarction, hypertension; peripheral neuropathy; diabetes, hyperlipidaemia (see also Lipodystrophy Syndrome, p. 382); renal failure; anaemia; *less commonly* pancreatitis, haematemesis, hepatitis, angina, bronchospasm, drowsiness, malaise, gynaecomastia, blurred vision, dry mouth, and sweating; also reported, haemorrhagic stroke and hypersensitivity reactions; see also Osteonecrosis, p. 382

Dose

- ADULT over 18 years, 200 mg twice daily after food

Missed dose If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time

Intelence® (Janssen-Cilag) ▼ PoM

Tablets, etravirine 100 mg, net price 120-tab pack = £301.27. Label: 21, counselling, rash and hypersensitivity reactions

Note Dispense in original container (contains desiccant). Patients with swallowing difficulties may disperse tablets in a glass of water just before administration

NEVIRAPINE

Indications HIV infection in combination with other antiretroviral drugs

Cautions chronic hepatitis B or C, high CD4 cell count, and women (all at greater risk of hepatic side-effects—if plasma HIV-1 RNA detectable, manufacturer advises avoid in women with CD4 cell count greater than 250 cells/mm^3 or in men with CD4 cell count greater than 400 cells/mm^3 unless potential benefit outweighs risk); **interactions:** Appendix 1 (nevirapine)

Hepatic disease Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 6 weeks; close monitoring required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction

Rash Rash, usually in first 6 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased after 14 days; monitor closely for skin reactions during first 18 weeks; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves

Counselling Patients should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions, or symptoms of hepatitis develop

Contra-indications acute porphyria (but see section 9.8.2); post-exposure prophylaxis

Hepatic impairment manufacturer advises caution in moderate impairment; avoid in severe impairment; see also Hepatic Disease, above

Pregnancy although manufacturer advises caution, may be appropriate to use if clearly indicated; see also p. 381

Breast-feeding see p. 381

Side-effects rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also Cautions above); nausea, hepatitis (see also Hepatic Disease above), headache; *less commonly* vomiting, abdominal pain, fatigue, fever, and myalgia; *rarely* diarrhoea, angioedema, anaphylaxis, hypersensitivity reactions (may involve hepatic reactions and rash, see Hepatic Disease above), arthralgia, anaemia, and granulocytopenia (more frequent in children); see also Osteonecrosis, p. 382

Dose

- ADULT and CHILD over 16 years, 200 mg once daily for first 14 days then (if no rash present) 200 mg twice daily; NEONATE and CHILD under 8 years, 150 mg/m^2 (max. 200 mg) once daily for first 14 days, then (if no rash present) 150 mg/m^2 (max. 200 mg) twice daily *or* 4 mg/kg (max. 200 mg) once daily for first 14 days then (if no rash present) 7 mg/kg (max. 200 mg) twice daily; CHILD 8–16 years, 150 mg/m^2 (max. 200 mg) once daily for first 14 days then (if no rash present) 150 mg/m^2 (max. 200 mg) twice daily *or* 4 mg/kg (max. 200 mg) once daily for first 14 days then (if no rash present) 4 mg/kg (max. 200 mg) twice daily
  Note Duration of once daily dose regimen should not exceed 28 days; if rash not resolved within 28 days, alternative treatment should be sought. If treatment interrupted for more than 7 days, restart using the lower dose for the first 14 days as for new treatment

Viramune® (Boehringer Ingelheim) PoM

Tablets, nevirapine 200 mg, net price 14-tab pack = £39.67, 60-tab pack = £170.00. Counselling, hypersensitivity reactions

Suspension, nevirapine 50 mg/5 mL, net price 240-mL pack = £50.40. Counselling, hypersensitivity reactions

Other antiretrovirals

ENFUVIRTIDE

Indications HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens

Cautions

Hypersensitivity reactions Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge

Counselling Patients should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop

Hepatic impairment manufacturer advises caution—no information available; chronic hepatitis B or C (possibly greater risk of hepatic side-effects)

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding see p. 381

Side-effects injection-site reactions; pancreatitis, gastro-oesophageal reflux disease, anorexia, weight loss; hypertriglyceridaemia; peripheral neuropathy, asthenia, tremor, anxiety, nightmares, irritability, impaired concentration, vertigo; pneumonia, sinusitis, influenza-like illness; diabetes mellitus; haematuria; renal calculi, lymphadenopathy; myalgia; conjunctivitis; dry skin, acne, erythema, skin papilloma; *less commonly* hypersensitivity reactions (see Cautions); see also Osteonecrosis, p. 382

Dose

- By subcutaneous injection, ADULT and ADOLESCENT over 16 years, 90 mg twice daily; CHILD 6–15 years, 2 mg/kg twice daily (max. 90 mg twice daily)

Fuzeon® (Roche) PoM

Injection, powder for reconstitution, enfuvirtide 108 mg (= enfuvirtide 90 mg/mL when reconstituted with 1.1 mL Water for Injections), net price 108-mg vial = £18.03 (with solvent, syringe, and alcohol swabs). Counselling, hypersensitivity reactions

MARAVIROC

Indications CCR5-tropic HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

Cautions cardiovascular disease; chronic hepatitis B or C; **interactions:** Appendix 1 (maraviroc)

Hepatic impairment manufacturer advises caution

Renal impairment if eGFR less than 80 mL/minute/1.73 m^2, consult product literature

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in *animal* studies

Breast-feeding see p. 381

Side-effects nausea, vomiting, abdominal pain, dyspepsia, constipation, diarrhoea; cough; dizziness, paraesthesia, asthenia, sleep disturbances, headache, weight loss; muscle spasms, back pain; taste disturbances; rash, pruritus; *less commonly* pancreatitis, hepatic cirrhosis, rectal bleeding, myocardial infarction, myocardial ischaemia, bronchospasm, seizures, hallucinations, loss of consciousness, polyneuropathy, pancytopenia, neutropenia, lymphadenopathy, renal failure, polyuria, and myositis; see also Osteonecrosis, p. 382

Dose

- ADULT over 18 years, 300 mg twice daily

Celsentri® (ViiV) ▼ PoM

Tablets, blue, f/c, maraviroc, 150 mg, net-price 60-tab pack = £519.14; 300 mg, 60-tab pack = £519.14

RALTEGRAVIR

Indications HIV infection in combination with other antiretroviral drugs

Cautions risk factors for myopathy or rhabdomyolysis; chronic hepatitis B or C (greater risk of hepatic side-effects); **interactions**: Appendix 1 (raltegravir)

Hepatic impairment manufacturer advises caution in severe impairment—no information available

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding see p. 381

Side-effects diarrhoea, nausea, vomiting, abdominal pain, flatulence, hypertriglyceridaemia, dizziness,

headache, insomnia, abnormal dreams, asthenia, rash (Stevens-Johnson syndrome reported); *less commonly* gastritis, hepatitis, pancreatitis, dry mouth, gastro-oesophageal reflux, taste disturbances, pain on swallowing, peptic ulcer, constipation, rectal bleeding, lipodystrophy (see Lipodystrophy Syndrome, p. 382), palpitation, ventricular extrasystoles, bradycardia, hypertension, flushing, chest pain, oedema, dysphonia, epistaxis, nasal congestion, drowsiness, anxiety, appetite changes, confusion, impaired memory and attention, depression, pyrexia, chills, carpal tunnel syndrome, tremor, peripheral neuropathy, erectile dysfunction, gynaecomastia, menopausal symptoms, osteopenia, renal failure, nocturia, polydipsia, anaemia, thrombocytopenia, neutropenia, arthralgia, myalgia, rhabdomyolysis, visual disturbances, tinnitus, gingivitis, glossitis, acne, pruritus, hyperhidrosis, dry skin, skin papilloma, and alopecia; *also reported* suicidal ideation; see also Osteonecrosis, p. 382

Dose

- ADULT and CHILD over 16 years, 400 mg twice daily

Isentress® (MSD) ▼ PoM

Tablets, pink, f/c, raltegravir (as potassium salt) 400 mg, net price 60-tab pack = £616.22. Label: 25

5.3.2 Herpesvirus infections

5.3.2.1 Herpes simplex and varicella–zoster infection

The two most important herpesvirus pathogens are herpes simplex virus (herpesvirus hominis) and varicella–zoster virus.

Herpes simplex infections Herpes infection of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection.

In individuals with good immune function, mild infection of the eye (ocular herpes, section 11.3.3) and of the lips (herpes labialis or cold sores, section 13.10.3) is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics (section 12.3.2). Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised patient may signal the development of resistance.

Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.

Varicella-zoster infections Regardless of immune function and the use of any immunoglobulins, neonates with *chickenpox* should be treated with a parenteral antiviral to reduce the risk of severe disease. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required.

Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.

Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella-zoster immunoglobulin (see under Disease Specific Immunoglobulins, section 14.5.2).

In *herpes zoster* (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.

Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management (section 4.7.3).

Choice **Aciclovir** is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin (section 13.10.3) and mucous membranes (section 7.2.2). It is used by mouth for severe herpetic stomatitis (see also p. 696). Aciclovir eye ointment (section 11.3.3) is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.

Famciclovir, a prodrug of penciclovir, is similar to aciclovir and is licensed for use in herpes zoster and genital herpes. Penciclovir itself is used as a cream for herpes simplex labialis (section 13.10.3).

Valaciclovir is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed for preventing cytomegalovirus disease following renal transplantation. Famciclovir or valaciclovir are suitable alternatives to aciclovir for oral lesions associated with herpes zoster. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought.

Idoxuridine (section 13.10.3) has been used topically for treating herpes simplex infections of the skin and external genitalia with variable results. Its value in the treatment of shingles is unclear.

Foscarnet (section 5.3.2.2) is used for mucocutaneous herpes simplex virus infection unresponsive to aciclovir in immunocompromised patients; it is toxic and can cause renal impairment.

Inosine pranobex has been used by mouth for herpes simplex infections; its effectiveness remains unproven.

ACICLOVIR
(Acyclovir)

Indications herpes simplex and varicella–zoster (see also under Dose)

Cautions maintain adequate hydration (especially with infusion or high doses, or during renal impairment); elderly (risk of neurological reactions); **interactions:** Appendix 1 (aciclovir)

Renal impairment see Cautions above; also risk of neurological reactions increased; use normal intravenous dose every 12 hours if eGFR 25–50 mL/minute/1.73 m^2 (every 24 hours if eGFR 10–25 mL/minute/1.73 m^2); consult product literature for intravenous dose if eGFR less than 10 mL/minute/1.73 m^2; for *herpes zoster*, use normal oral dose every 8 hours if eGFR 10–25 mL/minute/1.73 m^2 (every 12 hours if eGFR less than 10 mL/minute/1.73 m^2); for *herpes simplex*, use normal oral dose every 12 hours if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy not known to be harmful—manufacturers advise use only when potential benefit outweighs risk

Breast-feeding significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution

Side-effects nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; *very rarely* hepatitis, jaundice, dyspnoea, neurological reactions (including dizziness, confusion, hallucinations, convulsions, ataxia, dysarthria, and drowsiness), acute renal failure, anaemia, thrombocytopenia and leucopenia; on *intravenous infusion*, severe local inflammation (sometimes leading to ulceration), and *very rarely* agitation, tremors, psychosis and fever

Dose

- By mouth, non-genital herpes simplex, treatment, 200 mg (400 mg in the immunocompromised or if absorption impaired) 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing incomplete); CHILD 1 month–2 years, half adult dose, over 2 years, adult dose

  Genital herpes simplex, treatment of *first episode*, 200 mg 5 times daily *or* 400 mg 3 times daily usually for 5 days, longer if new lesions appear during treatment or if healing is incomplete (400 mg 5 times daily for 7–10 days in immunocompromised or HIV-positive patients); treatment of *recurrent infection*, 800 mg 3 times daily for 2 days *or* 200 mg 5 times daily for 5 days *or* 400 mg 3 times daily for 3–5 days (400 mg 3 times daily for 5–10 days in immunocompromised or HIV-positive patients)

  Herpes simplex, suppression, 400 mg twice daily *or* 200 mg 4 times daily; increased to 400 mg 3 times daily if recurrences occur on standard suppressive therapy or for suppression of genital herpes during late pregnancy (from 36 weeks gestation); therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences

  Herpes simplex, prophylaxis in the immunocompromised, 200–400 mg 4 times daily; CHILD 1 month–2 years, half adult dose, over 2 years, adult dose

  Varicella and herpes zoster, treatment, 800 mg 5 times daily for 7 days; CHILD, varicella, 1 month–2 years 200 mg 4 times daily for 5 days; 2–6 years 400 mg 4 times daily for 5 days; 6–12 years 800 mg 4 times daily for 5 days

  Attenuation of chickenpox (if varicella–zoster immunoglobulin not indicated) [unlicensed use], ADULT and CHILD 40 mg/kg daily in 4 divided doses for 7 days starting 1 week after exposure

- By intravenous infusion, treatment of herpes simplex in the immunocompromised, severe initial genital herpes, and varicella–zoster, 5 mg/kg every 8 hours usually for 5 days, doubled to 10 mg/kg every 8 hours in varicella–zoster in the immunocompromised and in simplex encephalitis (usually given for at least 10 days in encephalitis, possibly for 14–21 days); prophylaxis of herpes simplex in the immunocompromised, 5 mg/kg every 8 hours

  Note To avoid excessive dosage in obese patients, parenteral dose should be calculated on the basis of ideal weight for height

  NEONATE and INFANT up to 3 months, herpes simplex, 20 mg/kg every 8 hours for 14 days (21 days if CNS involvement); varicella–zoster [unlicensed use] 10–20 mg/kg every 8 hours for at least 7 days; CHILD 3 months–12 years, herpes simplex or varicella–zoster, 250 mg/m^2 every 8 hours usually for 5 days, doubled to 500 mg/m^2 every 8 hours for varicella–zoster in the immunocompromised and in simplex encephalitis (usually given for at least 10 days in encephalitis, possibly for 14–21 days)

- By topical application, see section 13.10.3 (skin) and section 11.3.3 (eye)

Note Aciclovir doses in BNF may differ from those in product literature

Aciclovir (Non-proprietary) PoM

Tablets, aciclovir 200 mg, net price 25-tab pack = £4.45; 400 mg, 56-tab pack = £8.10; 800 mg, 35-tab pack = £10.21. Label: 9
Brands include *Virovir®*
Dental prescribing on NHS Aciclovir Tablets 200 mg or 800 mg may be prescribed

Dispersible tablets, aciclovir 200 mg, net price 25-tab pack = £2.05; 400 mg, 56-tab pack = £7.24; 800 mg, 35-tab pack = £7.02. Label: 9

Suspension, aciclovir 200 mg/5 mL, net price 125 mL = £38.22; 400 mg/5 mL, 100 mL = £41.55. Label: 9
Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription
Dental prescribing on NHS Aciclovir Oral Suspension 200 mg/5 mL may be prescribed

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt), net price 250-mg vial = £9.13; 500-mg vial = £20.22
Electrolytes Na^+ 1.1 mmol/250-mg vial

Intravenous infusion, aciclovir (as sodium salt), 25 mg/mL, net price 10-mL (250-mg) vial = £10.37; 20-mL (500-mg) vial = £19.21; 40-mL (1-g) vial = £40.44
Electrolytes Na^+ 1.16 mmol/250-mg vial

Zovirax® (GSK) PoM

Tablets, all dispersible, f/c, aciclovir 200 mg, net price 25-tab pack = £17.71; 800 mg (scored, *Shingles Treatment Pack*), 35-tab pack = £65.80. Label: 9

Suspension, both off-white, sugar-free, aciclovir 200 mg/5 mL (banana-flavoured), net price 125 mL = £29.53; 400 mg/5 mL (*Double Strength Suspension*, orange-flavoured) 100 mL = £33.01. Label: 9

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt), net price 250-mg vial = £9.96; 500-mg vial = £17.72
Electrolytes Na^+ 1.1 mmol/250-mg vial

FAMCICLOVIR

Note Famciclovir is a pro-drug of penciclovir

Indications see under Dose

Cautions **interactions**: Appendix 1 (famciclovir)

Hepatic impairment usual dose in well compensated liver disease (information not available on decompensated)

Renal impairment reduce dose; consult product literature

Pregnancy manufacturers advise avoid unless potential benefit outweighs risk

Breast-feeding no information available—present in milk in *animal* studies

Side-effects nausea, vomiting, abdominal pain, diarrhoea; headache, fatigue; sweating, pruritus; *rarely* confusion; *very rarely* jaundice, dizziness, drowsiness, hallucinations, thrombocytopenia, rash (including Stevens-Johnson syndrome); also reported, constipation and fever

Dose

- Herpes zoster, treatment, 500 mg 3 times daily for 7 days *or* 750 mg 1–2 times daily for 7 days (in immunocompromised, 500 mg 3 times daily for 10 days)
- Genital herpes, treatment of *first episode*, 250 mg 3 times daily for 5 days, longer if new lesions appear during treatment or if healing incomplete (500 mg twice daily for 5–10 days in immunocompromised or HIV-positive patients); treatment of *recurrent infection*, 125 mg twice daily for 5 days *or* 1 g twice daily for 1 day (500 mg twice daily for 5–10 days in immunocompromised or HIV-positive patients)
- Genital herpes, suppression, 250 mg twice daily (500 mg twice daily in immunocompromised or HIV-positive patients); therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences
- Non-genital herpes simplex, treatment in the immunocompromised, 500 mg twice daily for 7 days
- CHILD not recommended

Note Famciclovir doses in BNF may differ from those in product literature

Famciclovir (Non-proprietary) PoM

Tablets, famciclovir 125 mg, net price 10-tab pack = £34.98; 250 mg, 15-tab pack = £109.49, 21-tab pack = £152.34, 56-tab pack = £408.74; 500 mg, 14-tab pack = £199.57, 30-tab pack = £433.69, 56-tab pack = £831.46; 750 mg, 7-tab pack = £143.05. Label: 9

Famvir® (Novartis) PoM

Tablets, all f/c, famciclovir 125 mg, net price 10-tab pack = £37.12; 250 mg, 15-tab pack = £111.35, 21-tab pack = £155.87; 56-tab pack = £415.67; 500 mg, 14-tab pack = £207.86, 30-tab pack = £445.28, 56-tab pack = £831.46; 750 mg, 7-tab pack = £148.79. Label: 9

INOSINE PRANOBEX

(Inosine acedoben dimepranol)

Indications see under Dose

Cautions history of gout or hyperuricaemia

Renal impairment manufacturer advises caution; metabolised to uric acid

Pregnancy manufacturer advises avoid

Side-effects reversible increase in serum and urinary uric acid; *less commonly* nausea, vomiting, epigastric discomfort, headache, vertigo, fatigue, arthralgia, rashes and itching; *rarely* diarrhoea, constipation, anxiety, sleep disturbances, and polyuria

Dose

- Mucocutaneous herpes simplex, 1 g 4 times daily for 7–14 days
- Adjunctive treatment of genital warts, 1 g 3 times daily for 14–28 days
- Subacute sclerosing panencephalitis, 50–100 mg/kg daily in 6 divided doses

Imunovir® (Newport) PoM

Tablets, scored, inosine pranobex 500 mg, net price 100-tab pack = £39.50. Label: 9

VALACICLOVIR

Note Valaciclovir is a pro-drug of aciclovir

Indications treatment of herpes zoster; treatment of initial and suppression of recurrent herpes simplex infections of skin and mucous membranes including initial and recurrent genital herpes; reduction of transmission of genital herpes; prevention of cytomegalovirus disease following solid organ transplantation when valganciclovir or ganciclovir cannot be used

Cautions see under Aciclovir

Hepatic impairment manufacturer advises caution with high doses used for herpes labialis and prevention of cytomegalovirus disease—no information available

Renal impairment maintain adequate hydration; for *herpes zoster*, 1 g every 12 hours if eGFR 30–50 mL/minute/1.73 m^2 (1 g every 24 hours if eGFR 10–30 mL/minute/1.73 m^2; 500 mg every 24 hours if eGFR less than 10 mL/minute/1.73 m^2); for *treatment of herpes simplex*, 500 mg (1 g in immunocompromised or HIV-positive patients) every 24 hours if eGFR less than 30 mL/minute/1.73 m^2; for *treatment of herpes labialis*, if eGFR 30–50 mL/minute/1.73 m^2, initially 1 g, then 1 g 12 hours after initial dose (if eGFR 10–30 mL/minute/1.73 m^2, initally 500 mg, then 500 mg 12 hours after initial dose; if eGFR less than 10 mL/minute/1.73 m^2, 500 mg as a single dose); for *suppression of herpes simplex*, 250 mg (500 mg in immunocompromised or HIV-positive patients) every 24 hours if eGFR less than 30 mL/minute/1.73 m^2; for *reduction of genital herpes transmission*, 250 mg every 24 hours if eGFR less than 15 mL/minute/1.73 m^2; reduce dose according to eGFR for *cytomegalovirus prophylaxis* following solid organ transplantation (consult product literature)

Pregnancy see under Aciclovir

Breast-feeding see under Aciclovir

Side-effects see under Aciclovir but neurological reactions more frequent with high doses

Dose

- Herpes zoster, 1 g 3 times daily for 7 days; CHILD 12–18 years see *BNF for Children*
- Herpes simplex, treatment of *first episode*, 500 mg twice daily for 5 days, longer if new lesions appear during treatment or if healing incomplete (1 g twice daily for 10 days in immunocompromised or HIV-

positive patients); treatment of *recurrent infection*, 500 mg twice daily for 3–5 days (1 g twice daily for 5–10 days in immunocompromised or HIV-positive patients); CHILD 12–18 years see *BNF for Children*

- Herpes labialis, treatment, ADULT and CHILD over 12 years, initially 2 g, then 2 g 12 hours after initial dose
- Herpes simplex, suppression, 500 mg daily in 1–2 divided doses (in immunocompromised or HIV positive patients, 500 mg twice daily); therapy interrupted every 6–12 months to reassess recurrence frequency—consider restarting after two or more recurrences; CHILD 12–18 years see *BNF for Children*
- Reduction of transmission of genital herpes, seek specialist advice, 500 mg once daily to be taken by the infected partner
- Prevention of cytomegalovirus disease following solid organ transplantation (preferably starting within 72 hours of transplantation), 2 g 4 times daily usually for 90 days; CHILD 12–18 years see *BNF for Children*

Valaciclovir (Non-proprietary) PoM

Tablets, valaciclovir 500 mg, net price 10-tab pack = £19.48, 42 tab-pack = £81.64. Label: 9

Valtrex® (GSK) PoM

Tablets, f/c, valaciclovir (as hydrochloride) 250 mg, net price 60-tab pack = £123.28; 500 mg, 10-tab pack = £20.59, 42-tab pack = £86.30. Label: 9

5.3.2.2 Cytomegalovirus infection

Recommendations for the optimum maintenance therapy of cytomegalovirus (CMV) infections and the duration of treatment are subject to rapid change.

Ganciclovir is related to aciclovir but it is more active against cytomegalovirus; it is also much more toxic than aciclovir and should therefore be prescribed only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the *initial treatment* of CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration; cross-resistance to cidofovir is common.

Valaciclovir (see p. 394) is licensed for prevention of cytomegalovirus disease following renal transplantation.

Valganciclovir is an ester of ganciclovir which is licensed for the *initial treatment* and *maintenance treatment* of CMV retinitis in AIDS patients. Valganciclovir is also licensed for preventing CMV disease following solid organ transplantation from a cytomegalovirus-positive donor.

Foscarnet is also active against cytomegalovirus; it is toxic and can cause renal impairment.

Cidofovir is given in combination with probenecid for CMV retinitis in AIDS patients when ganciclovir and foscarnet are contra-indicated. Cidofovir is nephrotoxic.

For local treatment of CMV retinitis, see section 11.3.3.

CIDOFOVIR

Indications cytomegalovirus retinitis in AIDS patients for whom other drugs are inappropriate

Cautions monitor renal function (serum creatinine and urinary protein) and neutrophil count within 24 hours before each dose; co-treatment with probenecid and prior hydration with intravenous fluids necessary to minimise potential nephrotoxicity (see below); diabetes mellitus (increased risk of ocular hypotony); **interactions:** Appendix 1 (cidofovir)

Nephrotoxicity Do not initiate treatment in renal impairment (assess creatinine clearance and proteinuria—consult product literature); discontinue treatment and give intravenous fluids if renal function deteriorates—consult product literature

Ocular disorders Regular ophthalmological examinations recommended; iritis and uveitis have been reported which may respond to a topical corticosteroid with or without a cycloplegic drug—discontinue cidofovir if no response to topical corticosteroid or if condition worsens, or if iritis or uveitis recurs after successful treatment

Contra-indications concomitant administration of potentially nephrotoxic drugs (discontinue potentially nephrotoxic drugs at least 7 days before starting cidofovir)

Renal impairment avoid if creatinine clearance less than 55 mL/minute; nephrotoxic

Pregnancy avoid (toxicity in *animal* studies); effective contraception required during and for 1 month after treatment; also men should avoid fathering a child during and for 3 months after treatment

Breast-feeding manufacturer advises avoid

Side-effects nephrotoxicity (see Cautions above); nausea, vomiting, diarrhoea; dyspnoea; headache, fever, asthenia; neutropenia; decreased intra-ocular pressure, iritis, uveitis (see Cautions above); alopecia, rash; *less commonly* Fanconi syndrome; also reported, hearing impairment and pancreatitis

Dose

- Initial (induction) treatment, ADULT over 18 years, by intravenous infusion over 1 hour, 5 mg/kg once weekly for 2 weeks (give probenecid and intravenous fluids with each dose, see below)
- Maintenance treatment, beginning 2 weeks after completion of induction, ADULT over 18 years, by intravenous infusion over 1 hour, 5 mg/kg once every 2 weeks (give probenecid and intravenous fluids with each dose, see below)

Probenecid co-treatment By mouth (preferably after food), probenecid 2 g 3 hours before cidofovir infusion followed by probenecid 1 g at 2 hours and 1 g at 8 hours after the end of cidofovir infusion (total probenecid 4 g); for cautions, contra-indications and side-effects of probenecid see section 10.1.4

Prior hydration Sodium chloride 0.9%, by intravenous infusion, 1 litre over 1 hour immediately before cidofovir infusion (if tolerated an additional 1 litre may be given over 1–3 hours, starting at the same time as the cidofovir infusion or immediately afterwards)

Vistide® (Gilead) PoM

Intravenous infusion, cidofovir 75 mg/mL, net price 5-mL vial = £653.22

Caution in handling Cidofovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with water

GANCICLOVIR

Indications life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only; prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation; local treatment of CMV retinitis (section 11.3.3)

Cautions close monitoring of full blood count (severe deterioration may require correction and possibly treatment interruption); history of cytopenia; potential carcinogen and teratogen; radiotherapy; ensure adequate hydration during intravenous administration; vesicant—infuse into vein with adequate flow preferably using plastic cannula; children (possible risk of long-term carcinogenic or reproductive toxicity); **interactions:** Appendix 1 (ganciclovir)

Contra-indications hypersensitivity to valganciclovir, ganciclovir, aciclovir, or valaciclovir; abnormally low haemoglobin, neutrophil, or platelet counts (consult product literature)

Renal impairment reduce dose if eGFR less than 70 mL/minute/1.73 m^2; consult product literature

Pregnancy avoid—teratogenic risk; ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment

Breast-feeding avoid—no information available

Side-effects diarrhoea, nausea, vomiting, dyspepsia, abdominal pain, constipation, flatulence, dysphagia, taste disturbance, hepatic dysfunction; dyspnoea, chest pain, cough; headache, insomnia, convulsions, dizziness, peripheral neuropathy, depression, anxiety, confusion, abnormal thinking, fatigue, weight loss, anorexia; infection, pyrexia, night sweats; anaemia, leucopenia, thrombocytopenia, pancytopenia, renal impairment; myalgia, arthralgia; macular oedema, retinal detachment, vitreous floaters, eye pain; ear pain; dermatitis, pruritus; injection-site reactions; *less commonly* mouth ulcers, pancreatitis, arrhythmias, hypotension, anaphylactic reactions, psychosis, tremor, male infertility, haematuria, disturbances in hearing and vision, and alopecia

Dose

- By intravenous infusion, initially (induction) 5 mg/kg every 12 hours for 14–21 days for treatment or for 7–14 days for prevention; maintenance (for patients at risk of relapse of retinitis) 6 mg/kg daily on 5 days per week *or* 5 mg/kg daily until adequate recovery of immunity; if retinitis progresses initial induction treatment may be repeated; CHILD under 18 years, see *BNF for Children*

Cymevene® (Roche) PoM

Intravenous infusion, powder for reconstitution, ganciclovir (as sodium salt). Net price 500-mg vial = £29.77

Electrolytes Na^+ 2 mmol/500-mg vial

Caution in handling Ganciclovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with soap and water

FOSCARNET SODIUM

Indications cytomegalovirus disease [licensed for cytomegalovirus retinitis in AIDS patients only]; mucocutaneous herpes simplex virus infections unresponsive to aciclovir in immunocompromised patients

Cautions monitor electrolytes, particularly calcium and magnesium; monitor serum creatinine every second day during induction and every week during maintenance; ensure adequate hydration; avoid rapid infusion; **interactions:** Appendix 1 (foscarnet)

Renal impairment reduce dose; consult product literature

Pregnancy manufacturer advises avoid

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, vomiting, diarrhoea (occasionally constipation and dyspepsia), abdominal pain, anorexia; changes in blood pressure and ECG; headache, fatigue, mood disturbances (including psychosis), asthenia, paraesthesia, convulsions, tremor, dizziness, and other neurological disorders; rash; impairment of renal function including acute renal failure; hypocalcaemia (sometimes symptomatic) and other electrolyte disturbances; abnormal liver function tests; decreased haemoglobin concentration, leucopenia, granulocytopenia, thrombocytopenia; thrombophlebitis if given undiluted by peripheral vein; genital irritation and ulceration (due to high concentrations excreted in urine); isolated reports of pancreatitis

Dose

- CMV disease [licensed for CMV retinitis only], by intravenous infusion, initially (induction) 60 mg/kg every 8 hours *or* 90 mg/kg every 12 hours, for 2–3 weeks; maintenance 60 mg/kg daily, increased to 90–120 mg/kg if tolerated; if disease progresses on maintenance dose, repeat induction regimen
- Mucocutaneous herpes simplex infection, by intravenous infusion, 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal

Note Foscarnet doses in BNF may differ from those in product literature

Foscavir® (Clinigen) PoM

Intravenous infusion, foscarnet sodium hexahydrate 24 mg/mL, net price 250-mL bottle = £34.49

VALGANCICLOVIR

Note Valganciclovir is a pro-drug of ganciclovir

Indications induction and maintenance treatment of cytomegalovirus retinitis in AIDS patients; prevention of cytomegalovirus disease following solid organ transplantation from a cytomegalovirus-positive donor.

Cautions see under Ganciclovir

Contra-indications see under Ganciclovir

Renal impairment reduce dose; consult product literature

Pregnancy see under Ganciclovir

Breast-feeding see under Ganciclovir

Side-effects see under Ganciclovir

Dose

- CMV retinitis, induction, ADULT over 18 years, 900 mg twice daily for 21 days then 900 mg once daily; induction regimen may be repeated if retinitis progresses
- Prevention of cytomegalovirus disease following solid organ transplantation (starting within 10 days of

transplantation), ADULT over 18 years, 900 mg once daily for 100 days (for 100–200 days following kidney transplantation)

Note Oral valganciclovir 900 mg twice daily is equivalent to intravenous ganciclovir 5 mg/kg twice daily

Valcyte® (Roche) PoM

Tablets, pink, f/c, valganciclovir (as hydrochloride) 450 mg, net price 60-tab pack = £1081.46. Label: 21

Oral solution, tutti-frutti flavoured, valganciclovir (as hydrochloride) 250 mg/5 mL when reconstituted with water, net price 100 mL = £230.32. Label: 21

Caution in handling Valganciclovir is a potential teratogen and carcinogen and caution is advised when handling the powder, reconstituted solution, or broken tablets; if these come into contact with skin or mucosa, wash off immediately with water; avoid inhalation of powder

5.3.3 Viral hepatitis

Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely symptomatic. Early treatment of acute hepatitis C with interferon alfa [unlicensed indication] may reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. For details on immunisation against hepatitis A and B infections, see section 14.4 (active immunisation), section 14.5.1 (passive immunisation against hepatitis A), and section 14.5.2 (passive immunisation against hepatitis B).

Chronic Hepatitis B **Peginterferon alfa** (section 8.2.4) is an option for the initial treatment of chronic hepatitis B and may be preferable to **interferon alfa**. The use of peginterferon alfa and interferon alfa is limited by a response rate of 30–40% and relapse is frequent. Treatment should be discontinued if no improvement occurs after 4 months. The manufacturers of peginterferon alfa-2a and interferon alfa contraindicate use in decompensated liver disease, but low doses can be used with great caution in these patients. Although interferon alfa is contra-indicated in patients receiving immunosuppressant treatment (or who have received it recently), cautious use of peginterferon alfa-2a may be justified in some cases.

Entecavir or **tenofovir disoproxil** (see p. 385) are options for the initial treatment of chronic hepatitis B. If the response is inadequate after 6–9 months of treatment, a change in treatment should be considered. Other drugs that are licensed for the treatment of chronic hepatitis B include **adefovir dipivoxil**, **lamivudine** (see p. 384), or **telbivudine** (but see NICE guidance below).

Entecavir alone, tenofovir disoproxil alone, or a combination of lamivudine with either adefovir dipivoxil or tenofovir disoproxil can be used in patients with decompensated liver disease; entecavir is not licensed for these patients.

If drug-resistant hepatitis B virus emerges during treatment, another antiviral drug with a different resistance profile should be added. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. Adefovir or tenofovir can be given with lamivudine in lamivudine-resistant chronic hepatitis B; telbivudine or entecavir should not be used because cross-resistance can occur.

If there is no toxicity or loss in efficacy, treatment with adefovir, entecavir, lamivudine, telbivudine, or tenofovir is usually continued until 6 months after adequate seroconversion has occurred. Treatment is usually continued long-term in patients with decompensated liver disease.

Tenofovir, or a combination of tenofovir with either emtricitabine or lamivudine may be used with other antiretrovirals, as part of 'highly active antiretroviral therapy' (section 5.3.1) in patients who require treatment for both HIV and chronic hepatitis B. If patients infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa or adefovir. Treatment may be continued long-term, even if adequate seroconversion occurs. Management of these patients should be coordinated between HIV and hepatology specialists.

NICE guidance

Entecavir and telbivudine for chronic hepatitis B (August 2008)

Entecavir is an option for the treatment of chronic hepatitis B.

Telbivudine is not recommended for the treatment of chronic hepatitis B. Patients currently receiving telbivudine can continue treatment until they and their clinician consider it appropriate to stop.

NICE guidance

Tenofovir disoproxil for the treatment of chronic hepatitis B (July 2009)

Tenofovir is an option for the treatment of chronic hepatitis B.

Chronic Hepatitis C Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load measured as this may affect the choice and duration of treatment. A combination of **ribavirin** (see p. 400) and **peginterferon alfa** (section 8.2.4) is used for the treatment of chronic hepatitis C (see NICE guidance, below). The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

NICE guidance

Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006 and September 2010)

The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage ('watchful waiting'). Peginterferon alfa alone can be used if ribavirin is contra-indicated or not tolerated.

NICE guidance

Peginterferon alfa, interferon alfa, and ribavirin for moderate to severe chronic hepatitis C (January 2004 and September 2010)

The combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:

- not previously treated with interferon alfa or peginterferon alfa;
- treated previously with interferon alfa alone or in combination with ribavirin;
- whose condition did not respond to peginterferon alfa alone or to a combination of peginterferon alfa and ribavirin, or responded but subsequently relapsed;
- co-infected with HIV.

Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa.

Full guidance available at www.nice.org.uk/TA075.

ADEFOVIR DIPIVOXIL

Indications chronic hepatitis B infection with *either* compensated liver disease with evidence of viral replication, and histologically documented active liver inflammation and fibrosis *or* decompensated liver disease

Cautions monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation); monitor renal function before treatment then every 3 months, more frequently in renal impairment or in patients receiving nephrotoxic drugs; elderly; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Renal impairment 10 mg every 48 hours if eGFR 30–50 mL/minute/1.73 m^2; 10 mg every 72 hours if eGFR 10–30 mL/minute/1.73 m^2; no information available if eGFR less than 10 mL/minute/1.73 m^2; see also Cautions above

Pregnancy toxicity in *animal* studies—manufacturer advises use only if potential benefit outweighs risk; effective contraception required during treatment

Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, dyspepsia, abdominal pain, flatulence, diarrhoea; asthenia, headache; renal failure; hypophosphataemia; rash and pruritus; also reported pancreatitis

Dose

- ADULT over 18 years, 10 mg once daily

Hepsera® (Gilead) PoM

Tablets, adefovir dipivoxil 10 mg, net price 30-tab pack = £296.73

ENTECAVIR

Indications chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis

Cautions monitor liver function tests every 3 months, and viral and serological markers for hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation); HIV infection—risk of HIV resistance in patients not receiving 'highly active antiretroviral therapy'; lamivudine-resistant chronic hepatitis B—risk of entecavir resistance; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis

Renal impairment reduce dose if eGFR less than 50 mL/minute/1.73 m^2; consult product literature

Pregnancy toxicity in *animal* studies—manufacturer advises use only if potential benefit outweighs risk; effective contraception required during treatment

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects nausea, vomiting, dyspepsia, diarrhoea, raised serum amylase and lipase, headache, fatigue, dizziness, sleep disturbances; *less commonly* thrombocytopenia, rash, alopecia

Dose

- ADULT over 18 years, not previously treated with nucleoside analogues, 500 micrograms once daily
- ADULT over 18 years with lamivudine-resistant chronic hepatitis B (but see notes above), 1 mg once daily; consider other treatment if inadequate response after 6 months

Counselling To be taken at least 2 hours before or 2 hours after food

Baraclude® (Bristol-Myers Squibb) ▼ PoM

Tablets, f/c, entecavir (as monohydrate) 500 micrograms (white), net price 30-tab pack = £363.26; 1 mg (pink), 30-tab pack = £363.26. Counselling, administration

Oral solution, entecavir (as monohydrate) 50 micrograms/mL, net price 210-mL pack (orange-flavoured) = £423.80. Counselling, administration

TELBIVUDINE

Indications chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis

Cautions monitor liver function tests every 3 months and viral and serological markers of hepatitis B every 3–6 months during treatment (continue monitoring for at least 1 year after discontinuation—recurrent hepatitis may occur on discontinuation); lamivudine-resistant chronic hepatitis B—risk of telbivudine resistance; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; **interactions:** Appendix 1 (telbivudine)

Counselling Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, or numbness, tingling or burning sensations

Renal impairment 600 mg every 48 hours if eGFR 30–49 mL/minute/1.73 m^2; 600 mg every 72 hours if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects nausea, diarrhoea, abdominal pain, raised serum amylase and lipase; cough; dizziness, headache, fatigue; rash; *less commonly*; taste disturbance, arthralgia, myalgia, myopathy (discontinue treatment), and peripheral neuropathy; also reported, lactic acidosis and rhabdomyolysis

Dose

- ADULT and CHILD over 16 years, 600 mg once daily

Sebivo® (Novartis) ▼ PoM

Tablets, f/c, telbivudine 600 mg, net price 28-tab pack = £290.33. Counselling, muscle effects, peripheral neuropathy

5.3.4 Influenza

For advice on immunisation against influenza, see section 14.4.

Oseltamivir and **zanamivir** reduce replication of influenza A and B viruses by inhibiting viral neuraminidase. They are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; they are licensed for use within 48 hours (within 36 hours for zanamivir in children) of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. Oseltamivir or zanamivir can reduce the risk of complications from influenza in the elderly and in patients with chronic disease (see also NICE guidance, below).

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza (see also NICE guidance, below). Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

There is evidence that some strains of influenza A virus have reduced susceptibility to oseltamivir, but may retain susceptibility to zanamivir.

Amantadine is licensed for prophylaxis and treatment of influenza A but it is no longer recommended (see NICE guidance).

Information on pandemic influenza, avian influenza, and swine influenza may be found at www.hpa.org.uk

Oseltamivir in children under 1 year of age Data on the use of oseltamivir in children under 1 year of age is limited. Furthermore oseltamivir may be ineffective in neonates because they may not be able to metabolise oseltamivir to its active form. In exceptional circumstances, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that during a pandemic, treatment with oseltamivir can be overseen by healthcare professionals experienced in assessing children.

Pregnancy and breast-feeding Although safety data are limited, either oseltamivir or zanamivir can be used in women who are pregnant or breast-feeding when the potential benefit outweighs the risk (e.g. during a pandemic). Zanamivir is the preferred drug during pregnancy; however, oseltamivir is recommended during severe infection or when zanamivir cannot be used. Oseltamivir is the preferred drug in women who are breast-feeding.

NICE guidance

Oseltamivir, zanamivir, and amantadine for prophylaxis and treatment of influenza (September 2008 and February 2009)

The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- Amantadine is **not** recommended for prophylaxis or treatment of influenza.
- Oseltamivir *or* zanamivir are **not** recommended for seasonal prophylaxis against influenza.
- When influenza is circulating in the community[1], either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza.
- When influenza is circulating in the community[1], either oseltamivir or zanamivir is recommended (in accordance with UK licensing) for the treatment of influenza in at-risk patients who can start treatment within 48 hours (within 36 hours for zanamivir in children) of the onset of symptoms.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for post-exposure prophylaxis or treatment in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At risk[2] patients include those aged over 65 years *or* those who have one or more of the following conditions:

- chronic respiratory disease (including asthma and chronic obstructive pulmonary disease);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

AMANTADINE HYDROCHLORIDE

Indications see under Dose; parkinsonism (section 4.9.1)

Cautions section 4.9.1

Contra-indications section 4.9.1

1. National surveillance schemes, including those run by the Health Protection Agency, should be used to indicate when influenza is circulating in the community.
2. The Department of Health in England has advised (November 2010) that 'at risk patients' also includes women who are pregnant.

Renal impairment section 4.9.1
Pregnancy section 4.9.1
Breast-feeding section 4.9.1
Side-effects section 4.9.1
Dose
- Influenza A (see also notes above), ADULT and CHILD over 10 years, treatment, 100 mg daily for 4–5 days; prophylaxis, 100 mg daily usually for 6 weeks *or* with influenza vaccination for 2–3 weeks after vaccination

Lysovir® (Alliance) PoM
Capsules, red-brown, amantadine hydrochloride 100 mg, net price 5-cap pack = £2.40, 14-cap pack = £5.76. Counselling, driving

Symmetrel® (Alliance) PoM
Section 4.9.1

OSELTAMIVIR

Indications see notes above
Renal impairment for *treatment*, use 75 mg once daily *or* 30 mg twice daily if eGFR 10–30 mL/minute/1.73 m^2; for *prevention*, use 75 mg every 48 hours *or* 30 mg once daily if eGFR 10–30 mL/minute/1.73 m^2; avoid for *treatment* and *prevention* if eGFR less than 10 mL/minute/1.73 m^2
Pregnancy use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 399
Breast-feeding amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 399
Side-effects nausea, vomiting, abdominal pain, diarrhoea; headache; conjunctivitis; *less commonly* eczema; also reported hepatitis, gastro-intestinal bleeding, arrhythmias, neuropsychiatric disorders (more frequent in children and adolescents), visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis
Dose
- Prevention of influenza, ADULT and CHILD over 13 years, 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic; CHILD under 1 month (see notes above), 2 mg/kg once daily for 10 days for post-exposure prophylaxis; 1–3 months (see notes above), 2.5 mg/kg once daily for 10 days for post–exposure prophylaxis; 3 months–1 year (see notes above), 3 mg/kg once daily for 10 days for post-exposure prophylaxis; 1–13 years, body-weight under 15 kg, 30 mg once daily for 10 days for post-exposure prophylaxis (for up to 6 weeks during an epidemic); body-weight 15–23 kg, 45 mg once daily for 10 days for post-exposure prophylaxis (for up to 6 weeks during an epidemic); body-weight 23–40 kg, 60 mg once daily for 10 days for post-exposure prophylaxis (for up to 6 weeks during an epidemic); body-weight over 40 kg, adult dose
- Treatment of influenza, ADULT and CHILD over 13 years, 75 mg every 12 hours for 5 days; CHILD under 1 month (see notes above), 2 mg/kg every 12 hours for 5 days; 1–3 months (see notes above), 2.5 mg/kg every 12 hours for 5 days; 3 months–1 year (see notes above), 3 mg/kg every 12 hours for 5 days; 1–13 years, body-weight under 15 kg, 30 mg every 12 hours for 5 days, body-weight 15–23 kg, 45 mg every 12 hours for 5 days, body-weight 23–40 kg, 60 mg every 12 hours for 5 days, body-weight over 40 kg, adult dose
  Note Not licensed for use in children under 1 year of age unless there is a pandemic

[1] **Tamiflu®** (Roche) PoM
Capsules, oseltamivir (as phosphate) 30 mg (yellow), net price 10-cap pack = £7.71; 45 mg (grey), 10-cap pack = £15.41; 75 mg (grey-yellow), 10-cap pack = £15.41. Label: 9
Note If suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as sugar water or chocolate syrup, just before administration
Suspension, sugar-free, tutti-frutti-flavoured, oseltamivir (as phosphate) for reconstitution with water, 60 mg/5 mL, net price 75 mL = £15.41. Label: 9
Excipients include sorbitol 1.7 g/5 mL
Note Solutions prepared by 'special order' manufacturers may be a different concentration
1. NHS except for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription 'SLS'

ZANAMIVIR

Indications see notes above
Cautions asthma and chronic pulmonary disease (risk of bronchospasm—short-acting bronchodilator should be available; avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm); uncontrolled chronic illness; other inhaled drugs should be administered before zanamivir)
Pregnancy use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 399
Breast-feeding amount probably too small to be harmful; use only if potential benefit outweighs risk (e.g. during a pandemic); see also p. 399
Side-effects *very rarely*, bronchospasm, respiratory impairment, angioedema, urticaria, and rash; also reported, neuropsychiatric disorders (especially in children and adolescents), Stevens-Johnson syndrome, toxic epidermal necrolysis
Dose
- By inhalation of powder, post-exposure prophylaxis of influenza, ADULT and CHILD over 5 years, 10 mg once daily for 10 days
  Prevention of influenza during an epidemic, ADULT and CHILD over 5 years, 10 mg once daily for up to 28 days
  Treatment of influenza, ADULT and CHILD over 5 years, 10 mg twice daily for 5 days

[1] **Relenza®** (GSK) PoM
Dry powder for inhalation disks containing 4 blisters of zanamivir 5 mg/blister, net price 5 disks with *Diskhaler®* device = £16.36
1. NHS except for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription 'SLS'

5.3.5 Respiratory syncytial virus

Ribavirin inhibits a wide range of DNA and RNA viruses. It is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis. Ribavirin is given by mouth with peginterferon alfa or interferon alfa for the treatment of chronic hepatitis C infection (see Viral Hepatitis, p. 397). Ribavirin is also effective in Lassa fever [unlicensed indication].

Palivizumab is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation.

Palivizumab is recommended for:

- children under 9 months of age with chronic lung disease (defined as requiring oxygen for at least 28 days from birth) and who were born preterm[1];
- children under 6 months of age with haemodynamically significant, acyanotic congenital heart disease who were born preterm[1].

Palivizumab should be considered for:

- children under 2 years of age with severe combined immunodeficiency syndrome;
- children under 1 year of age who require long-term ventilation;
- children 1–2 years of age who require long-term ventilation and have an additional co-morbidity (including cardiac disease or pulmonary hypertension).

PALIVIZUMAB

Indications see notes above

Cautions moderate to severe acute infection or febrile illness; thrombocytopenia; serum-palivizumab concentration may be reduced after cardiac surgery

Contra-indications hypersensitivity to humanised monoclonal antibodies

Side-effects fever, injection-site reactions, nervousness; *less commonly* diarrhoea, vomiting, constipation, haemorrhage, rhinitis, cough, wheeze, pain, drowsiness, asthenia, hyperkinesia, leucopenia, and rash; also reported, apnoea, hypersensitivity reactions (including anaphylaxis), convulsions and thombocytopenia

Dose

- By intramuscular injection (preferably in anterolateral thigh), 15 mg/kg once a month during season of RSV risk (child undergoing cardiac bypass surgery, 15 mg/kg as soon as stable after surgery, then once a month during season of risk); injection volume over 1 mL should be divided between more than one site

Synagis® (Abbott) ▼ PoM

Injection, powder for reconstitution, palivizumab, net price 50-mg vial = £360.40; 100-mg vial = £663.11

RIBAVIRIN
(Tribavirin)

Indications severe respiratory syncytial virus bronchiolitis in infants and children; in combination with peginterferon alfa or interferon alfa for chronic hepatitis C in patients without liver decompensation (see also section 5.3.3)

Cautions

Specific cautions for inhaled treatment Maintain standard supportive respiratory and fluid management therapy; monitor electrolytes closely; monitor equipment for precipitation; pregnant women (and those planning pregnancy) should avoid exposure to aerosol

Specific cautions for oral treatment Exclude pregnancy before treatment; effective contraception essential during treatment and for 4 months after treatment in women and for 7 months after treatment in men; routine monthly pregnancy tests recommended; condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen); cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration); gout; determine full blood count, platelets, electrolytes, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop (consult product literature); eye examination recommended before treatment; eye examination also recommended during treatment if pre-existing ophthalmological disorder or if decrease in vision reported—discontinue treatment if ophthalmological disorder deteriorates or if new ophthalmological disorder develops; test thyroid function before treatment and then every 3 months in children; risk of growth retardation in children, the reversibility of which is uncertain—if possible, consider starting treatment after pubertal growth spurt

Interactions: Appendix 1 (ribavirin)

Contra-indications

Specific contra-indications for oral treatment Severe cardiac disease, including unstable or uncontrolled cardiac disease in previous 6 months; haemoglobinopathies; severe debilitating medical conditions; autoimmune disease (including autoimmune hepatitis); uncontrolled severe psychiatric condition; history of severe psychiatric condition in children

Hepatic impairment no dosage adjustment required; use oral ribavirin with caution in severe hepatic dysfunction or decompensated cirrhosis

Renal impairment plasma-ribavirin concentration increased; avoid oral ribavirin unless essential if eGFR less than 50 mL/minute/1.73 m^2—monitor haemoglobin concentration closely

Pregnancy avoid; teratogenicity in *animal* studies; see also Cautions above

Breast-feeding avoid—no information available

Side-effects

Specific side-effects for inhaled treatment Worsening respiration, bacterial pneumonia, and pneumothorax reported; rarely non-specific anaemia and haemolysis

Specific side-effects for oral treatment Haemolytic anaemia (anaemia may be improved by epoetin); also (in combination with peginterferon alfa or interferon alfa) nausea, vomiting, dyspepsia, abdominal pain, flatulence, constipation, diarrhoea, colitis, chest pain, palpitation, tachycardia, peripheral oedema, changes in blood pressure, syncope, flushing, cough, dyspnoea, headache, dizziness, asthenia, impaired concentration and memory, sleep disturbances, abnormal dreams, anxiety, depression, suicidal ideation (more frequent in children), psychoses, dysphagia, weight loss, dysphonia, paraesthesia, hypoaesthesia, ataxia, hypertonia, influenza-like symptoms, thyroid disorders, hyperglycaemia, menstrual disturbances, breast pain, prostatitis, sexual dysfunction, micturition disorders, leucopenia, thrombocytopenia, lymphadenopathy, dehydration, hypocalcaemia, myalgia, arthralgia, hyperuricaemia, visual disturbances, eye pain, dry eyes, hearing impairment, tinnitus, earache, dry mouth, taste disturbances, mouth ulcers, stomatitis, glossitis, tooth disorder, gingivitis, alopecia, pruritus, dry skin, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), increased sweating, psoriasis, photosensitivity, and acne; *less commonly* pancreatitis, gastro-intestinal bleeding, and hypertriglyceridaemia; *rarely* peptic ulcer, arrhythmias, cardiomyopathy, myocardial infarction, pericarditis, stroke, interstitial pneumonitis, pulmonary embolism, seizures, renal failure, vasculitis, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, optic neuropathy, and retinal haemorrhage; *very rarely* aplastic anaemia and peripheral ischaemia; *in children* also growth retardation (including decrease in height and weight), pallor, tachypnoea, hyperkinesia, virilism, and skin discoloration

Dose

- See preparations below

1. For details of the preterm age groups included in the recommendations, see *Immunisation against Infectious Disease* (2006), available at www.dh.gov.uk/immunisation

Copegus® (Roche) PoM

Tablets, f/c, ribavirin 200 mg (pink), net price 42-tab pack = £92.50, 112-tab pack = £246.65, 168-tab pack = £369.98; 400 mg (red-brown), 56-tab pack = £246.65. Label: 21

Dose chronic hepatitis C (in combination with interferon alfa or peginterferon alfa), ADULT over 18 years, body-weight under 75 kg, 400 mg in the morning and 600 mg in the evening; body-weight 75 kg and over, 600 mg twice daily

Note Patients with chronic hepatitis C genotype 2 or 3 (not previously treated), or patients infected with HIV and hepatitis C require a lower dose of *Copegus®* (in combination with peginterferon alfa), usual dose 400 mg twice daily

Rebetol® (Schering-Plough) PoM

Capsules, ribavirin 200 mg, net price 84-cap pack = £160.69, 140-cap pack = £267.81, 168-cap pack = £321.38. Label: 21

Oral solution, ribavirin 200 mg/5 mL, net price 100 mL (bubble-gum-flavoured) = £67.08. Label: 21

Dose chronic hepatitis C (in combination with interferon alfa or peginterferon alfa), ADULT over 18 years, body-weight under 65 kg, 400 mg twice daily; body-weight 65–81 kg, 400 mg in the morning and 600 mg in the evening; body-weight 81–105 kg, 600 mg twice daily; body-weight over 105 kg, 600 mg in the morning and 800 mg in the evening; CHILD 3–18 years, body-weight under 47 kg, 15 mg/kg daily in 2 divided doses; body-weight 47–50 kg, 200 mg in the morning and 400 mg in the evening; body-weight 50–65 kg, 400 mg twice daily; body-weight over 65 kg, as adult

Virazole® (Meda) PoM

Inhalation, ribavirin 6 g for reconstitution with 300 mL water for injections. Net price 3 × 6-g vials = £349.00

Dose bronchiolitis, by aerosol inhalation *or* nebulisation (via small particle aerosol generator) of solution containing 20 mg/mL for 12–18 hours for at least 3 days; max. 7 days

5.4 Antiprotozoal drugs

5.4.1 Antimalarials
5.4.2 Amoebicides
5.4.3 Trichomonacides
5.4.4 Antigiardial drugs
5.4.5 Leishmaniacides
5.4.6 Trypanocides
5.4.7 Drugs for toxoplasmosis
5.4.8 Drugs for pneumocystis pneumonia

Advice on specific problems available from:

Advice for healthcare professionals

HPA (Health Protection Agency) Malaria Reference Laboratory	(020) 7637 0248 (fax) (prophylaxis only)
www.hpa.org.uk/infections/topics_az/malaria	
National Travel Health Network and Centre	0845 602 6712
Travel Medicine Team, Health Protection Scotland (registered users of Travax only) www.travax.nhs.uk (for registered users of the NHS Travax website only)	(0141) 300 1100 (weekdays 2–4 p.m. only)
Birmingham	(0121) 424 0357
Liverpool	(0151) 705 3100
London	0845 155 5000 (treatment)
Oxford	(01865) 225 430

Advice for travellers

Hospital for Tropical Diseases Travel Healthline	(020) 7950 7799
www.fitfortravel.nhs.uk	
WHO advice on international travel and health www.who.int/ith	
National Travel Health Network and Centre (NaTHNaC) www.nathnac.org/travel/index.htm	

5.4.1 Antimalarials

Recommendations on the prophylaxis and treatment of malaria reflect guidelines agreed by UK malaria specialists.

The centres listed above should be consulted for advice on special problems.

Treatment of malaria

If the infective species is **not known**, or if the infection is **mixed**, initial treatment should be as for *falciparum malaria* with quinine, *Malarone®* (proguanil with atovaquone), or *Riamet®* (artemether with lumefantrine). Falciparum malaria can progress rapidly in unprotected individuals and antimalarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.

Falciparum malaria (treatment)

Falciparum malaria (malignant malaria) is caused by *Plasmodium falciparum*. In most parts of the world *P. falciparum* is now resistant to chloroquine which should not therefore be given for treatment.

Quinine, ***Malarone®*** (proguanil with atovaquone), or ***Riamet®*** (artemether with lumefantrine) can be given *by mouth* if the patient can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given *by intravenous infusion* (see below) if the patient is seriously ill or unable to take tablets. Mefloquine is now rarely used for treatment because of concerns about resistance.

Oral. The adult dosage regimen for **quinine** *by mouth* is:

600 mg (of quinine salt[1]) every 8 hours for 5–7 days *together with or followed by*

either **doxycycline** 200 mg once daily for 7 days

or **clindamycin** 450 mg every 8 hours for 7 days [unlicensed indication].

If the parasite is likely to be sensitive, **pyrimethamine** 75 mg with **sulfadoxine** 1.5 g as a single dose [unlicensed] may be given (instead of either clindamycin or doxycycline) together with, or after, a course of quinine.

Alternatively, ***Malarone®*** or ***Riamet®*** may be given instead of quinine. It is not necessary to give

1. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine bisulphate which contains a correspondingly smaller amount of quinine.

doxycycline, clindamycin or pyrimethamine with sulfadoxine after *Malarone®* or *Riamet®* treatment.

The adult dose of ***Malarone®*** *by mouth* is:

4 ('standard') tablets once daily for 3 days.

The dose of ***Riamet®*** *by mouth* for adult with body-weight over 35 kg is:

4 tablets initially, followed by 5 further doses of 4 tablets each given at 8, 24, 36, 48, and 60 hours (total 24 tablets over 60 hours).

Parenteral. If the patient is seriously ill or unable to take tablets, **quinine** should be given *by intravenous infusion* [unlicensed]. The adult dosage regimen for quinine *by infusion* is:

loading dose[1] of 20 mg/kg[2] (up to maximum 1.4 g) of quinine salt[3] infused over 4 hours *then 8 hours after the start of the loading dose,* maintenance dose of 10 mg/kg[4] (up to maximum 700 mg) of quinine salt[3] infused over 4 hours every 8 hours (until patient can swallow tablets to complete the 7-day course *together with or followed by either* doxycycline or clindamycin as above).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous **artesunate** may be available for 'named-patient' use.

Children

Oral. **Quinine** is well tolerated by children although the salts are bitter. The dosage regimen for quinine *by mouth* for children is:

10 mg/kg (of quinine salt[3]; max. 600 mg) every 8 hours for 7 days *together with or followed by*

Clindamycin 7–13 mg/kg (max. 450 mg) every 8 hours for 7 days [unlicensed indication]

or in children over 12 years, **doxycycline** 200 mg once daily for 7 days

or if the parasite is likely to be sensitive, **pyrimethamine** with **sulfadoxine** as a single dose [unlicensed]: up to 4 years and body-weight over 5 kg, pyrimethamine 12.5 mg with sulfadoxine 250 mg; 5–6 years, pyrimethamine 25 mg with sulfadoxine 500 mg; 7–9 years, pyrimethamine 37.5 mg with sulfadoxine 750 mg; 10–14 years, pyrimethamine 50 mg with sulfadoxine 1 g; 14–18 years, pyrimethamine 75 mg with sulfadoxine 1.5 g

Alternatively, ***Malarone®*** or ***Riamet®*** may be given instead of quinine; it is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after *Malarone®* or *Riamet®* treatment. The dose regimen for *Malarone®* *by mouth* for children over 40 kg is the same as for adults (see above); the dose regimen for *Malarone®* for smaller children is reduced as follows:

body-weight 5–8 kg, 2 'paediatric' tablets once daily for 3 days; body-weight 9–10 kg, 3 'paediatric' tablets once daily for 3 days; body-weight 11–20 kg, 1 'standard' tablet once daily for 3 days; body-weight 21–30 kg, 2 'standard' tablets once daily for 3 days; body-weight 31–40 kg, 3 'standard' tablets once daily for 3 days.

The dose regimen of *Riamet®* *by mouth* for children over 12 years and body-weight over 35 kg is the same as for adults (see above). The dose regimen for *Riamet®* for children under 12 years is as follows:

body-weight 5–15 kg 1 tablet initially, followed by 5 further doses of 1 tablet each given at 8, 24, 36, 48, and 60 hours (total 6 tablets over 60 hours); body-weight 15–25 kg 2 tablets initially, followed by 5 further doses of 2 tablets each given at 8, 24, 36, 48, and 60 hours (total 12 tablets over 60 hours); body-weight 25–35 kg 3 tablets initially, followed by 5 further doses of 3 tablets each given at 8, 24, 36, 48, and 60 hours (total 18 tablets over 60 hours)

Parenteral. The dose regimen for quinine *by intravenous infusion* for children is calculated on a mg/kg basis as for adults (see above).

Pregnancy Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The adult treatment doses of oral and intravenous quinine given above (including the loading dose) can safely be given to pregnant women. Clindamycin 450 mg every 8 hours for 7 days [unlicensed indication] should be given with or after quinine. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development); pyrimethamine with sulfadoxine, *Malarone®*, and *Riamet®* are also best avoided until more information is available. Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for 'named patient' use.

Benign malarias (treatment)

Benign malaria is usually caused by *Plasmodium vivax* and less commonly by *P. ovale* and *P. malariae*. **Chloroquine**[5] is the drug of choice for the treatment of benign malarias (but chloroquine-resistant *P. vivax* infection has been reported from Indonesia, New Guinea and some adjacent islands).

The adult dosage regimen for **chloroquine** *by mouth* is:

initial dose of 620 mg of base *then*

a single dose of 310 mg of base after 6 to 8 hours *then*

a single dose of 310 mg of base daily for 2 days

(approximate total cumulative dose of 25 mg/kg of base)

Chloroquine alone is adequate for *P. malariae* infections but in the case of *P. vivax* and *P. ovale*, a *radical*

1. In intensive care units the loading dose can alternatively be given as quinine salt[3] 7 mg/kg infused over 30 minutes followed immediately by 10 mg/kg over 4 hours then (after 8 hours) maintenance dose as described.
2. **Important:** the loading dose of 20 mg/kg should **not** be used if the patient has received quinine or mefloquine during the previous 12 hours.
3. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine bisulphate which contains a correspondingly smaller amount of quinine.
4. Maintenance dose should be reduced to 5–7 mg/kg of quinine salt[3] in patients with severe renal impairment, severe hepatic impairment, or if parenteral treatment is required for more than 48 hours.
5. For the treatment of chloroquine-resistant benign malaria, *Malarone®* [unlicensed indication], quinine, or *Riamet®* [unlicensed indication] can be used; as with chloroquine, primaquine should be given for radical cure.

cure (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with **primaquine**[1] [unlicensed] given after chloroquine; in *P. vivax* infection primaquine is given in an adult dosage of 30 mg daily for 14 days and for *P. ovale* infection it is given in an adult dosage of 15 mg daily for 14 days.

Children The dosage regimen of chloroquine for benign malaria in children is:

initial dose of 10 mg/kg of base (max. 620 mg) *then*

a single dose of 5 mg/kg of base (max. 310 mg) after 6–8 hours *then*

a single dose of 5 mg/kg of base (max. 310 mg) daily for 2 days

For a *radical cure*, primaquine[1] [unlicensed] is then given to children over 6 months of age; specialist advice should be sought for children under 6 months of age. In *P. vivax* infection primaquine is given in a dose of 500 micrograms/kg (max. 30 mg) daily for 14 days, and for *P. ovale* infection it is given in a dose of 250 micrograms/kg (max. 15 mg) daily for 14 days.

Parenteral If the patient is unable to take oral therapy, **quinine** can be given by *intravenous infusion* [unlicensed]. The dose (for adults and children) is 10 mg/kg[2] (max. 700 mg) of quinine salt[3] infused over 4 hours every 8 hours, changed to oral chloroquine as soon as the patient's condition permits.

Pregnancy The adult treatment doses of chloroquine can be given for benign malaria. In the case of *P. vivax* or *P. ovale*, however, the radical cure with primaquine should be **postponed** until the pregnancy is over; instead chloroquine should be continued at a dose of 310 mg each week during the pregnancy.

Prophylaxis against malaria

The recommendations on prophylaxis reflect guidelines agreed by UK malaria specialists; the advice is aimed at residents of the UK who travel to endemic areas. The choice of drug for a particular individual should take into account:

risk of exposure to malaria;

extent of drug resistance;

efficacy of the recommended drugs;

side-effects of the drugs;

patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen).

Protection against bites **Prophylaxis is not absolute**, and breakthrough infection can occur with any of the drugs recommended. Personal protection against being bitten is very important. Mosquito nets impregnated with permethrin provide the most effective barrier protection against insects; mats and vaporised insecticides are also useful. Diethyltoluamide (DEET) 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. Long sleeves and trousers worn after dusk also provide protection.

Length of prophylaxis In order to determine tolerance and to establish habit, prophylaxis should generally be started one week (preferably 2–3 weeks in the case of mefloquine) before travel into an endemic area (or if not possible at earliest opportunity up to 1 or 2 days before travel); *Malarone*® or doxycycline prophylaxis should be started 1–2 days before travel. Prophylaxis should be continued for **4 weeks after leaving** (except for *Malarone*® prophylaxis which should be stopped 1 week after leaving).

In those requiring long-term prophylaxis, chloroquine and proguanil may be used for periods of over 5 years. Mefloquine is licensed for up to 1 year (although it has been used for up to 3 years without undue problems). Doxycycline can be used for up to 2 years. *Malarone*® is licensed for use for up to 28 days but can be used for up to 1 year (and possibly longer) with caution. Specialist advice should be sought for long-term prophylaxis.

Return from malarial region It is important to be aware that **any illness** that occurs within 1 year and **especially within 3 months of return might be malaria** even if all recommended precautions against malaria were taken. Travellers should be **warned** of this and told that if they develop any illness **particularly within 3 months** of their return they should go **immediately** to a doctor and specifically mention their exposure to malaria.

Children Prophylactic doses are based on guidelines agreed by UK malaria experts and may differ from advice in product literature. Weight is a better guide than age. If in doubt telephone centres listed on p. 402.

Epilepsy Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in individuals with a history of epilepsy. In areas *without chloroquine resistance* proguanil 200 mg daily alone is recommended; in areas *with chloroquine resistance*, doxycycline or *Malarone*® may be considered; the metabolism of doxycycline may be influenced by antiepileptics (see **interactions**: Appendix 1 (tetracyclines)).

Asplenia Asplenic individuals (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.

Renal impairment Avoidance (or dosage reduction) of proguanil is recommended since it is excreted by the kidneys. *Malarone*® should not be used for prophylaxis in patients with estimated glomerular filtration rate less than 30 mL/minute/1.73 m^2. Chloroquine is only partially excreted by the kidneys and reduction of the dose for prophylaxis is not required except in severe impairment. Mefloquine is considered to be appropriate

1. Before starting primaquine, blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity since the drug can cause haemolysis in G6PD-deficient patients. Specialist advice should be obtained in G6PD deficiency; in mild G6PD deficiency primaquine in a dose for adults of 45 mg once a week (children 750 micrograms/kg once a week; max. 45 mg once a week) for 8 weeks, has been found useful and without undue harmful effects.
2. Maintenance dose should be reduced to 5–7 mg/kg of quinine salt[3] in patients with severe renal impairment, severe hepatic impairment, or if parenteral treatment is required for more than 48 hours.
3. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine bisulphate which contains a correspondingly smaller amount of quinine.

to use in renal impairment and does not require dosage reduction. Doxycycline is also considered to be appropriate.

Pregnancy Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable, effective prophylaxis must be used. Chloroquine and proguanil can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined, particularly in Sub-Saharan Africa; in the case of proguanil, folic acid 5 mg daily should be given. The centres listed on p. 402 should be consulted for advice on prophylaxis in chloroquine-resistant areas. Although the manufacturer advises that mefloquine should not be used during pregnancy, particularly in the first trimester, unless the potential benefit outweighs the risk, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas. Doxycycline is contra-indicated during pregnancy. *Malarone®* should be avoided during pregnancy unless there is no suitable alternative.

Breast-feeding Prophylaxis is required in **breast-fed infants**; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants Travellers taking warfarin should begin chemoprophylaxis at least 1 week (2–3 weeks for mefloquine) before departure. The INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Specific recommendations

Where a journey requires two regimens, the regimen for the higher risk area should be used for the whole journey. Those travelling to remote or little-visited areas may require expert advice.

Risk may vary in different parts of a country—check under all risk levels

Important Settled immigrants (or long-term visitors) to the UK may be unaware that they will have **lost some of their immunity** and also that the areas where they previously lived **may now be malarious**

North Africa, the Middle East, and Central Asia

Very low risk Risk *very low* in Algeria, Egypt (but *low risk* in El Faiyum, see below), Georgia (south-east, July–October), Kyrgystan (but *low risk* in south-west, see below), Libya, most tourist areas of Turkey (but *low risk* in Adana and border with Syria, see below), Uzbekistan (extreme south-east only):

chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever presents

Low risk Risk *low* in Armenia (June–October), Azerbaijan (southern border areas, June–September), Egypt (El Faiyum only, June–October), Iran (northern border with Azerbaijan, May–October; *variable risk* in rural south-east provinces; see below), rural north Iraq (May–November), Kyrgystan (south-west, May–October), north border of Syria (May–October), Turkey (plain around Adana and east of there, border with Syria, March–November):

preferably

chloroquine *or* (if chloroquine not appropriate) proguanil hydrochloride

Variable risk Risk *variable* and *chloroquine resistance present* in Afghanistan (below 2000 m, May–November), Iran (rural south-east provinces, March–November, see also *Low Risk* above), Oman (remote rural areas only), Saudi Arabia (south-west and rural areas of western region; no risk in Mecca, Medina, Jeddah, or high-altitude areas of Asir Province), Tajikistan (June–October), Yemen (no risk in Sana'a):

chloroquine + proguanil hydrochloride *or* (if chloroquine + proguanil not appropriate) doxycycline

Sub-Saharan Africa

No chemoprophylaxis recommended for Cape Verde (some risk on São Tiago) and Mauritius (but avoid mosquito bites and consider malaria if fever presents)

Very high risk Risk *very high* (or *locally very high*) and *chloroquine resistance very widespread* in Angola, Benin, Botswana (northern half, November–June), Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Democratic Republic of the Congo (formely Zaïre), Djibouti, Equatorial Guinea, Eritrea, Ethiopia (below 2000 m; no risk in Addis Ababa), Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania (all year in south; July–October in north), Mozambique, Namibia (all year along Kavango and Kunene rivers; November–June in northern third), Niger, Nigeria, Principe, Rwanda, São Tomé, Senegal, Sierra Leone, Somalia, South Africa (low-altitude areas of Mpumalanga and Limpopo Provinces, Kruger National Park, and north-east KwaZulu-Natal as far south as Jozini), Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe (all year in Zambezi valley; November–June in other areas below 1200 m; risk negligible in Harare and Bulawayo):

mefloquine *or* doxycycline *or* *Malarone®*

Note In Zimbabwe and neighbouring countries, pyrimethamine with dapsone (also known as *Deltaprim®*) prophylaxis is used by local residents (sometimes with chloroquine)—this regimen is not recommended.

South Asia

Low risk Risk low in Bangladesh (but *high risk* in Chittagong Hill Tracts, see below), India (Kerala [southern states], Tamil Nadu, Karnataka, Southern Andhra Pradesh [including Hyderabad], Mumbai, Rajasthan [including Jaipur], Uttar Pradesh [including Agra], Haryana, Uttaranchal, Himachal Pradesh, Jammu, Kashmir, Punjab, Delhi; *variable risk* in other areas, see below; *high risk* in Assam), Sri Lanka (but *variable risk* north of Vavuniya, see below):

chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever present

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Variable risk Risk *variable* and *chloroquine resistance usually moderate* in southern districts of Bhutan, India (*low risk* in some areas, see above; *high risk* in Assam, see below), Nepal (below 1500 m, especially Terai districts; no risk in Kathmandu), Pakistan (below 2000 m), Sri Lanka (north of Vavuniya; *low risk* in other areas, see above):

chloroquine + proguanil hydrochloride *or* (if chloroquine + proguanil not appropriate) mefloquine *or* doxycycline *or Malarone®*

High risk Risk *high* and *chloroquine resistance high* in Bangladesh (only in Chittagong Hill Tracts; *low risk* in other areas, see above), India (Assam only; see also *Low Risk* and *Variable Risk* above):

mefloquine *or* doxycycline *or Malarone®* *or* (if mefloquine, doxycycline, or *Malarone®* not appropriate) chloroquine + proguanil hydrochloride

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South-East Asia

Very low risk Risk *very low* in Bali, Brunei, Cambodia (Angkor Wat and Siem Reap, but no risk in Phnom Penh; *substantial risk* in other areas, see below; *great risk* in western provinces, see below), main tourist areas of China (but *substantial risk* in Yunnan and Hainan, see below; *chloroquine prophylaxis* appropriate for other remote areas), Hong Kong, Korea (both North and South), Malaysia (both East and West including Cameron Highlands, but *substantial risk* in Sabah [except Kota Kinabalu], and *variable risk* in deep forests, see below), Singapore, Thailand (**important:** regional risk exists, see under *Great Risk*, below), Vietnam (cities, coast between Ho Chi Minh and Hanoi, and Mekong River until close to Cambodian border; *substantial risk* in other areas, see below):

chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever presents

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Variable risk Risk *variable* and *some chloroquine resistance* in Indonesia (*very low risk* in Bali, and cities but *substantial risk* in Irian Jaya [West Papua] and Lombok, see below), rural Philippines below 600 m (no risk in cities, Cebu, Bohol, and Catanduanes), deep forests of peninsular Malaysia and Sarawak (but *substantial risk* in Sabah, see below):

chloroquine + proguanil hydrochloride *or* (if chloroquine + proguanil not appropriate) mefloquine *or* doxycycline *or Malarone®*

Substantial risk Risk *substantial* and *drug resistance common* in Cambodia (no risk or *very low risk* in some areas, see above; *great risk* in western provinces, see below), China (Yunnan and Hainan; *chloroquine prophylaxis* appropriate for other remote areas; see also *Very Low Risk* above), East Timor, Irian Jaya [West Papua], Laos (no risk in Vientiane), Lombok, Malaysia (Sabah; see also *Very Low Risk* and *Variable Risk* above), Myanmar (formerly Burma; see also *Great Risk* below), Vietnam (*very low risk* in some areas, see above):

mefloquine *or* doxycycline *or Malarone®*

Great risk and drug resistance present Risk *great and widespread chloroquine and mefloquine resistance present* in western provinces of Cambodia (see also *Very Low Risk* and *Substantial Risk* above), borders of Thailand with Cambodia, Laos and Myanmar (*very low risk* in Chang Rai and Kwai Bridge, see above), Myanmar (eastern Shan State):

doxycycline *or Malarone®*

Oceania

Risk Risk *high* and *chloroquine resistance high* in Papua New Guinea (below 1800 m), Solomon Islands, Vanuatu:

doxycycline *or* mefloquine *or Malarone®*

Central and South America and the Caribbean

Very low risk Risk *very low* in Jamaica:

chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever presents

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Variable to low risk Risk *variable to low* in Argentina (rural areas along northern borders only), rural Belize (except Belize district), Costa Rica (Limon Province except Puerto Limon and northern canton of Pococci), Dominican Republic, El Salvador (Santa Ana province in west), Guatemala (below 1500 m), Haiti, Honduras, Mexico (states of Oaxaca and Chiapas), Nicaragua,

Panama (west of Panama Canal but *variable to high risk* east of Panama Canal, see below), rural Paraguay:

chloroquine *or* (if chloroquine not appropriate) proguanil hydrochloride

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Variable to high risk Risk *variable to high* and *chloroquine resistance present* in rural areas of Bolivia (below 2500 m), Ecuador (below 1500 m; no malaria in Galapagos Islands and Guayaquil; see below for Esmeraldas Province), Panama (east of Panama Canal), Peru (rural areas east of the Andes and west of the Amazon basin area below 1500 m; see below for Amazon basin area), Venezuela (north of Orinoco river; *high risk* south of and including Orinoco river and Amazon basin area, see below; Caracas free of malaria):

chloroquine + proguanil hydrochloride *or* (if chloroquine + proguanil not appropriate) mefloquine *or* doxycycline *or* *Malarone®*

High risk Risk *high* and *marked chloroquine resistance* in Bolivia (Amazon basin area; see also *variable to high risk* above), Brazil (throughout 'Legal Amazon' area which includes the Amazon basin area, Mato Grosso and Maranhao only; elsewhere *very low risk*—no chemoprophylaxis), Colombia (most areas below 800 m), Ecuador (Esmeraldas Province; *variable to high risk* in other areas, see above), French Guiana, all interior regions of Guyana, Peru (Amazon basin area), Suriname (except Paramaribo and coast), Venezuela (Amazon basin area, areas south of and including Orinoco river):

mefloquine *or* doxycycline *or* *Malarone®*

Standby treatment

Travellers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be **avoided** if medical help is accessible.

In order to avoid excessive self-medication, the traveller should be provided with **written instructions** that urgent medical attention should be sought if fever (38°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

In view of the continuing emergence of resistant strains and of the different regimens required for different areas expert advice should be sought on the best treatment course for an individual traveller.

A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Artemether with lumefantrine

Artemether with lumefantrine is licensed for the *treatment of acute uncomplicated falciparum malaria*.

ARTEMETHER WITH LUMEFANTRINE

Indications treatment of acute uncomplicated falciparum malaria; treatment of benign malaria [unlicensed indication]

Cautions electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; monitor patients unable to take food (greater risk of recrudescence); **interactions:** Appendix 1 (artemether with lumefantrine)

Driving Dizziness may affect performance of skilled tasks (e.g. driving)

Contra-indications history of arrhythmias, of clinically relevant bradycardia, and of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital QT interval prolongation

Hepatic impairment manufacturer advises caution in severe impairment—monitor ECG and plasma-potassium concentration

Renal impairment manufacturer advises caution in severe impairment—monitor ECG and plasma potassium concentration

Pregnancy toxicity in *animal* studies with artemether; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid breast-feeding for at least 1 week after last dose; present in milk in *animal* studies

Side-effects abdominal pain, anorexia, diarrhoea, vomiting, nausea; palpitation, prolonged QT interval; cough; headache, dizziness, sleep disturbances, asthenia, paraesthesia; arthralgia, myalgia; pruritus, rash; *less commonly* ataxia, hypoaesthesia, and clonus

Dose

- Treatment of malaria, see p. 402

Riamet® (Novartis) ▼ PoM

Tablets, yellow, artemether 20 mg, lumefantrine 120 mg, net price 24-tab pack = £22.50. Label: 21, counselling, driving

Note Tablets may be crushed just before administration

Chloroquine

Chloroquine is used for the *prophylaxis of malaria* in areas of the world where the *risk of chloroquine-resistant falciparum malaria is still low*. It is also used with proguanil when chloroquine-resistant falciparum malaria is present but this regimen may not give optimal protection (see specific recommendations by country, p. 405).

Chloroquine is **no longer recommended** for the *treatment of falciparum malaria* owing to widespread resistance, nor is it recommended if the infective species is *not known* or if the infection is *mixed*; in these cases treatment should be with quinine, *Malarone®*, or *Riamet®* (for details, see p. 402). It is still recommended for the *treatment of benign malarias* (for details, see p. 403).

CHLOROQUINE

Indications chemoprophylaxis and treatment of malaria; rheumatoid arthritis and lupus erythematosus (section 10.1.3)

Cautions may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy, see notes above); may aggravate myasthenia gravis; severe gastro-intestinal disorders; G6PD deficiency (see section 9.1.5); ophthalmic examination and long-term therapy, see under Chloroquine, section 10.1.3; avoid concurrent therapy with hepatotoxic drugs—other **interactions:** Appendix 1 (chloroquine and hydroxychloroquine)

Hepatic impairment use with caution in moderate to severe impairment

Renal impairment manufacturers advise caution; see also Prophylaxis Against Malaria, p. 404

Pregnancy benefit of prophylaxis and treatment in malaria outweighs risk; see also Benign Malarias (treatment), p. 404 and Prophylaxis Against Malaria, p. 405

Breast-feeding amount in milk probably too small to be harmful; see also Prophylaxis Against Malaria, p. 405

Side-effects gastro-intestinal disturbances, headache; also hypotension, convulsions, visual disturbances, depigmentation or loss of hair, skin reactions (rashes, pruritus); rarely, bone-marrow suppression, hypersensitivity reactions such as urticaria and angio-edema; other side-effects (not usually associated with malaria prophylaxis or treatment), see under Chloroquine, section 10.1.3; very toxic in **overdosage**—immediate advice from poisons centres essential (see also p. 37)

Dose

Note Doses expressed as chloroquine base

- Prophylaxis of malaria, preferably started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above), 310 mg once weekly; INFANT up to 12 weeks body-weight under 6 kg, 37.5 mg once weekly; 12 weeks–1 year body-weight 6–10 kg, 75 mg once weekly; CHILD 1–4 years body-weight 10–16 kg, 112.5 mg once weekly; 4–8 years body-weight 16–25 kg, 150 mg once weekly (or 155 mg once weekly if tablets used); 8–13 years body-weight 25–45 kg, 225 mg once weekly (or 232.5 mg once weekly if tablets used); over 13 years body-weight over 45 kg, adult dose
- Treatment of benign malarias, see p. 403

Counselling Warn travellers about **importance** of avoiding mosquito bites, **importance** of taking prophylaxis regularly, and **importance** of immediate visit to doctor if ill within 1 year and **especially** within 3 months of return. For details, see notes above

Note Chloroquine doses in BNF may differ from those in product literature

[1] **Avloclor®** (AstraZeneca) PoM

Tablets, scored, chloroquine phosphate 250 mg (≡ chloroquine base 155 mg). Net price 20-tab pack = £1.22. Label: 5, counselling, prophylaxis, see above

[1] **Malarivon®** (Wallace Mfg) PoM

Syrup, chloroquine phosphate 80 mg/5 mL (≡ chloroquine base 50 mg/5 mL), net price 75 mL = £8.75. Label: 5, counselling, prophylaxis, see above

[1] **Nivaquine®** (Sanofi-Aventis) PoM

Syrup, golden, chloroquine sulphate 68 mg/5 mL (≡ chloroquine base 50 mg/5 mL), net price 100 mL = £4.60. Label: 5, counselling, prophylaxis, see above

With proguanil

For cautions and side-effects of proguanil see Proguanil; for dose see Chloroquine and Proguanil

[1] **Paludrine/Avloclor®** (AstraZeneca)

Tablets, travel pack of 14 tablets of chloroquine phosphate 250 mg (≡ chloroquine base 155 mg) and 98 tablets of proguanil hydrochloride 100 mg, net price 112-tab pack = £8.79. Label: 5, 21, counselling, prophylaxis, see above

Mefloquine

Mefloquine is used for the *prophylaxis of malaria* in areas of the world where there is a *high risk of chloroquine-resistant falciparum malaria* (for details, see specific recommendations by country, p. 405).

Mefloquine is now rarely used for the *treatment of falciparum malaria* because of increased resistance. It is rarely used for the treatment of benign malarias because better tolerated alternatives are available. Mefloquine should not be used for treatment if it has been used for prophylaxis.

MEFLOQUINE

Indications chemoprophylaxis of malaria, treatment of malaria, see notes above

Cautions cardiac conduction disorders; epilepsy (avoid for prophylaxis); not recommended in infants under 3 months (5 kg); **interactions:** Appendix 1 (mefloquine)

Driving Dizziness or a disturbed sense of balance may affect performance of skilled tasks (e.g. driving); effects may persist for up to 3 weeks

Contra-indications hypersensitivity to quinine; avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions

Hepatic impairment avoid for prophylaxis in severe liver disease

Pregnancy manufacturer advises adequate contraception during prophylaxis and for 3 months after stopping (teratogenicity in *animal* studies), but see also p. 405

Breast-feeding present in milk but risk to infant minimal; see also p. 405

Side-effects nausea, vomiting, dyspepsia, abdominal pain, diarrhoea; headache, dizziness, sleep disturbances; *less frequently* anorexia, bradycardia, fatigue, abnormal dreams, fever, tinnitus, and neuropsychiatric reactions (including sensory and motor neuropathies, tremor, ataxia, anxiety, depression, panic attacks, agitation, hallucinations, psychosis, convulsions); *rarely* suicidal ideation; *very rarely* pneumonitis; also reported, circulatory disorders (including hypotension and hypertension), chest pain, tachycardia, palpitation, cardiac conduction disorders, oedema, dyspnoea, encephalopathy, leucopenia,

1. Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed

leucocytosis, thrombocytopenia, muscle weakness, myalgia, arthralgia, visual disturbances, vestibular disorders, rash (including Stevens-Johnson syndrome), pruritus, and alopecia

Dose

- Prophylaxis of malaria, preferably started 2½ weeks before entering endemic area and continued for 4 weeks after leaving (see notes above), ADULT and CHILD body-weight over 45 kg, 250 mg once weekly; body-weight 6–16 kg, 62.5 mg once weekly; body-weight 16–25 kg, 125 mg once weekly; body-weight 25–45 kg, 187.5 mg once weekly
- Treatment of malaria, see notes above

Counselling Inform travellers about adverse reactions of mefloquine and, if they occur, to seek medical advice on alternative antimalarials before the next dose is due. Also warn travellers about **importance** of avoiding mosquito bites, **importance** of taking prophylaxis regularly, and **importance** of immediate visit to doctor if ill within 1 year and **especially** within 3 months of return. For details, see notes above

Note Mefloquine doses in BNF may differ from those in product literature

[1] **Lariam®** (Roche) PoM

Tablets, scored, mefloquine (as hydrochloride) 250 mg. Net price 8-tab pack = £14.53. Label: 21, 25, 27, counselling, driving, prophylaxis, see above

Note Tablet may be crushed and mixed with food such as jam or honey just before administration

Primaquine

Primaquine is used to eliminate the liver stages of *P. vivax or P. ovale following chloroquine treatment* (for details, see p. 403).

PRIMAQUINE

Indications adjunct in the treatment of *Plasmodium vivax* and *P. ovale* malaria (eradication of liver stages)

Cautions G6PD deficiency (test blood, see under Benign Malarias (treatment), p. 403); systemic diseases associated with granulocytopenia (e.g. rheumatoid arthritis, lupus erythematosus); **interactions:** Appendix 1 (primaquine)

Pregnancy risk of neonatal haemolysis and methaemoglobinaemia in third trimester; see also p. 404

Breast-feeding no information available; theoretical risk of haemolysis in G6PD-deficient infants

Side-effects nausea, vomiting, anorexia, abdominal pain; less commonly methaemoglobinaemia, haemolytic anaemia especially in G6PD deficiency, leucopenia

Dose

- Treatment of benign malarias, see p. 403

Primaquine (Non-proprietary)

Tablets, primaquine (as phosphate) 7.5 mg or 15 mg

Available from 'special-order' manufacturers or specialist-importing companies, see p. 988

Proguanil

Proguanil is used (usually *with chloroquine*, but occasionally *alone*) for the *prophylaxis of malaria*, (for details, see specific recommendations by country, p. 405).

Proguanil used alone is not suitable for the *treatment of malaria*; however, *Malarone®* (a combination of atovaquone with proguanil) is licensed for the treatment of acute uncomplicated falciparum malaria. *Malarone®* is also used for the *prophylaxis of falciparum malaria* in areas of *widespread mefloquine or chloroquine resistance*. *Malarone®* is also used as an alternative to mefloquine or doxycycline. *Malarone®* is particularly suitable for short trips to highly chloroquine-resistant areas because it needs to be taken only for 7 days after leaving an endemic area.

PROGUANIL HYDROCHLORIDE

Indications chemoprophylaxis of malaria

Cautions **interactions:** Appendix 1 (proguanil)

Renal impairment 100 mg once daily if eGFR 20–60 mL/minute/1.73 m^2; 50 mg on alternate days if eGFR 10–20 mL/minute/1.73 m^2; 50 mg once weekly if eGFR less than 10 mL/minute/1.73 m^2 (increased risk of haematological toxicity)

Pregnancy benefit of prophylaxis in malaria outweighs risk; adequate folate supplements should be given to mother; see also p. 405

Breast-feeding amount in milk probably too small to be harmful when used for malaria prophylaxis; see also p. 405

Side-effects mild gastric intolerance, diarrhoea, and constipation; occasionally mouth ulcers and stomatitis; *very rarely* cholestasis, vasculitis, skin reactions, and hair loss

Dose

- Prophylaxis of malaria, preferably started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above), 200 mg once daily; INFANT up to 12 weeks body-weight under 6 kg, 25 mg once daily; 12 weeks–1 year body-weight 6–10 kg, 50 mg once daily; CHILD 1–4 years body-weight 10–16 kg, 75 mg once daily; 4–8 years body-weight 16–25 kg, 100 mg once daily; 8–13 years, body-weight 25–45 kg, 150 mg once daily; over 13 years body-weight over 45 kg, adult dose

Counselling Warn travellers about **importance** of avoiding mosquito bites, **importance** of taking prophylaxis regularly, and **importance** of immediate visit to doctor if ill within 1 year and **especially** within 3 months of return. For details, see notes above

Note Proguanil doses in BNF may differ from those in product literature.

[2] **Paludrine®** (AstraZeneca)

Tablets, scored, proguanil hydrochloride 100 mg. Net price 98-tab pack = £7.43. Label: 21, counselling, prophylaxis, see above

Note Tablet may be crushed and mixed with food such as milk, jam, or honey just before administration

With chloroquine

See under Chloroquine

PROGUANIL HYDROCHLORIDE WITH ATOVAQUONE

Indications treatment of acute uncomplicated falciparum malaria and prophylaxis of falciparum malaria, particularly where resistance to other antimalarial

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed

2. Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed

drugs suspected; treatment of benign malaria [unlicensed indication]

Cautions diarrhoea or vomiting (reduced absorption of atovaquone); efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure); **interactions:** see Appendix 1 (proguanil, atovaquone)

Renal impairment avoid for malaria prophylaxis (and if possible for malaria treatment) if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid unless essential

Breast-feeding use only if no suitable alternative available; see also p. 405

Side-effects abdominal pain, nausea, vomiting, diarrhoea; cough; headache, dizziness, insomnia, abnormal dreams, depression, anorexia, fever; rash, pruritus; *less frequently* stomatitis, palpitation, anxiety, blood disorders, hyponatraemia, and hair loss; also reported, hepatitis, cholestasis, tachycardia, hallucinations, seizures, vasculitis, mouth ulcers, and Stevens-Johnson syndrome

Dose

- See preparations

Counselling Warn travellers about **importance** of avoiding mosquito bites, **importance** of taking prophylaxis regularly, and **importance** of immediate visit to doctor if ill within 1 year and **especially** within 3 months of return. For details, see notes above

[1] **Malarone®** (GSK) PoM

Tablets ('standard'), pink, f/c, proguanil hydrochloride 100 mg, atovaquone 250 mg. Net price 12-tab pack = £25.21. Label: 21, counselling, prophylaxis, see above

Dose prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 1 week after leaving, ADULT and CHILD over 40 kg, 1 tablet daily

Treatment of malaria, ADULT and CHILD body-weight over 40 kg, 4 tablets once daily for 3 days; CHILD body-weight 11–21 kg 1 tablet daily for 3 days; body-weight 21–31 kg 2 tablets once daily for 3 days; body-weight 31–40 kg 3 tablets once daily for 3 days

[1] **Malarone® Paediatric** (GSK) PoM

Paediatric tablets, pink, f/c proguanil hydrochloride 25 mg, atovaquone 62.5 mg, net price 12-tab pack = £6.26. Label: 21, counselling, prophylaxis, see above

Dose prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 1 week after leaving, CHILD body-weight 11–21 kg, 1 tablet once daily; body-weight 21–31 kg, 2 tablets once daily; body-weight 31–40 kg, 3 tablets once daily; body-weight over 40 kg use *Malarone®* ('standard') tablets

Treatment of malaria, CHILD body-weight 5–9 kg, 2 tablets once daily for 3 days; body-weight 9–11 kg, 3 tablets once daily for 3 days; body-weight 11 kg and over use *Malarone®* ('standard') tablets

Note Tablets may be crushed and mixed with food or milky drink just before administration

Pyrimethamine

Pyrimethamine should not be used alone, but is used with sulfadoxine.

Pyrimethamine with sulfadoxine is not recommended for the *prophylaxis of malaria*, but it can be used in the treatment of *falciparum malaria with (or following) quinine*.

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed

PYRIMETHAMINE

Indications malaria (but used only in combined preparations incorporating sulfadoxine); toxoplasmosis—section 5.4.7

Cautions blood counts required with prolonged treatment; history of seizures—avoid large loading doses; **interactions:** Appendix 1 (pyrimethamine)

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy theoretical teratogenic risk in *first trimester* (folate antagonist); adequate folate supplements should be given to mother

Breast-feeding significant amount in milk—avoid administration of other folate antagonists to infant; avoid breast-feeding during toxoplasmosis treatment

Side-effects depression of haematopoiesis with high doses, rashes, insomnia

Dose

- Malaria, no dose stated because not recommended alone, see Pyrimethamine with Sulfadoxine below
- Toxoplasmosis, section 5.4.7

Daraprim® (GSK) PoM

Tablets, scored, pyrimethamine 25 mg. Net price 30-tab pack = £2.60

PYRIMETHAMINE WITH SULFADOXINE

Indications adjunct to quinine in treatment of *Plasmodium falciparum* malaria; **not** recommended for prophylaxis

Cautions see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); not recommended for prophylaxis (severe side-effects on long-term use); **interactions:** Appendix 1 (pyrimethamine, sulfonamides)

Contra-indications see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); sulfonamide allergy

Pregnancy possible teratogenic risk in *first trimester* (pyrimethamine a folate antagonist); in *third trimester*—risk of neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded; see also p. 403

Breast-feeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfadoxine)

Side-effects see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); pulmonary infiltrates (e.g. eosinophilic or allergic alveolitis) reported—discontinue if cough or shortness of breath

Dose

- Treatment of falciparum malaria, see p. 402
- Prophylaxis, not recommended by UK malaria experts

Pyrimethamine with sulfadoxine (Non-proprietary) PoM

Tablets, scored, pyrimethamine 25 mg, sulfadoxine 500 mg, net price 3-tab pack = 74p

Note Also known as *Fansidar®*

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Quinine

Quinine is not suitable for the *prophylaxis of malaria*.

Quinine is used for the *treatment of falciparum malaria* or if the infective species is *not known* or if the infection is *mixed* (for details see p. 402).

QUININE

Indications falciparum malaria; nocturnal leg cramps, see section 10.2.2

Cautions cardiac disease (including atrial fibrillation, conduction defects, heart block), elderly—monitor ECG during parenteral treatment; monitor blood glucose and electrolyte concentration during parenteral treatment; G6PD deficiency (see section 9.1.5); **interactions:** Appendix 1 (quinine)

Contra-indications haemoglobinuria, myasthenia gravis, optic neuritis, tinnitus

Hepatic impairment for treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt

Renal impairment for treatment of malaria in severe impairment, reduce parenteral maintenance dose to 5–7 mg/kg of quinine salt

Pregnancy high doses are teratogenic in *first trimester*; but in malaria benefit of treatment outweighs risk; see also p. 403

Breast-feeding present in milk but not known to be harmful

Side-effects cinchonism, including tinnitus, hearing impairment, vertigo, headache, nausea, vomiting, abdominal pain, diarrhoea, visual disturbances (including temporary blindness), confusion; cardiovascular effects (see Cautions); dyspnoea; hypersensitivity reactions including angioedema, rashes, hot and flushed skin; hypoglycaemia (especially after parenteral administration); blood disorders (including thrombocytopenia and intravascular coagulation); acute renal failure; muscle weakness; photosensitivity; very toxic in **overdosage**—immediate advice from poisons centres essential (see also p. 37)

Dose

- Treatment of malaria, see p. 402

  Note Quinine (anhydrous base) 100 mg ≡ quinine bisulphate 169 mg ≡ quinine dihydrochloride 122 mg ≡ quinine hydrochloride 122 mg ≡ quinine sulphate 121 mg. Quinine bisulphate 300-mg tablets are available but provide less quinine than 300 mg of the dihydrochloride, hydrochloride, or sulphate

Quinine Sulphate (Non-proprietary) PoM

Tablets, coated, quinine sulphate 200 mg, net price 28-tab pack = £2.20; 300 mg, 28-tab pack = £2.12

Quinine Dihydrochloride (Non-proprietary) PoM

Injection, quinine dihydrochloride 300 mg/mL. For dilution and use as an infusion. 1- and 2-mL amps

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

Note Intravenous injection of quinine is so hazardous that it has been superseded by infusion

Tetracyclines

Doxycycline (section 5.1.3) is used for the *prophylaxis of malaria* in areas of *widespread mefloquine or chloroquine resistance*. Doxycycline is also used as an alternative to mefloquine or *Malarone®* (for details, see specific recommendations by country, p. 405).

Doxycycline is also used as an *adjunct to quinine in the treatment of falciparum malaria* (for details see p. 402).

DOXYCYCLINE

Indications prophylaxis of malaria; adjunct to quinine in treatment of *Plasmodium falciparum* malaria; see also section 5.1.3

Cautions section 5.1.3

Contra-indications section 5.1.3

Hepatic impairment section 5.1.3

Renal impairment section 5.1.3

Pregnancy section 5.1.3

Breast-feeding section 5.1.3

Side-effects section 5.1.3

Dose

- Prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 4 weeks after leaving (see notes above), ADULT and CHILD over 12 years, 100 mg once daily
- Treatment of falciparum malaria, see p. 402

Preparations

Section 5.1.3

5.4.2 Amoebicides

Metronidazole is the drug of choice for *acute invasive amoebic dysentery* since it is very effective against vegetative forms of *Entamoeba histolytica* in ulcers; it is given in an adult dose of 800 mg three times daily for 5 days. **Tinidazole** is also effective. Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver. Treatment with metronidazole (or tinidazole) is followed by a 10-day course of diloxanide furoate.

Diloxanide furoate is the drug of choice for asymptomatic patients with *E. histolytica* cysts in the faeces; metronidazole and tinidazole are relatively ineffective. Diloxanide furoate is relatively free from toxic effects and the usual course is of 10 days, given alone for chronic infections or following metronidazole or tinidazole treatment.

For *amoebic abscesses* of the liver **metronidazole** is effective; tinidazole is an alternative. Aspiration of the abscess is indicated where it is suspected that it may rupture or where there is no improvement after 72 hours of metronidazole; the aspiration may need to be repeated. Aspiration aids penetration of metronidazole and, for abscesses with more than 100 mL of pus, if carried out in conjunction with drug therapy, may reduce the period of disability.

Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

DILOXANIDE FUROATE

Indications see notes above; chronic amoebiasis and as adjunct to metronidazole or tinidazole in acute amoebiasis

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid

Side-effects flatulence, vomiting, urticaria, pruritus

Dose

- 500 mg every 8 hours for 10 days; CHILD body-weight over 25 kg, 20 mg/kg daily in 3 divided doses for 10 days; body-weight under 25 kg, see *BNF for Children*

See also notes above

Diloxanide (Sovereign) PoM

Tablets, diloxanide furoate 500 mg, net price 30-tab pack = £93.50. Label: 9

METRONIDAZOLE

Indications see under Dose below; anaerobic infections, section 5.1.11

Cautions section 5.1.11

Hepatic impairment section 5.1.11

Pregnancy section 5.1.11

Breast-feeding section 5.1.11

Side-effects section 5.1.11

Dose

- By mouth, invasive intestinal amoebiasis, extra-intestinal amoebiasis (including liver abcess), 800 mg every 8 hours for 5 days in intestinal infection (for 5–10 days in extra-intestinal infection); CHILD 1–3 years 200 mg every 8 hours; 3–7 years 200 mg every 6 hours; 7–10 years 400 mg every 8 hours

  Urogenital trichomoniasis, 200 mg every 8 hours for 7 days *or* 400–500 mg every 12 hours for 5–7 days, *or* 2 g as a single dose; CHILD 1–3 years 50 mg every 8 hours for 7 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours

  Giardiasis, 2 g daily for 3 days *or* 400 mg 3 times daily for 5 days *or* 500 mg twice daily for 7–10 days; CHILD 1–3 years 500 mg daily for 3 days; 3–7 years 600–800 mg daily; 7–10 years 1 g daily

Preparations

Section 5.1.11

TINIDAZOLE

Indications see under Dose below; anaerobic infections, section 5.1.11

Cautions section 5.1.11

Pregnancy section 5.1.11

Breast-feeding section 5.1.11

Side-effects section 5.1.11

Dose

- Intestinal amoebiasis, 2 g daily for 2–3 days; CHILD 50–60 mg/kg daily for 3 days
- Amoebic involvement of liver, 1.5–2 g daily for 3–6 days; CHILD 50–60 mg/kg daily for 5 days
- Urogenital trichomoniasis and giardiasis, single 2 g dose; CHILD single dose of 50–75 mg/kg (repeated once if necessary)

Preparations

Section 5.1.11

5.4.3 Trichomonacides

Metronidazole (section 5.4.2) is the treatment of choice for *Trichomonas vaginalis* infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, **tinidazole** (section 5.4.2) may be tried.

5.4.4 Antigiardial drugs

Metronidazole (section 5.4.2) is the treatment of choice for *Giardia lamblia* infections. Alternative treatments are **tinidazole** (section 5.4.2) or **mepacrine hydrochloride**.

MEPACRINE HYDROCHLORIDE

Indications giardiasis; discoid lupus erythematosus (Antimalarials, section 10.1.3)

Cautions hepatic impairment, elderly, history of psychosis; avoid in psoriasis; **interactions:** Appendix 1 (mepacrine)

Side-effects gastro-intestinal disturbances; dizziness, headache; with large doses nausea, vomiting and occasionally transient acute toxic psychosis and CNS stimulation; on prolonged treatment yellow discoloration of skin and urine, chronic dermatoses (including severe exfoliative dermatitis), hepatitis, aplastic anaemia; also reported blue/black discoloration of palate and nails and corneal deposits with visual disturbances

Dose

- Giardiasis [unlicensed], 100 mg every 8 hours for 5–7 days

Mepacrine Hydrochloride

Tablets, mepacrine hydrochloride 100 mg. Label: 4, 9, 14, 21

Available from 'special-order' manufacturers or specialist importing companies, see p. 988

5.4.5 Leishmaniacides

Cutaneous leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate, an organic pentavalent antimony compound, is used for visceral leishmaniasis. The dose is 20 mg/kg daily (max. 850 mg) by intramuscular or intravenous injection for 28 days in visceral leishmaniasis and for 20 days in cutaneous infection; the dosage varies with different geographical regions and expert advice should be obtained. Some early non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate under specialist supervision.

Amphotericin is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (*AmBisome*®—section 5.2) at a dose of 1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg *or* at a dose of 3 mg/kg for 5 consecutive days followed by a single dose of

3 mg/kg 6 days later. *Abelcet®*, a lipid formulation of amphotericin is also likely to be effective but less information is available.

Pentamidine isetionate (pentamidine isethionate) (section 5.4.8) has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988).

SODIUM STIBOGLUCONATE

Indications leishmaniasis

Cautions intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); monitor ECG before and during treatment; heart disease (withdraw if conduction disturbances occur); treat intercurrent infection (e.g. pneumonia)

Mucocutaneous disease Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroid

Hepatic impairment use with caution

Renal impairment avoid in significant impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount probably too small to be harmful

Side-effects anorexia, nausea, vomiting, abdominal pain, diarrhoea; ECG changes; coughing (see Cautions); headache, lethargy; arthralgia, myalgia; *rarely* jaundice, flushing, bleeding from nose or gum, substernal pain (see Cautions), vertigo, fever, sweating, and rash; also reported pancreatitis and anaphylaxis; pain and thrombosis on intravenous administration, intramuscular injection also painful

Dose

- See notes above

Pentostam® (GSK) PoM

Injection, sodium stibogluconate equivalent to pentavalent antimony 100 mg/mL. Net price 100-mL bottle = £66.43

Note Injection should be filtered immediately before administration using a filter of 5 microns or less

5.4.6 Trypanocides

The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

5.4.7 Drugs for toxoplasmosis

Most infections caused by *Toxoplasma gondii* are self-limiting, and treatment is not necessary. Exceptions are patients with eye involvement (toxoplasma choroidoretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine and sulfadiazine, given for several weeks (expert advice **essential**). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folinic acid supplements and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin or clarithromycin or azithromycin. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus. Spiramycin [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) may reduce the risk of transmission of maternal infection to the fetus.

5.4.8 Drugs for pneumocystis pneumonia

Pneumonia caused by *Pneumocystis jirovecii (Pneumocystis carinii)* occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

Treatment

Mild to moderate disease **Co-trimoxazole** (section 5.1.8) in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

Atovaquone is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole. A combination of **dapsone** 100 mg daily (section 5.1.10) with **trimethoprim** 5 mg/kg every 6–8 hours (section 5.1.8) is given by mouth for the treatment of mild to moderate disease [unlicensed indication].

A combination of **clindamycin** 600 mg by mouth every 8 hours (section 5.1.6) and **primaquine** 30 mg daily by mouth (section 5.4.1) is used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

Severe disease **Co-trimoxazole** (section 5.1.8) in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. **Pentamidine isetionate** given by intravenous infusion is an alternative for patients who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion.

Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia (see Adjunctive Therapy below).

Adjunctive therapy In moderate to severe infections associated with HIV infection, prednisolone 50–80 mg daily is given by mouth for 5 days (alternatively, hydrocortisone may be given parenterally); the dose is then reduced to complete 21 days of treatment. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

Prophylaxis

Prophylaxis against pneumocystis pneumonia should be given to all patients with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients. Prophylaxis should continue until immunity recovers sufficiently. It should not be discontinued if the patient has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy.

Co-trimoxazole by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. It is given in a dose of 960 mg daily or 960 mg on alternate days (3 times a week); the dose may be reduced to co-trimoxazole 480 mg daily to improve tolerance.

Inhaled **pentamidine isetionate** is better tolerated than parenteral pentamidine. Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in patients unable to tolerate co-trimoxazole. It is effective but patients may be prone to extrapulmonary infection. Alternatively, **dapsone** 100 mg daily (section 5.1.10) can be used. **Atovaquone** 750 mg twice daily has also been used for prophylaxis [unlicensed indication].

ATOVAQUONE

Indications treatment of mild to moderate *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia in patients intolerant of co-trimoxazole

Cautions initial diarrhoea and difficulty in taking with food may reduce absorption (and require alternative therapy); other causes of pulmonary disease should be sought and treated; elderly; **interactions:** Appendix 1 (atovaquone)

Hepatic impairment manufacturer advises caution—monitor more closely

Renal impairment manufacturer advises caution—monitor more closely

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk—no information available

Breast-feeding manufacturer advises avoid

Side-effects nausea, diarrhoea, vomiting; headache, insomnia; fever; anaemia, neutropenia, hyponatraemia; rash, pruritus; also reported, Stevens-Johnson syndrome

Dose

- 750 mg twice daily with food (particularly high fat) for 21 days; CHILD not recommended

Wellvone® (GSK) PoM

Suspension, sugar-free, atovaquone 750 mg/5 mL, net price 226 mL (tutti-frutti-flavoured) = £405.31. Label: 21

With proguanil hydrochloride

See section 5.4.1

PENTAMIDINE ISETIONATE

Indications see under Dose (should only be given by specialists)

Cautions risk of severe hypotension following administration (monitor blood pressure before starting treatment, during administration, and at regular intervals, until treatment concluded; patient should be lying down when receiving drug parenterally); hypokalaemia, hypomagnesaemia, coronary heart disease, bradycardia, history of ventricular arrhythmias, concomitant use with other drugs which prolong QT-interval; hypertension or hypotension; hyperglycaemia or hypoglycaemia; leucopenia, thrombocytopenia, or anaemia; carry out laboratory monitoring according to product literature; care required to protect personnel during handling and administration; **interactions:** Appendix 1 (pentamidine isetionate)

Hepatic impairment manufacturer advises caution

Renal impairment reduce intravenous dose for pneumocystis pneumonia if creatinine clearance less than 10 mL/minute: in *life-threatening infection*, use 4 mg/kg once daily for 7–10 days, then 4 mg/kg on alternate days to complete course of at least 14 doses; in *less severe infection*, use 4 mg/kg on alternate days for at least 14 doses

Pregnancy manufacturer advises avoid unless essential

Breast-feeding manufacturer advises avoid unless essential—no information available

Side-effects severe reactions, sometimes fatal, due to hypotension, hypoglycaemia, pancreatitis, and arrhythmias; also leucopenia, thrombocytopenia, acute renal failure, hypocalcaemia; also reported: azotaemia, abnormal liver-function tests, anaemia, hyperkalaemia, nausea and vomiting, dizziness, syncope, flushing, hyperglycaemia, rash, and taste disturbances; Stevens-Johnson syndrome reported; on inhalation, bronchoconstriction (may be prevented by prior use of bronchodilators), cough, and shortness of breath; discomfort, pain, induration, abscess formation, and muscle necrosis at injection site

Dose

- Treatment of *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia, by intravenous infusion, 4 mg/kg once daily for at least 14 days
- Prophylaxis of *Pneumocystis jirovecii (Pneumocystis carinii)* pneumonia, by inhalation of nebulised solution (using suitable equipment—consult product literature), 300 mg every 4 weeks *or* 150 mg every 2 weeks [unlicensed for primary prevention]
- Visceral leishmaniasis (kala-azar, section 5.4.5), by deep intramuscular injection, 3–4 mg/kg on alternate days to max. total of 10 injections; course may be repeated if necessary
- Cutaneous leishmaniasis, by deep intramuscular injection, 3–4 mg/kg once or twice weekly until condition resolves (but see also section 5.4.5)
- Trypanosomiasis, by deep intramuscular injection *or* intravenous infusion, 4 mg/kg daily or on alternate days to total of 7–10 injections

Note Direct intravenous injection should be avoided whenever possible and **never** given rapidly; intramuscular injections should be deep and preferably given into the buttock

Pentacarinat® (Sanofi-Aventis) PoM

Injection, powder for reconstitution, pentamidine isetionate, net price 300-mg vial = £30.45

Nebuliser solution, pentamidine isetionate, net price 300-mg bottle = £32.15

Caution in handling Pentamidine isetionate is toxic and personnel should be adequately protected during handling and administration—consult product literature

5.5 Anthelmintics

5.5.1 Drugs for threadworms
5.5.2 Ascaricides
5.5.3 Drugs for tapeworm infections
5.5.4 Drugs for hookworms
5.5.5 Schistosomicides
5.5.6 Filaricides
5.5.7 Drugs for cutaneous larva migrans
5.5.8 Drugs for strongyloidiasis

Advice on prophylaxis and treatment of helminth infections is available from:

Birmingham	(0121) 424 0357
Scottish Centre for Infection and Environmental Health (registered users of Travax only)	(0141) 300 1100 (weekdays 2–4 p.m. only)
Liverpool	(0151) 708 9393
London	0845 155 5000 (treatment)

5.5.1 Drugs for threadworms (pinworms, Enterobius vermicularis)

Anthelmintics are effective in threadworm infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment.

Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Washing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole is the drug of choice for treating threadworm infection in patients of all ages over 2 years. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

Piperazine is available in combination with sennosides as a single-dose preparation.

MEBENDAZOLE

Indications threadworm, roundworm, whipworm, and hookworm infections

Cautions **interactions:** Appendix 1 (mebendazole)

Note The package insert in the *Vermox®* pack includes the statement that it is not suitable for women known to be pregnant or children under 2 years

Pregnancy manufacturer advises toxicity in *animal* studies

Breast-feeding amount too small to be harmful but manufacturer advises avoid

Side-effects abdominal pain; *less commonly* diarrhoea, flatulence, rash; *very rarely* hepatitis, convulsions, neutropenia, urticaria, alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis

Dose

- Threadworms, ADULT and CHILD over 2 years, 100 mg as a single dose; if reinfection occurs second dose may be needed after 2 weeks; CHILD under 2 years, see *BNF for Children*
- Whipworms, ADULT and CHILD over 2 years, 100 mg twice daily for 3 days; CHILD under 2 years, see *BNF for Children*
- Roundworms—section 5.5.2
- Hookworms—section 5.5.4

[1] **Mebendazole** (Non-proprietary) PoM

Tablets, chewable, mebendazole 100 mg

1. Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg

Vermox® (Janssen-Cilag) PoM

Tablets, orange, scored, chewable, mebendazole 100 mg. Net price 6-tab pack = £1.36

Oral suspension, mebendazole 100 mg/5 mL (banana-flavoured). Net price 30 mL = £1.59

PIPERAZINE

Indications threadworm and roundworm infections

Cautions epilepsy; packs on sale to the general public carry a warning to avoid in epilepsy, or in liver or kidney disease, and to seek medical advice in pregnancy

Hepatic impairment manufacturer advises avoid

Renal impairment use with caution; avoid in severe renal impairment; risk of neurotoxicity

Pregnancy not known to be harmful but manufacturer advises avoid in first trimester

Breast-feeding present in milk—manufacturer advises avoid breast-feeding for 8 hours after dose (express and discard milk during this time)

Side-effects nausea, vomiting, colic, diarrhoea, allergic reactions including urticaria, bronchospasm, and rare reports of arthralgia, fever, Stevens-Johnson syndrome and angioedema; rarely dizziness, muscular incoordination ('worm wobble'); drowsiness, nystagmus, vertigo, blurred vision, confusion and clonic contractions in patients with neurological or renal abnormalities

Dose

- See under Preparation, below

With sennosides

For cautions, contra-indications, side-effects of senna see section 1.6.2

Pripsen® (Thornton & Ross)

Oral powder, piperazine phosphate 4 g, total sennosides (calculated as sennoside B) 15.3 mg/sachet. Net price two-dose sachet pack = £1.98. Label: 13

Dose threadworms, stirred into milk or water, ADULT and CHILD over 6 years, content of 1 sachet as a single dose (bedtime in adults or morning in children), repeated after 14 days; INFANT 3 months–1 year, 1 level 2.5-mL spoonful in the morning, repeated after 14 days; CHILD 1–6 years, 1 level 5-mL spoonful in the morning, repeated after 14 days

Roundworms, first dose as for threadworms; repeat at monthly intervals for up to 3 months if reinfection risk

5.5.2 Ascaricides
(common roundworm infections)

Mebendazole (section 5.5.1) is effective against *Ascaris lumbricoides* and is generally considered to be the drug of choice; the usual dose is 100 mg twice daily for 3 days *or* 500 mg as a single dose [unlicensed single dose].

Levamisole [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is an alternative when mebendazole cannot be used. It is very well tolerated; mild nausea or vomiting has been reported in about 1% of treated patients; it is given as a single dose of 120–150 mg in adults.

Piperazine may be given in a single adult dose, see Piperazine, above.

5.5.3 Drugs for tapeworm infections

Taenicides

Niclosamide [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus; it is not effective against larval worms. Fears of developing cysticercosis in *Taenia solium* infections have proved unfounded. All the same, an antiemetic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is as effective as niclosamide and is given as a single dose of 5–10 mg/kg after a light breakfast (a single dose of 25 mg/kg for *Hymenolepis nana*).

Hydatid disease

Cysts caused by *Echinococcus granulosus* grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. **Albendazole** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Alveolar echinococcosis due to *E. multilocularis* is usually fatal if untreated. Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

5.5.4 Drugs for hookworms
(ancylostomiasis, necatoriasis)

Hookworms live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole (section 5.5.1) has a useful broad-spectrum activity, and is effective against hookworms; the usual dose is 100 mg twice daily for 3 days. **Albendazole** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) given as a single dose of 400 mg, is an alternative.

5.5.5 Schistosomicides
(bilharziasis)

Adult *Schistosoma haematobium* worms live in the genito-urinary veins and adult *S. mansoni* in those of the colon and mesentery. *S. japonicum* is more widely distributed in veins of the alimentary tract and portal system.

Praziquantel [unlicensed] is available from Merck Serono (*Cysticide*®) and is effective against all human schistosomes. The dose is 20 mg/kg followed after 4–6 hours by one further dose of 20 mg/kg (20 mg/kg given 3 times on one day for *S. japonicum* infections). No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

Hycanthone, lucanthone, niridazole, oxamniquine, and sodium stibocaptate have now been superseded.

5.5.6 Filaricides

Diethylcarbamazine [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is effective against microfilariae and adults of *Loa loa*, *Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions treatment is commenced with a dose of diethylcarbamazine citrate 1 mg/kg on the first day and increased gradually over 3 days to 6 mg/kg daily in divided doses (up to 9 mg/kg daily in divided doses for *Loa loa*); this dosage is maintained for a further period. Close medical supervision is necessary particularly in the early phase of treatment.

In heavy infections there may be a febrile reaction, and in heavy *Loa loa* infection there is a small risk of encephalopathy. In such cases specialist advice should be sought, and treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement.

Ivermectin [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is very effective in *onchocerciasis* and it is now the drug of choice. A single dose of 150 micrograms/kg by mouth produces a prolonged reduction in microfilarial levels. Retreatment at intervals of 6 to 12 months depending on symptoms must be given until the adult worms die out. Reactions are usually slight and most commonly take the form of temporary aggravation of itching and rash. Diethylcarbamazine or suramin should no longer be used for onchocerciasis because of their toxicity.

5.5.7 Drugs for cutaneous larva migrans
(creeping eruption)

Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical tiabendazole (no commercial preparation available). Multiple infections respond to **ivermectin**, **albendazole** or **tiabendazole** (thiabendazole) by mouth [all unlicensed] and available from 'special-order' manufacturers or specialist importing companies, see p. 988).

5.5.8 Drugs for strongyloidiasis

Adult *Strongyloides stercoralis* live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. **Ivermectin** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) in a dose of 200 micrograms/kg daily for 2 days is the treatment of choice for chronic *Strongyloides* infection. **Albendazole** [unlicensed] (available from 'special-order' manufacturers or specialist importing companies, see p. 988) is an alternative given in a dose of 400 mg twice daily for 3 days, repeated after 3 weeks if necessary.

6 Endocrine system

6.1 Drugs used in diabetes 418
6.1.1 Insulins 419
6.1.1.1 Short-acting insulins 422
6.1.1.2 Intermediate- and long-acting insulins 423
6.1.1.3 Hypodermic equipment 426
6.1.2 Antidiabetic drugs 427
6.1.2.1 Sulfonylureas 427
6.1.2.2 Biguanides 429
6.1.2.3 Other antidiabetic drugs 430
6.1.3 Diabetic ketoacidosis 435
6.1.4 Treatment of hypoglycaemia 435
6.1.5 Treatment of diabetic nephropathy and neuropathy 436
6.1.6 Diagnostic and monitoring devices for diabetes mellitus 437
6.2 Thyroid and antithyroid drugs 439
6.2.1 Thyroid hormones 439
6.2.2 Antithyroid drugs 440
6.3 Corticosteroids 442
6.3.1 Replacement therapy 442
6.3.2 Glucocorticoid therapy 442
6.4 Sex hormones 449
6.4.1 Female sex hormones 449
6.4.1.1 Oestrogens and HRT 449
6.4.1.2 Progestogens 456
6.4.2 Male sex hormones and antagonists 458
6.4.3 Anabolic steroids 461
6.5 Hypothalamic and pituitary hormones and anti-oestrogens 461
6.5.1 Hypothalamic and anterior pituitary hormones and anti-oestrogens 461
6.5.2 Posterior pituitary hormones and antagonists 466
6.6 Drugs affecting bone metabolism 469
6.6.1 Calcitonin and parathyroid hormone 470
6.6.2 Bisphosphonates and other drugs affecting bone metabolism 471
6.7 Other endocrine drugs 477
6.7.1 Bromocriptine and other dopaminergic drugs 477
6.7.2 Drugs affecting gonadotrophins 479
6.7.3 Metyrapone and trilostane 482
6.7.4 Somatomedins 483

This chapter also includes advice on the drug management of the following:

- Adrenal suppression during illness, trauma or surgery, p. 444
- Serious infections in patients taking corticosteroids, p. 444
- Osteoporosis, p. 469
- Breast pain (mastalgia), p. 482

For hormonal contraception, see section 7.3.

6.1 Drugs used in diabetes

6.1.1 Insulins
6.1.2 Antidiabetic drugs
6.1.3 Diabetic ketoacidosis
6.1.4 Treatment of hypoglycaemia
6.1.5 Treatment of diabetic nephropathy and neuropathy
6.1.6 Diagnostic and monitoring devices for diabetes mellitus

Diabetes mellitus occurs because of a lack of insulin or resistance to its action. It is diagnosed by measuring fasting or random blood-glucose concentration (and occasionally by oral glucose tolerance test). Although there are many subtypes, the two principal classes of diabetes are type 1 diabetes and type 2 diabetes.

Type 1 diabetes, (formerly referred to as insulin-dependent diabetes mellitus (IDDM)), occurs as a result of a deficiency of insulin following autoimmune destruction of pancreatic beta cells. Patients with type 1 diabetes require administration of insulin.

Type 2 diabetes, (formerly referred to as non-insulin-dependent diabetes (NIDDM)), is due to reduced secretion of insulin or to peripheral resistance to the action of insulin or to a combination of both. Although patients may be controlled on diet alone, many also require oral antidiabetic drugs or insulin (or both) to maintain satisfactory control. In overweight individuals, type 2 diabetes may be prevented by losing weight and increasing physical activity; use of the anti-obesity drug orlistat (section 4.5.1) may be considered in obese patients.

Treatment of diabetes Treatment of all forms of diabetes should be aimed at alleviating symptoms and minimising the risk of long-term complications (see below); tight control of diabetes is essential.

Diabetes is a strong risk factor for cardiovascular disease (section 2.12). Other risk factors for cardiovascular disease such as smoking (section 4.10.2), hypertension (section 2.5), obesity (section 4.5), and hyperlipidaemia

(section 2.12) should be addressed. Cardiovascular risk in patients with diabetes can be further reduced by the use of an ACE inhibitor (section 2.5.5.1), low-dose aspirin (section 2.9) and a lipid-regulating drug (section 2.12).

Prevention of diabetic complications Optimal glycaemic control in both type 1 diabetes and type 2 diabetes reduces, in the long term, the risk of microvascular complications including retinopathy, development of proteinuria and to some extent neuropathy. However, a temporary deterioration in established diabetic retinopathy may occur when normalising blood-glucose concentration. For reference to the use of an ACE inhibitor or an angiotensin-II receptor antagonist in the management of diabetic nephropathy, see section 6.1.5.

A measure of the total glycosylated (or glycated) haemoglobin (HbA_t) or a specific fraction (HbA_{1c}) provides a good indication of glycaemic control over the previous 2–3 months. Overall it is ideal to aim for an HbA_{1c} (glycosylated haemoglobin) concentration of 48–59 mmol/mol (6.5–7.5%) or less (reference range 20–42 mmol/mol *or* 4–6%) but this cannot always be achieved and for those using insulin there is a significantly increased risk of disabling hypoglycaemia; in those at risk of arterial disease, the aim should be to maintain the HbA_{1c} concentration at 48 mmol/mol (6.5%) or less. HbA_{1c} should be measured every 3–6 months.

Measurement of HbA_{1c}

HbA_{1c} values currently expressed as a percentage, are aligned to the assay used in the Diabetes Control and Complications Trial (DCCT). A new standard, specific for HbA_{1c}, has been created by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), which expresses HbA_{1c} values in *mmol of glycosylated haemoglobin per mol of haemoglobin*. UK laboratories now express results in both IFCC-standardised units (mmol/mol) and DCCT-aligned units (%). From **1 June 2011**, results will only be reported in IFCC-standardised units.

Equivalent values

IFCC-HbA_{1c} (mmol/mol)	DCCT-HbA_{1c} (%)
42	6.0
48	6.5
53	7.0
59	7.5
64	8.0
75	9.0

Laboratory measurement of serum-fructosamine concentration is technically simpler and cheaper than the measurement of HbA_{1c} and can be used to assess control over short periods of time, particularly when HbA_{1c} monitoring is invalid (e.g. disturbed erythrocyte turnover or abnormal haemoglobin type).

Tight control of blood pressure in hypertensive patients with type 2 diabetes reduces mortality and protects visual acuity (by reducing considerably the risks of maculopathy and retinal photocoagulation) (see also section 2.5).

Driving Drivers with diabetes are required to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition if they are treated with insulin or if they are treated with oral antidiabetic drugs and also have complications. Detailed guidance on eligibility to drive is available from the DVLA (www.dvla.gov.uk/medical.aspx). Driving is not permitted when hypoglycaemic awareness is impaired or frequent hypoglycaemic episodes occur.

Drivers need to be particularly careful to avoid hypoglycaemia (see also above) and should be warned of the problems. Drivers treated with insulin should normally check their blood-glucose concentration before driving and, on long journeys, at 2-hour intervals; these precautions may also be necessary for drivers taking oral antidiabetic drugs who are at particular risk of hypoglycaemia. Drivers treated with insulin should ensure that a supply of sugar is always available in the vehicle and they should avoid driving if their meal is delayed. If hypoglycaemia occurs, or warning signs develop, the driver should:

- stop the vehicle in a safe place;
- switch off the ignition;
- eat or drink a suitable source of sugar;
- wait until recovery is complete before continuing journey; recovery may take 15 minutes or longer and should preferably be confirmed by checking blood-glucose concentration.

6.1.1 Insulins

6.1.1.1 Short-acting insulins
6.1.1.2 Intermediate- and long-acting insulins
6.1.1.3 Hypodermic equipment

Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism. It is a polypeptide hormone of complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogues. Insulin may be extracted from pork pancreas and purified by crystallisation; it may also be extracted from beef pancreas, but beef insulins are now rarely used. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin (emp) or biosynthetically by recombinant DNA technology using bacteria (crb, prb) or yeast (pyr).

All insulin preparations are to a greater or lesser extent immunogenic in man but immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic, but no real advantage has been shown in trials.

Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin is usually injected into the upper arms, thighs, buttocks, or abdomen; absorption from a limb site may be increased if the limb is used in strenuous exercise after the injection. Generally subcutaneous insulin injections cause few problems; lipodystrophy may occur but can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin is needed by all patients with ketoacidosis, and it is likely to be needed by most patients with:

- rapid onset of symptoms;
- substantial loss of weight;
- weakness;
- ketonuria;
- a first-degree relative who has type 1 diabetes.

Insulin is required by almost all children with diabetes. It is also needed for type 2 diabetes when other methods have failed to achieve good control, and temporarily in the presence of intercurrent illness or peri-operatively. Pregnant women with type 2 diabetes may be treated with insulin when diet alone fails. For advice on use of oral antidiabetic drugs in the management of diabetes in pregnancy, see section 6.1.2.

NHS Diabetes guidance
Safe and Effective Use of Insulin in Hospitalised Patients (March 2010)
Available at www.diabetes.nhs.uk

Management of diabetes with insulin The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the patient obsessional and to avoid disabling hypoglycaemia; close co-operation is needed between the patient and the medical team because good control reduces the risk of complications.

Insulin preparations can be divided into 3 types:

- those of **short** duration which have a relatively rapid onset of action, namely soluble insulin and the rapid-acting insulin analogues, insulin aspart, insulin glulisine, and insulin lispro (section 6.1.1.1);
- those with an **intermediate** action, e.g. isophane insulin (section 6.1.1.2); and
- those whose action is slower in onset and lasts for **long** periods, e.g. protamine zinc insulin, insulin detemir, and insulin glargine (section 6.1.1.2).

The duration of action of a particular type of insulin varies considerably from one patient to another, and needs to be assessed individually.

Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual patient. Treatment should be started with a short-acting insulin (e.g. soluble insulin) or a rapid-acting insulin analogue (e.g. insulin aspart) given before meals with intermediate-acting or long-acting insulin once or twice daily. Alternatively, for those who have difficulty with, or prefer not to use, multiple injection regimens, a mixture of premixed short-acting insulin or rapid acting insulin analogue with an intermediate-acting or long-acting insulin (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) can be given once or twice daily. The dose of short-acting or rapid-acting insulin (or the proportion of the short-acting soluble insulin component in premixed insulin) can be increased in those with excessive post-prandial hyperglycaemia. The dose of insulin is increased gradually according to the patient's individual requirements, taking care to avoid troublesome hypoglycaemic reactions.

Insulin requirements may be increased by infection, stress, accidental or surgical trauma, and during puberty. Requirements may be decreased in those with certain endocrine disorders (e.g. Addison's disease, hypopituitarism), or in coeliac disease.

Examples of recommended insulin regimens

- Multiple injection regimen: short-acting insulin or rapid-acting insulin analogue, before meals
  With intermediate-acting or long-acting insulin, once or twice daily;
- Short-acting insulin or rapid-acting insulin analogue mixed with intermediate-acting or long-acting insulin, once or twice daily (before meals);
- Intermediate-acting or long-acting insulin, once or twice daily
  With or without short-acting insulin or rapid-acting insulin before meals;
- Continuous subcutaneous insulin infusion (see below).

Hepatic impairment Insulin requirements may be decreased in patients with hepatic impairment.

Renal impairment Insulin requirements may fall in patients with renal impairment and therefore dose reduction may be necessary. The compensatory response to hypoglycaemia is impaired in renal impairment.

Pregnancy and breast-feeding During pregnancy and breast-feeding, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician. The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy. The short-acting insulin analogues, insulin aspart and insulin lispro, are not known to be harmful, and may be used during pregnancy and lactation. The safety of long-acting insulin analogues in pregnancy has not been established, therefore isophane insulin is recommended where longer-acting insulins are needed.

Insulin administration Insulin is generally given by *subcutaneous injection*; the injection site should be rotated to prevent lipodystrophy. Injection devices ('pens') (section 6.1.1.3), which hold the insulin in a cartridge and meter the required dose, are convenient to use. Insulin syringes (for use with needles) are required for insulins not available in cartridge form.

For intensive insulin regimens multiple subcutaneous injections (3 or more times daily) are usually recommended.

Short-acting injectable insulins (soluble insulin, insulin aspart, insulin glulisine, and insulin lispro) can also be given by *continuous subcutaneous infusion* using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique can be useful for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens (see also NICE guidance, below). Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.

NICE guidance

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008)

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, **or**
- whose glycaemic control remains inadequate (HbA_{1c} over 8.5%) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

Soluble insulin by the *intravenous route* is reserved for urgent treatment, e.g. in diabetic ketoacidosis, and for fine control in serious illness and in the peri-operative period (see under Diabetes and Surgery, below).

Units The word 'unit' should **not** be abbreviated.

Monitoring Many patients now monitor their own blood-glucose concentrations (section 6.1.6). Since blood-glucose concentration varies substantially throughout the day, 'normoglycaemia' cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia. It is therefore best to recommend that patients should maintain a blood-glucose concentration of between 4 and 9 mmol/litre for most of the time (4–7 mmol/litre before meals and less than 9 mmol/litre after meals), while accepting that on occasions, for brief periods, it will be above these values; strenuous efforts should be made to prevent the blood-glucose concentration from falling below 4 mmol/litre. Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen. The intake of energy and of simple and complex carbohydrates should be adequate to allow normal growth and development but obesity must be avoided.

Hypoglycaemia Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it.

Loss of warning of hypoglycaemia among insulin-treated patients can be a serious hazard, especially for drivers and those in dangerous occupations. Very tight control of diabetes lowers the blood-glucose concentration needed to trigger hypoglycaemic symptoms; an increase in the frequency of hypoglycaemic episodes may reduce the warning symptoms experienced by the patient. Beta-blockers can also blunt hypoglycaemic awareness (and also delay recovery).

To restore the warning signs, episodes of hypoglycaemia must be minimised; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Some patients have reported loss of hypoglycaemia warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemia awareness. If a patient believes that human insulin is responsible for the loss of warning it is reasonable to revert to animal insulin and essential to educate the patient about avoiding hypoglycaemia. Great care should be taken to specify whether a human or an animal preparation is required.

Few patients are now treated with beef insulins; when undertaking conversion from beef to human insulin, the total dose should be reduced by about 10% with careful monitoring for the first few days. When changing between pork and human-sequence insulins, a dose change is not usually needed, but careful monitoring is still advised.

Diabetes and surgery Perioperative control of blood-glucose concentrations in patients with type 1 diabetes is achieved via an adjustable, continuous, intravenous infusion of insulin. Detailed local protocols should be available to all healthcare professionals involved in the treatment of these patients; in general, the following steps should be followed:

- Give an injection of the patient's usual insulin on the night before the operation;
- Early on the day of the operation, start an intravenous infusion of glucose containing potassium chloride (provided that the patient is not hyperkalaemic) and infuse at a constant rate appropriate to the patient's fluid requirements (usually 125 mL per hour); make up a solution of soluble insulin in sodium chloride 0.9% and infuse intravenously using a syringe pump piggy-backed to the intravenous infusion. Glucose and potassium infusions, and insulin infusions should be made up according to locally agreed protocols;
- The rate of the insulin infusion should be adjusted according to blood-glucose concentration (frequent monitoring necessary) in line with locally agreed protocols. Other factors affecting the rate of infusion include the patient's volume depletion, cardiac function, and age.

Protocols should include specific instructions on how to manage resistant cases (such as patients who are in shock or severely ill or those receiving corticosteroids or sympathomimetics) and those with hypoglycaemia.

If a syringe pump is not available, soluble insulin should be added to the intravenous infusion of glucose and potassium chloride (provided the patient is not hyperkalaemic), and the infusion run at the rate appropriate to the patient's fluid requirements (usually 125 mL per hour) with the insulin dose adjusted according to blood-glucose concentration in line with locally agreed protocols.

Once the patient starts to eat and drink, give subcutaneous insulin before breakfast and stop intravenous insulin 30 minutes later; the dose may need to be 10–20% more than usual if the patient is still in bed or unwell. If the patient was not previously receiving insulin, an appropriate initial dose is 30–40 units daily in four divided doses using soluble insulin before meals and intermediate-acting insulin at bedtime and the dose adjusted from day to day. Patients with hyperglycaemia

often relapse after conversion back to subcutaneous insulin calling for one of the following approaches:

- additional doses of soluble insulin at any of the four injection times (before meals or bedtime) *or*
- temporary addition of intravenous insulin infusion (while continuing the subcutaneous regimen) until blood-glucose concentration is satisfactory *or*
- complete reversion to the intravenous regimen (especially if the patient is unwell).

6.1.1.1 Short-acting insulins

Soluble insulin is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals.

Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies e.g. diabetic ketoacidosis (section 6.1.3) and at the time of surgery. It can be given intravenously and intramuscularly, as well as subcutaneously.

When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.

When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

The rapid-acting human insulin analogues, **insulin aspart**, **insulin glulisine**, and **insulin lispro** have a faster onset and shorter duration of action than soluble insulin; as a result, compared to soluble insulin, fasting and preprandial blood-glucose concentrations are a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently. Subcutaneous injection of insulin analogues may be convenient for those who wish to inject shortly before or, when necessary, shortly after a meal. They can also help those susceptible to hypoglycaemia before lunch and those who eat late in the evening and are prone to nocturnal hypoglycaemia. They can also be administered by subcutaneous infusion (see Insulin Administration, above). Insulin aspart and insulin lispro can be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

INSULIN

(Insulin Injection; Neutral Insulin; Soluble Insulin)

A sterile solution of insulin (i.e. bovine or porcine) or of human insulin; pH 6.6–8.0

Indications diabetes mellitus; diabetic ketoacidosis (section 6.1.3)

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see notes above; transient oedema; local reactions and fat hypertrophy at injection site; *rarely* hypersensitivity reactions including urticaria, rash; overdose causes hypoglycaemia

Dose

- By subcutaneous, intramuscular *or* intravenous injection *or* intravenous infusion, according to requirements

Highly purified animal

Counselling Show container to patient and confirm that patient is expecting the version dispensed

Hypurin® Bovine Neutral (Wockhardt) PoM
Injection, soluble insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48; cartridges (for *Autopen® Classic*) 5 × 3 mL = £27.72

Hypurin® Porcine Neutral (Wockhardt) PoM
Injection, soluble insulin (porcine, highly purified) 100 units/mL. Net price 10-mL vial = £16.80; cartridges (for *Autopen® Classic*) 5 × 3 mL = £25.20

Human sequence

Counselling Show container to patient and confirm that patient is expecting the version dispensed

Actrapid® (Novo Nordisk) PoM
Injection, soluble insulin (human, pyr) 100 units/mL. Net price 10-mL vial = £7.48
Note Not recommended for use in subcutaneous insulin infusion pumps—may precipitate in catheter or needle

Humulin S® (Lilly) PoM
Injection, soluble insulin (human, prb) 100 units/mL. Net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for most *Autopen® Classic* or *HumaPen®*) = £19.08

Insuman® Rapid (Sanofi-Aventis) PoM
Injection, soluble insulin (human, crb) 100 units/mL, net price 5 × 3-mL cartridge (for *ClikSTAR®* and *OptiPen® Pro 1*) = £17.50; 5 × 3-mL *Insuman® Rapid OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £17.50
Note Not recommended for use in subcutaneous insulin infusion pumps

Mixed preparations

See Biphasic Isophane Insulin (section 6.1.1.2)

INSULIN ASPART

(Recombinant human insulin analogue)

Indications diabetes mellitus

Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment section 6.1.1

Renal impairment section 6.1.1

Pregnancy section 6.1.1

Breast-feeding section 6.1.1

Side-effects see under Insulin

Dose

- By subcutaneous injection, ADULT and CHILD over 2 years, immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, intravenous injection *or* intravenous infusion, ADULT and CHILD over 2 years, according to requirements

NovoRapid® (Novo Nordisk) PoM
Injection, insulin aspart (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £16.28; *Penfill®* cartridge (for *NovoPen®* devices) 5 × 3-mL = £28.84; 5 × 3-mL *FlexPen®* prefilled

disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £32.00
Counselling Show container to patient and confirm that patient is expecting the version dispensed

INSULIN GLULISINE
(Recombinant human insulin analogue)

Indications diabetes mellitus
Cautions section 6.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin
Dose

- By subcutaneous injection, ADULT and CHILD over 6 years, immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, *or* intravenous infusion ADULT and CHILD over 6 years, according to requirements

Apidra® (Sanofi-Aventis) PoM
Injection, insulin glulisine (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £16.60; 5× 3-mL cartridge (for *ClikSTAR®*, *OptiPen® Pro 1*, and *Autopen® 24*) = £28.30; 5 × 3-mL *OptiClik®* cartridge (for *OptiClik® Pen*) = £30.27; 5 × 3-mL *Apidra® Optiset®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £28.30; 5 × 3-mL *Apidra® SoloStar®* prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £25.00
Counselling Show container to patient and confirm that patient is expecting the version dispensed
Note The *Scottish Medicines Consortium* (p. 4) has advised (October 2008) that *Apidra®* is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate

INSULIN LISPRO
(Recombinant human insulin analogue)

Indications diabetes mellitus
Cautions section 6.1.1; children (use only if benefit likely compared to soluble insulin); **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin
Dose

- By subcutaneous injection shortly before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, *or* intravenous injection, *or* intravenous infusion, according to requirements

Humalog® (Lilly) PoM
Injection, insulin lispro (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £16.61; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £28.31; 5 × 3-mL *Humalog®-Pen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 × 3-mL *Humalog® KwikPen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46
Counselling Show container to patient and confirm that patient is expecting the version dispensed

6.1.1.2 Intermediate- and long-acting insulins

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–35 hours. Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily, particularly in elderly patients. Soluble insulin can be mixed with intermediate and long-acting insulins (except insulin detemir and insulin glargine) in the syringe, essentially retaining the properties of the two components, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin, see below).

Isophane insulin is a suspension of insulin with protamine; it is of particular value for initiation of twice-daily insulin regimens. Patients usually mix isophane with soluble insulin but ready-mixed preparations may be appropriate (**biphasic isophane insulin**, **biphasic insulin aspart**, or **biphasic insulin lispro**).

Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.

Insulin glargine and **insulin detemir** are both long-acting human insulin analogues with a prolonged duration of action; insulin glargine is given once daily and insulin detemir is given once or twice daily. NICE (December 2002) has recommended that insulin glargine should be available as an option for patients with type 1 diabetes.

NICE (May 2009) has recommended that, if insulin is required in patients with type 2 diabetes, insulin detemir or insulin glargine may be considered for those:

- who require assistance with injecting insulin *or*
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia *or*
- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs *or*
- who cannot use the device needed to inject isophane insulin.

INSULIN DETEMIR
(Recombinant human insulin analogue—long acting)

Indications diabetes mellitus
Cautions section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1

Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1)
Dose
- By subcutaneous injection, ADULT and CHILD over 6 years, according to requirements

Levemir® (Novo Nordisk) PoM
Injection, insulin detemir (recombinant human insulin analogue) 100 units/mL, net price 5 × 3-mL cartridge (for *NovoPen®* devices) = £42.00; 5 × 3-mL *FlexPen®* prefilled disposable injection device (range 1–60 units, allowing 1-unit dosage adjustment) = £42.00; 5 × 3-mL *Levemir InnoLet®* prefilled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £44.85
Counselling Show container to patient and confirm that patient is expecting the version dispensed

INSULIN GLARGINE

(Recombinant human insulin analogue—long acting)

Indications diabetes mellitus
Cautions section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1)
Dose
- By subcutaneous injection, ADULT and CHILD over 6 years, according to requirements

Lantus® (Sanofi-Aventis) PoM
Injection, insulin glargine (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £26.00; 5 × 3-mL cartridge (for *ClikSTAR®*, *OptiPen® Pro 1*, and *Autopen® 24*) = £39.00; 5 × 3-mL *OptiClik®* cartridge (for *OptiClik® Pen*) = £40.36; 5 × 3-mL *Lantus® OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £39.00; 5 × 3-mL *Lantus® SoloStar®* prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £40.36
Note The *Scottish Medicines Consortium* (p. 4) has advised (October 2002) that insulin glargine is accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:
- in those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
- as a once daily insulin therapy for patients who require a carer to administer their insulin.

It is **not** recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.
Counselling Show container to patient and confirm that patient is expecting the version dispensed

INSULIN ZINC SUSPENSION

(Insulin Zinc Suspension (Mixed)—long acting)

A sterile neutral suspension of bovine and/or porcine insulin or of human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns)

Indications diabetes mellitus
Cautions section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1)
Dose
- By subcutaneous injection, according to requirements

Highly purified animal

Hypurin® Bovine Lente (Wockhardt) PoM
Injection, insulin zinc suspension (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72
Counselling Show container to patient and confirm that patient is expecting the version dispensed

ISOPHANE INSULIN

(Isophane Insulin Injection; Isophane Protamine Insulin Injection; Isophane Insulin (NPH)—intermediate acting)

A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulphate or another suitable protamine

Indications diabetes mellitus
Cautions section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1); protamine may cause allergic reactions
Dose
- By subcutaneous injection, according to requirements

Highly purified animal

Counselling Show container to patient and confirm that patient is expecting the version dispensed

Hypurin® Bovine Isophane (Wockhardt) PoM
Injection, isophane insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72; cartridges (for *Autopen® Classic*) 5 × 3 mL = £41.58

Hypurin® Porcine Isophane (Wockhardt) PoM
Injection, isophane insulin (porcine, highly purified) 100 units/mL. Net price 10-mL vial = £25.20; cartridges (for *Autopen® Classic*) 5 × 3 mL = £37.80

Human sequence

Counselling Show container to patient and confirm that patient is expecting the version dispensed

Insulatard® (Novo Nordisk) PoM
Injection, isophane insulin (human, pyr) 100 units/mL. Net price 10-mL vial = £7.48; *Insulatard Penfill®* cartridge (for *Novopen®* devices) 5 × 3 mL = £22.90; 5 × 3-mL *Insulatard InnoLet®* prefilled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £20.40

Humulin I® (Lilly) PoM
Injection, isophane insulin (human, prb) 100 units/mL. Net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £19.08; 5 × 3-mL *Humulin I-Pen®* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £28.44; 5 × 3-mL *Humulin I KwikPen®* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £21.70

Insuman® Basal (Sanofi-Aventis) PoM
Injection, isophane insulin (human, crb) 100 units/mL, net price 5-mL vial = £5.61; 5 × 3-mL cartridge (for *ClikSTAR®* and *OptiPen® Pro 1*) = £17.50; 5 × 3-mL *Insuman® Basal OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £17.50

Mixed preparations

See Biphasic Isophane Insulin (below)

PROTAMINE ZINC INSULIN

(Protamine Zinc Insulin Injection—long acting)

A sterile suspension of insulin in the form of a complex obtained by the addition of a suitable protamine and zinc chloride; this preparation was included in BP 1980 but is not included in BP 1988

Indications diabetes mellitus
Cautions section 6.1.1.1; see also notes above; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1); protamine may cause allergic reactions
Dose
- By subcutaneous injection, according to requirements

Hypurin® Bovine Protamine Zinc (Wockhardt) PoM
Injection, protamine zinc insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £27.72
Counselling Show container to patient and confirm that patient is expecting the version dispensed

Biphasic insulins

BIPHASIC INSULIN ASPART

(Intermediate-acting insulin)

Indications diabetes mellitus
Cautions see section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1); protamine may cause allergic reactions
Dose
- By subcutaneous injection, up to 10 minutes before or soon after a meal, according to requirements

NovoMix® 30 (Novo Nordisk) PoM
Injection, biphasic insulin aspart (recombinant human insulin analogue), 30% insulin aspart, 70% insulin aspart protamine, 100 units/mL, net price 5 × 3-mL *Penfill®* cartridges (for *NovoPen®* devices) = £28.84; 5 × 3-mL *FlexPen®* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £32.00
Counselling Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

BIPHASIC INSULIN LISPRO

(Intermediate-acting insulin)

Indications diabetes mellitus
Cautions see section 6.1.1.1 and Insulin Lispro; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1); protamine may cause allergic reactions
Dose
- By subcutaneous injection, up to 15 minutes before or soon after a meal, according to requirements

Humalog® Mix25 (Lilly) PoM
Injection, biphasic insulin lispro (recombinant human insulin analogue), 25% insulin lispro, 75% insulin lispro protamine, 100 units/mL, net price 10-mL vial = £16.61; 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £29.46; 5 × 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98; 5 × 3-mL *Humalog® Mix25 KwikPen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98
Counselling Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Humalog® Mix50 (Lilly) PoM
Injection, biphasic insulin lispro (recombinant human insulin analogue), 50% insulin lispro, 50% insulin lispro protamine, 100 units/mL, net price 5 × 3-mL cartridge (for *Autopen® Classic* or *HumaPen®*) = £29.46; 5 × 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 × 3-mL *Humalog® Mix50 KwikPen* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98
Counselling Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

BIPHASIC ISOPHANE INSULIN

(Biphasic Isophane Insulin Injection—intermediate acting)

A sterile buffered suspension of either porcine or human insulin complexed with protamine sulphate (or another suitable protamine) in a solution of insulin of the same species

Indications diabetes mellitus
Cautions section 6.1.1.1; **interactions:** Appendix 1 (antidiabetics)
Hepatic impairment section 6.1.1
Renal impairment section 6.1.1
Pregnancy section 6.1.1
Breast-feeding section 6.1.1
Side-effects see under Insulin (section 6.1.1.1); protamine may cause allergic reactions
Dose
- By subcutaneous injection, according to requirements

Highly purified animal

Counselling Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Hypurin® Porcine 30/70 Mix (Wockhardt) PoM

Injection, biphasic isophane insulin (porcine, highly purified), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £16.80; cartridges (for *Autopen® Classic*) 5 × 3 mL = £25.20

Human sequence

Counselling Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked **carefully** (the order in which the proportions are stated may not be the same in other countries)

Humulin M3® (Lilly) PoM

Injection, biphasic isophane insulin (human, prb), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £15.68; 5 × 3-mL cartridge (for most *Autopen® Classic* or *HumaPen®*) = £19.08; 5 × 3-mL *Humulin M3 KwikPen®* prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £21.70

Insuman® Comb 15 (Sanofi-Aventis) PoM

Injection, biphasic isophane insulin (human, crb), 15% soluble, 85% isophane, 100 units/mL, net price 5 × 3-mL *Insuman® Comb 15 OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £17.50

Insuman® Comb 25 (Sanofi-Aventis) PoM

Injection, biphasic isophane insulin (human, crb), 25% soluble, 75% isophane, 100 units/mL, net price 5-mL vial = £5.61; 5 × 3-mL cartridge (for *ClikSTAR®* and *OptiPen® Pro 1*) = £17.50; 5 × 3-mL *Insuman® Comb 25 OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £17.50; 5 × 3-mL *Insuman® Comb 25 SoloStar®* prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £19.80

Insuman® Comb 50 (Sanofi-Aventis) PoM

Injection, biphasic isophane insulin (human, crb), 50% soluble, 50% isophane, 100 units/mL, net price 5 × 3-mL cartridge (for *ClikSTAR®* and *OptiPen® Pro 1*) = £17.50; 5 × 3-mL *Insuman® Comb 50 OptiSet®* prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £17.50

6.1.1.3 Hypodermic equipment

Patients should be advised on the safe disposal of lancets, single-use syringes, and needles. Suitable arrangements for the safe disposal of contaminated waste must be made before these products are prescribed for patients who are carriers of infectious diseases.

Injection devices

Autopen® (Owen Mumford)

Injection device, *Autopen® 24* (for use with Sanofi-Aventis 3-mL insulin cartridges), allowing 1-unit dosage adjustment, max. 21 units (single-unit version) *or* 2-unit dosage adjustment, max. 42 units (2-unit version), net price (both) = £15.73; *Autopen® Classic* (for use with Lilly and Wockhardt 3-mL insulin cartridges), allowing 1-unit dosage adjustment, max. 21 units (single-unit version) *or* 2-unit dosage adjustment, max. 42 units (2-unit version), net price (all) = £15.97

ClikSTAR® (Sanofi-Aventis)

Injection device, for use with *Lantus®*, *Apidra®*, and *Insuman®* 3-mL insulin cartridges; allowing 1-unit dose adjustment, max. 80 units, net price = £25.00

HumaPen® Luxura (Lilly)

Injection device, for use with *Humulin®* and *Humalog®* 3-mL cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £26.36

HumaPen® Luxura HD (Lilly)

Injection device, for use with *Humulin®* and *Humalog®* 3-mL cartridges; allowing 0.5-unit dosage adjustment, max. 30 units, net price = £26.36

NovoPen® (Novo Nordisk)

Injection device; for use with *Penfill®* insulin cartridges; *NovoPen® Junior* (for 3-mL cartridges), allowing 0.5-unit dosage adjustment, max. 35 units, net price = £24.79; *NovoPen® 3 Demi* (for 3-mL cartridges), allowing 0.5-unit dosage adjustment, max. 35 units, net price = £25.21; *NovoPen® 4* (for 3-mL cartridges), allowing 1-unit dosage adjustment, max. 60 units, net price = £26.56

OptiClik® (Sanofi-Aventis)

Injection device, for use with *Lantus OptiClik®* or *Apidra Opticlik®* insulin cartridges, allowing 1-unit dosage adjustment, max. 80 units, net price = £20.13

OptiPen® Pro 1 (Sanofi-Aventis)

Injection device, for use with *Insuman®* insulin cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £22.00

Lancets

Lancets—sterile, single use (Drug Tariff)

[1] *Ascensia Microlet®* 100 = £3.76, 200 = £7.17; *BD Micro-Fine®+* 100 = £3.16, 200 = £6.13; *CareSens®* 100 = £2.95; *Cleanlet Fine®* 100 = £3.19, 200 = £6.13; *Fastclix®* 204 = £9.20; [1] *Finepoint®* 100 = £3.54; [1] *FreeStyle®* 200 = £7.02; [1] *Milward Steri-Let®*, 23 gauge, 100 = £3.00, 200 = £5.70, 28 gauge, 100 = £3.00, 200 = £5.70; [1] *Monolet®* 100 = £3.28, 200 = £6.24; *Monolet Extra®* 100 = £3.28; *MPD Ultra Thin®* 100 = £3.30, 200 = £6.50; *Multiclix®* 204 = £9.27; *One Touch Comfort®* 200 = £7.22; [1] *One Touch UltraSoft®* 100 = £3.61; [2] *Softclix®* 200 = £7.40; [2] *Softclix XL®* 50 = £1.85; *Thin Lancets* (formerly *MediSense Thin®*), 200 = £7.16; [1] *Unilet ComforTouch®* 100 = £3.60, 200 = £6.83; *Unilet Eco®* 100 = £2.94, 200 = £5.49; [1] *Unilet General Purpose Superlite®* 100 = £3.67, 200 = £6.96; *Unistik 3 Comfort®*, 28-gauge, 100 = £6.24, 200 = £12.20; *Unistik 3 Extra®*, 21-gauge, 100 = £6.24, 200 = £12.20; *Unistik 3 Normal®*, 23-gauge, 100 = £6.24, 200 = £12.20; *Universal®* (formerly *VitalCare®*), 200 = £6.37; *Vitrex Soft®*, 23-gauge, 100 = £3.00, 200 = £5.70; *Vitrex Gentle®* 28-gauge, 100 = £3.19, 200 = £6.13; *WaveSense Ultra-Thin®*, 28-gauge, 200 = £6.90, 33-gauge, 200 = £6.90

Compatible finger-pricking devices (unless indicated otherwise, see footnotes), all NHS: *B-D Optimus®*, *Glucolet®*, *Monojector®*, *Penlet II®*, *Soft Touch®*

1. NHS *Autolet®* and NHS *Autolet Impression®* are also compatible finger-pricking devices
2. Use NHS *Softclix®* finger-pricking device

Needles

Hypodermic Needle, Sterile single use (Drug Tariff)

For use with reusable glass syringe, sizes 0.5 mm (25G), 0.45 mm (26G), 0.4 mm (27G). Net price 100-needle pack = £2.74

Brands include *Microlance®*, *Monoject®*

Needles for Prefilled and Reusable Pen Injectors (Drug Tariff)

Screw on, needle length 6.1 mm or less, net price 100-needle pack = £12.53; 6.2–9.9 mm, 100-needle pack = £8.89; 10 mm or more, 100-needle pack = £8.89

Brands include *BD Micro-Fine®* +, *NovoFine®*, *NovoTwist®*, *Unifine® Pentips*

Snap on, needle length 6.1 mm or less, net price 100-needle pack = £12.02; 6.2–9.9 mm, 100-needle pack = £8.52; 10 mm or more, 100-needle pack = £8.52

Brands include *Penfine®*

Syringes

Hypodermic Syringe (Drug Tariff)

Calibrated glass with Luer taper conical fitting, for use with U100 insulin. Net price 0.5 mL and 1 mL = £9.22

Brands include *Abcare®*

Pre-Set U100 Insulin Syringe (Drug Tariff)

Calibrated glass with Luer taper conical fitting, supplied with dosage chart and strong box, for blind patients. Net price 1 mL = £21.99

U100 Insulin Syringe with Needle (Drug Tariff)

Disposable with fixed or separate needle for single use or single patient-use, colour coded orange. Needle length 8 mm, diameters 0.33 mm (29G), 0.3 mm (30G), net price 10 (with needle), 0.3 mL = £1.38, 0.5 mL = £1.33, 1 mL = £1.32; needle length 12 mm, diameters 0.45 mm (26G), 0.4 mm (27G), 0.36 mm (28G), 0.33 mm (29G), net price 10 (with needle), 0.3 mL = £1.45; 0.5 mL = £1.43; 1 mL = £1.44

Brands include *BD Micro-Fine®+*, *Clinipak®*, *Insupak®*, *Monoject® Ultra*, *Omnikan®*, *Plastipak®*

Accessories

Needle Clipping (Chopping) Device (Drug Tariff)

Consisting of a clipper to remove needle from its hub and container from which cut-off needles cannot be retrieved; designed to hold 1500 needles, not suitable for use with lancets. Net price = £1.35

Brands include *BD Safe-Clip®*

Sharpsguard (Drug Tariff)

Net price 1-litre sharpsbin = 85p

6.1.2 Antidiabetic drugs

6.1.2.1 Sulfonylureas
6.1.2.2 Biguanides
6.1.2.3 Other antidiabetic drugs

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus. They should be prescribed only if the patient fails to respond adequately to at least 3 months' restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

For patients not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy. When insulin is added to oral therapy, it is generally given at bedtime as isophane or long-acting insulin, and when insulin replaces an oral regimen it may be given as twice-daily injections of a biphasic insulin (or isophane insulin mixed with soluble insulin), or a multiple injection regimen. Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin.

Exenatide and liraglutide, both given by subcutaneous injection, are also available for the treatment of type 2 diabetes, see section 6.1.2.3.

Pregnancy and breast-feeding During pregnancy, women with *pre-existing diabetes* can be treated with metformin [unlicensed use], either alone or in combination with insulin (section 6.1.1). Metformin can be continued, or glibenclamide resumed, during breast-feeding for those with pre-existing diabetes. Women with *gestational diabetes* may be treated, with or without concomitant insulin (section 6.1.1), with glibenclamide from 11 weeks gestation (after organogenesis) [unlicensed use] or with metformin [unlicensed use]. Women with gestational diabetes should discontinue hypoglycaemic treatment after giving birth.

Other oral hypoglycaemic drugs, exenatide, and liraglutide are contra-indicated in pregnancy.

6.1.2.1 Sulfonylureas

The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulfonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.

Sulfonylureas are considered for patients who are not overweight, or in whom metformin is contra-indicated or not tolerated. Several sulfonylureas are available and choice is determined by side-effects and the duration of action as well as the patient's age and renal function. **Glibenclamide**, a long-acting sulfonylurea, is associated with a greater risk of hypoglycaemia; for this reason it should be avoided in the elderly, and shorter-acting alternatives, such as **gliclazide** or **tolbutamide**, should be used instead.

When the combination of strict diet and sulfonylurea treatment fails, other options include:

- combining with metformin (section 6.1.2.2) (reports of increased hazard with this combination remain unconfirmed);
- combining with pioglitazone, but see section 6.1.2.3;
- combining with saxagliptin, sitagliptin, or vildagliptin (section 6.1.2.3);
- combining with exenatide or liraglutide (section 6.1.2.3);
- combining with acarbose (section 6.1.2.3), which may have a small beneficial effect, but flatulence can be a problem;
- combining with bedtime isophane insulin (section 6.1.1) but weight gain and hypoglycaemia can occur.

The risk of hypoglycaemia associated with sulfonylureas (see notes above) should be discussed with the patient, especially when concomitant glucose-lowering drugs are prescribed.

Insulin therapy should be instituted temporarily during intercurrent illness (such as myocardial infarction, coma, infection, and trauma). Sulfonylureas should be

omitted on the morning of surgery; insulin is required because of the ensuing hyperglycaemia in these circumstances.

Cautions Sulfonylureas can encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting; metformin (section 6.1.2.2) is considered the drug of choice in obese patients. Caution is needed in the elderly.

Contra-indications Sulfonylureas should be avoided where possible in acute porphyria (section 9.8.2). Sulfonylureas are contra-indicated in the presence of ketoacidosis.

Hepatic impairment Sulfonylureas should be avoided or a reduced dose should be used in severe hepatic impairment, because there is an increased risk of hypoglycaemia. Jaundice may occur.

Renal impairment Sulfonylureas should be used with care in those with mild to moderate renal impairment, because of the hazard of hypoglycaemia; they should be avoided where possible in severe renal impairment. Glipizide should also be avoided if the patient has both renal and hepatic impairment. If necessary, the short-acting drug tolbutamide can be used in renal impairment, as can gliclazide which is principally metabolised in the liver, but careful monitoring of blood-glucose concentration is essential; care is required to use the lowest dose that adequately controls blood glucose.

Pregnancy The use of sulfonylureas in pregnancy should generally be avoided because of the risk of neonatal hypoglycaemia; however, glibenclamide can be used during the second and third trimesters of pregnancy in women with gestational diabetes, see section 6.1.2.

Breast-feeding The use of sulfonylureas (except glibenclamide [unlicensed use], see section 6.1.2) in breast-feeding should be avoided because there is a theoretical possibility of hypoglycaemia in the infant.

Side-effects Side-effects of sulfonylureas are generally mild and infrequent and include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea, and constipation. Hyponatraemia has been reported with glimepiride and glipizide.

Sulfonylureas can occasionally cause a disturbance in liver function, which may rarely lead to cholestatic jaundice, hepatitis, and hepatic failure. Hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy. They consist mainly of allergic skin reactions which progress rarely to erythema multiforme and exfoliative dermatitis, fever, and jaundice; photosensitivity has rarely been reported with glipizide. Blood disorders are also rare but may include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia.

GLIBENCLAMIDE

Indications type 2 diabetes mellitus
Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose

- Initially 5 mg daily with or immediately after breakfast, dose adjusted according to response (ELDERLY avoid, see notes above); max. 15 mg daily

Glibenclamide (Non-proprietary) PoM
Tablets, glibenclamide 2.5 mg, net price 28-tab pack = 95p; 5 mg, 28-tab pack = £1.07

GLICLAZIDE

Indications type 2 diabetes mellitus
Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose

- Initially, 40–80 mg daily, adjusted according to response; up to 160 mg as a single dose, with breakfast; higher doses divided; max. 320 mg daily

Gliclazide (Non-proprietary) PoM
Tablets, scored, gliclazide 80 mg, net price 28-tab pack = £1.10, 60-tab pack = £1.52
Brands include *DIAGLYK®*

Diamicron® (Servier) PoM
Tablets, scored, gliclazide 80 mg, net price 60-tab pack = £4.38

Modified release

Diamicron® MR (Servier) PoM
Tablets, m/r, gliclazide 30 mg, net price 28-tab pack = £2.81, 56-tab pack = £5.62. Label: 25
Dose initially 30 mg daily with breakfast, adjusted according to response every 4 weeks (after 2 weeks if no decrease in blood glucose); max. 120 mg daily
Note *Diamicron® MR* 30 mg may be considered to be approximately equivalent in therapeutic effect to standard formulation *Diamicron®* 80 mg

GLIMEPIRIDE

Indications type 2 diabetes mellitus
Cautions see notes above; manufacturer recommends regular hepatic and haematological monitoring but limited evidence of clinical value; **interactions**: Appendix 1 (antidiabetics)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose

- Initially 1 mg daily, adjusted according to response in 1-mg steps at 1–2 week intervals; usual max. 4 mg daily (exceptionally, up to 6 mg daily may be used); taken shortly before or with first main meal

Glimepiride (Non-proprietary) PoM
Tablets, glimepiride 1 mg, net price 30-tab pack = £1.40; 2 mg, 30-tab pack = £1.38; 3 mg, 30-tab pack = £4.57; 4 mg, 30-tab pack = £1.75

Amaryl® (Sanofi-Aventis) PoM
Tablets, all scored, glimepiride 1 mg (pink), net price 30-tab pack = £4.33; 2 mg (green), 30-tab pack = £7.13; 3 mg (yellow), 30-tab pack = £10.75; 4 mg (blue), 30-tab pack = £14.24

GLIPIZIDE

Indications type 2 diabetes mellitus
Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also dizziness, drowsiness
Dose
- Initially 2.5–5 mg daily shortly before breakfast or lunch, adjusted according to response; max. 20 mg daily; up to 15 mg may be given as a single dose; higher doses divided

Glipizide (Non-proprietary) PoM
Tablets, glipizide 5 mg, net price 56-tab pack = £4.23

Minodiab® (Pharmacia) PoM
Tablets, scored, glipizide 5 mg, net price 28-tab pack = £1.26

TOLBUTAMIDE

Indications type 2 diabetes mellitus
Cautions see notes above; **interactions:** Appendix 1 (antidiabetics)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above; also headache, tinnitus
Dose
- 0.5–1.5 g (max. 2 g) daily in divided doses with or immediately after meals *or* as a single dose with or immediately after breakfast

Tolbutamide (Non-proprietary) PoM
Tablets, tolbutamide 500 mg, net price 28-tab pack = £1.74

6.1.2.2 Biguanides

Metformin, the only available biguanide, has a different mode of action from the sulfonylureas, and is not interchangeable with them. It exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose; since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

Metformin is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, if appropriate it may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulfonylurea treatment. When the combination of strict diet and metformin treatment fails, other options include:

- combining with a sulfonylurea (section 6.1.2.1) (reports of increased hazard with this combination remain unconfirmed);
- combining with pioglitazone (section 6.1.2.3);
- combining with repaglinide or nateglinide (section 6.1.2.3);
- combining with saxagliptin, sitagliptin, or vildagliptin (section 6.1.2.3);
- combining with exenatide or liraglutide (section 6.1.2.3);
- combining with acarbose (section 6.1.2.3), which may have a small beneficial effect, but flatulence can be a problem;
- combining with insulin (section 6.1.1) but weight gain and hypoglycaemia can be problems (weight gain minimised if insulin given at night).

Insulin treatment is almost always required in medical and surgical emergencies; insulin should also be substituted before elective surgery (omit metformin on the morning of surgery and give insulin if required).

Hypoglycaemia does not usually occur with metformin; other advantages are the lower incidence of weight gain and lower plasma-insulin concentration. It does not exert a hypoglycaemic action in non-diabetic subjects unless given in overdose.

Gastro-intestinal side-effects are initially common with metformin, and may persist in some patients, particularly when very high doses such as 3 g daily are given.

Very rarely, metformin can provoke lactic acidosis. It is most likely to occur in patients with renal impairment, see Lactic Acidosis below.

Metformin is used for the symptomatic management of polycystic ovary syndrome [unlicensed indication]; however, treatment should be initiated by a specialist. Metformin improves insulin sensitivity, may aid weight reduction, helps to normalise menstrual cycle (increasing the rate of spontaneous ovulation), and may improve hirsutism.

METFORMIN HYDROCHLORIDE

Indications diabetes mellitus (see notes above); polycystic ovary syndrome [unlicensed indication]
Cautions see notes above; determine renal function before treatment and at least annually (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration suspected); **interactions:** Appendix 1 (antidiabetics)
Lactic acidosis Use with caution in renal impairment—increased risk of lactic acidosis; avoid in significant renal impairment. NICE[1] recommends that the dose should be reviewed if eGFR less than 45 mL/minute/1.73 m^2 and to

1. NICE clinical guideline 87 (May 2009): Type 2 diabetes: The management of type 2 diabetes

avoid if eGFR less than 30 mL/minute/1.73 m^2. Withdraw or interrupt treatment in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction

Contra-indications ketoacidosis, see also Lactic Acidosis above; use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to baseline)

Iodine-containing X-ray contrast media Intravascular administration of iodinated contrast agents can cause renal failure. Suspend metformin prior to the test; restart at least 48 hours after the test if renal function has returned to baseline

Hepatic impairment withdraw if tissue hypoxia likely

Renal impairment see under Cautions

Pregnancy used in pregnancy for both pre-existing and gestational diabetes—see also p. 427

Breast-feeding may be used during breast-feeding—see p. 427

Side-effects anorexia, nausea, vomiting, diarrhoea (usually transient), abdominal pain, taste disturbance, *rarely* lactic acidosis (withdraw treatment), decreased vitamin-B_{12} absorption, erythema, pruritus and urticaria; hepatitis also reported

Dose

- Diabetes mellitus, ADULT and CHILD over 10 years initially 500 mg with breakfast for at least 1 week then 500 mg with breakfast and evening meal for at least 1 week then 500 mg with breakfast, lunch and evening meal; usual max. 2 g daily in divided doses
- Polycystic ovary syndrome [unlicensed], initially 500 mg with breakfast for 1 week, then 500 mg with breakfast and evening meal for 1 week, then 1.5–1.7 g daily in 2–3 divided doses

Note Metformin doses in the BNF may differ from those in the product literature

Metformin (Non-proprietary) PoM

Tablets, coated, metformin hydrochloride 500 mg, net price 28-tab pack = £1.07, 84-tab pack = £1.57; 850 mg, 56-tab pack = £1.67. Label: 21

Oral solution, sugar-free, metformin hydrochloride 500 mg/5 mL, net price 100 mL = £62.48. Label: 21

Brands include *Metsol®*

Glucophage® (Merck Serono) PoM

Tablets, f/c, metformin hydrochloride 500 mg, net price 84-tab pack = £2.88; 850 mg, 56-tab pack = £3.20. Label: 21

Oral powder, sugar-free, metformin hydrochloride 500 mg/sachet, net price 30-sachet pack = £3.29, 60-sachet pack = £6.58; 1 g/sachet, 30-sachet pack = £6.58, 60-sachet pack = £13.16. Label: 13, 21, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling The contents of each sachet should be mixed with 150 mL of water and taken immediately

The *Scottish Medicines Consortium* (p. 4) has advised (March 2010) that *Glucophage®* oral powder is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients who are unable to swallow the solid dosage form.

Modified release

Metformin (Non-Proprietary)

Tablets, m/r, metformin hydrochloride 500 mg, net price 28 tab-pack = £3.07, 56 tab-pack = £6.14. Label: 21, 25

Dose initially 500 mg once daily, increased every 10–15 days, max. 2 g once daily with evening meal; if control not achieved, use 1 g twice daily with meals, and if control still not achieved change to standard-release tablets

Note Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of metformin modified release; not suitable if dose of standard-release tablets more than 2 g daily

Brands include *Bolamyn® SR*, *Metabet® SR*

Glucophage® SR (Merck Serono) PoM

Tablets, m/r, metformin hydrochloride 500 mg, net price 28-tab pack = £3.07, 56-tab pack = £6.14; 750 mg, 28-tab pack = £3.20, 56-tab pack = £6.40; 1 g, 28-tab pack = £4.26, 56-tab pack = £8.52. Label: 21, 25

Dose initially 500 mg once daily, increased every 10–15 days, max. 2 g once daily with evening meal; if control not achieved, use 1 g twice daily with meals, and if control still not achieved change to standard-release tablets

Note Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of *Glucophage® SR*; not suitable if dose of standard-release tablets more than 2 g daily

The *Scottish Medicines Consortium* (p. 4) has advised (September 2009) that *Glucophage® SR* is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in adult patients who are intolerant of standard-release metformin, and in whom the prolonged-release tablet allows the use of a dose of metformin not previously tolerated, or in patients for whom a once daily preparation offers a clinically significant benefit.

With pioglitazone

Section 6.1.2.3

With sitagliptin

Section 6.1.2.3

With vildagliptin

Section 6.1.2.3

6.1.2.3 Other antidiabetic drugs

Acarbose, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose. Use of acarbose is usually reserved for when other oral hypoglycaemics are not tolerated or are contra-indicated. Postprandial hyperglycaemia in type 1 diabetes can be reduced by acarbose, but it has been little used for this purpose. Flatulence deters some from using acarbose although this side-effect tends to decrease with time.

Nateglinide and **repaglinide** stimulate insulin release. Both drugs have a rapid onset of action and short duration of activity, and should be administered shortly before each main meal. Repaglinide may be given as monotherapy for patients who are not overweight or for those in whom metformin is contra-indicated or not tolerated, or it may be given in combination with metformin. Nateglinide is licensed only for use with metformin.

The thiazolidinedione, **pioglitazone**, reduces peripheral insulin resistance, leading to a reduction of blood-glucose concentration. Pioglitazone can be used alone or in combination with metformin or with a sulfonylurea (if metformin inappropriate), or with both; the combination of pioglitazone plus metformin is preferred to pioglitazone plus sulfonylurea, particularly for obese patients. Inadequate response to a combination of metformin and sulfonylurea may indicate failing insulin release; the introduction of pioglitazone has a limited role in these circumstances and the initiation of insulin is often more appropriate. Pioglitazone is also licensed in combination

with insulin, in patients who have not achieved adequate glycaemic control with insulin alone, when metformin is inappropriate. Blood-glucose control may deteriorate temporarily when pioglitazone is substituted for an oral antidiabetic drug that is being used in combination with another. Long-term benefits of pioglitazone have not yet been demonstrated. NICE (May 2009) has recommended that, when glycaemic control is inadequate with existing treatment, pioglitazone can be added to:

- a sulfonylurea, if metformin is contra-indicated or not tolerated;
- metformin, if risks of hypoglycaemia with sulfonylurea are unacceptable or a sulfonylurea is contra-indicated or not tolerated;
- a combination of metformin and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese.

NICE has recommended that treatment with pioglitazone is continued only if HbA_{1c} concentration is reduced by at least 0.5% within 6 months of starting treatment.

The *Scottish Medicines Consortium* (p. 4) accepts use of pioglitazone (February 2007) with metformin and a sulfonylurea, for patients (especially if overweight) whose glycaemic control is inadequate despite the use of 2 oral hypoglycaemic drugs and who are unable or unwilling to take insulin; treatment should be initiated and monitored by an experienced diabetes physician.

MHRA/CHM advice

Pioglitazone cardiovascular safety (December 2007 and January 2011)

Incidence of heart failure is increased when pioglitazone is combined with insulin especially in patients with predisposing factors e.g. previous myocardial infarction. Patients who take pioglitazone should be closely monitored for signs of heart failure; treatment should be discontinued if any deterioration in cardiac status occurs.

Pioglitazone should not be used in patients with heart failure or a history of heart failure.

Rosiglitazone

The marketing authorisation for rosiglitazone (*Avandia®*, *Avandamet®*) has been suspended (September 2010) following a review by the European Medicines Agency. The European Medicines Agency concluded that the benefits of rosiglitazone treatment do not outweigh the cardiovascular risks. Prescribers should not issue new or repeat prescriptions for rosiglitazone. Treatment of patients who are taking rosiglitazone should be reviewed.

Saxagliptin, **sitagliptin**, and **vildagliptin** inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion. They are licensed for use in type 2 diabetes in combination with metformin or a sulfonylurea (if metformin inappropriate) or pioglitazone, when treatment with either metformin or a sulfonylurea or pioglitazone fails to achieve adequate glycaemic control. Sitagliptin is also licensed for use as monotherapy (if metformin inappropriate), or in combination with both metformin and a sulfonylurea, or both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control. The combination of sitagliptin and insulin (with or without metformin) is also licensed for use when a stable dose of insulin has not provided adequate glycaemic control.

NICE (May 2009) has recommended that, when glycaemic control is inadequate with existing treatment:

- sitagliptin or vildagliptin (instead of a sulfonylurea) can be added to metformin, if there is a significant risk of hypoglycaemia *or* if a sulfonylurea is contra-indicated or not tolerated;
- sitagliptin or vildagliptin can be added to a sulfonylurea, if metformin is contra-indicated or not tolerated;
- sitagliptin can be added to both metformin and a sulfonylurea, if insulin is unacceptable because of lifestyle or other personal issues, or because the patient is obese.

NICE has recommended that treatment with sitagliptin or vildagliptin is continued only if HbA_{1c} concentration is reduced by at least 0.5% within 6 months of starting treatment.

The *Scottish Medicines Consortium* (p. 4) has advised that vildagliptin (*Galvus®*) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with metformin when addition of a sulfonylurea is inappropriate (March 2008), and also in combination with a sulfonylurea if metformin is inappropriate (September 2009).

Exenatide and **liraglutide** both bind to, and activate, the GLP-1 (glucagon-like peptide-1) receptor to increase insulin secretion, suppress glucagon secretion, and slow gastric emptying. Treatment with exenatide and liraglutide is associated with the prevention of weight gain and possible promotion of weight loss which can be beneficial in overweight patients. They are both given by subcutaneous injection for the treatment of type 2 diabetes mellitus.

Exenatide is licensed in combination with metformin or a sulfonylurea, or both, or with pioglitazone, or with both metformin and pioglitazone, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination.

NICE (May 2009) has recommended that, when glycaemic control is inadequate with metformin and sulfonylurea treatment, the addition of exenatide may be considered if the patient has:

- a body mass index of 35 kg/m^2 or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems *or*
- a body mass index less than 35 kg/m^2, and insulin would be unacceptable for occupational reasons *or* weight loss would benefit other significant obesity-related comorbidities.

NICE has recommended that treatment with exenatide is continued only if HbA_{1c} concentration is reduced by at least 1% and a weight loss of at least 3% is achieved within 6 months of starting treatment.

The *Scottish Medicines Consortium* (p. 4) has advised (June 2007) that exenatide (*Byetta®*) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin or sulfonylurea (or both), as an alternative to treatment with insulin in patients where treatment with metformin or sulfonylurea (or both) at maximally tolerated doses

has been inadequate, and treatment with insulin would be the next option.

Liraglutide is licensed for the treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Liraglutide is also licensed for use in combination with both metformin and pioglitazone when dual therapy with these drugs fails to achieve adequate glycaemic control.

NICE guidance

Liraglutide for the treatment of type 2 diabetes mellitus (October 2010)

Liraglutide in triple therapy regimens (in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended for the treatment of type 2 diabetes, only when glycaemic control is inadequate, and the patient has:

- a body mass index of 35 kg/m^2 or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems, *or*
- a body mass index of less than 35 kg/m^2, and insulin would be unacceptable for occupational reasons *or* weight loss would benefit other significant obesity-related comorbidities.

Treatment with liraglutide in a triple therapy regimen should be continued only if HbA_{1c} concentration is reduced by at least 1% and a weight loss of at least 3% is achieved within 6 months of starting treatment.

Liraglutide in dual therapy regimens (in combination with metformin or a sulfonylurea) is recommended only if:

- treatment with metformin or a sulfonylurea is contra-indicated or not tolerated, *and*
- treatment with thiazolidinediones and dipeptidylpeptidase-4 inhibitors is contra-indicated or not tolerated.

Liraglutide, in combination with metformin or a sulfonylurea should be continued only if HbA_{1c} concentration is reduced by at least 1% within 6 months of starting treatment.

Liraglutide 1.8 mg daily is not recommended.

ACARBOSE

Indications diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs

Cautions monitor liver function; may enhance hypoglycaemic effects of insulin and sulfonylureas (hypoglycaemic episodes may be treated with oral glucose but not with sucrose); **interactions:** Appendix 1 (antidiabetics)

Contra-indications inflammatory bowel disease, predisposition to partial intestinal obstruction; hernia, previous abdominal surgery

Hepatic impairment avoid

Renal impairment avoid if eGFR less than 25 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding avoid

Side-effects flatulence, soft stools, diarrhoea (may need to reduce dose or withdraw), abdominal distention and pain; *rarely*, nausea, abnormal liver function tests and skin reactions; *very rarely* ileus, oedema, jaundice, and hepatitis

Note Antacids unlikely to be beneficial for treating side-effects

Dose

- ADULT over 18 years, initially 50 mg daily increased to 50 mg 3 times daily, then increased if necessary after 6–8 weeks to 100 mg 3 times daily; max. 200 mg 3 times daily

  Counselling Tablets should be chewed with first mouthful of food or swallowed whole with a little liquid immediately before food. To counteract possible hypoglycaemia, patients receiving insulin or a sulfonylurea as well as acarbose need to carry glucose (not sucrose—acarbose interferes with sucrose absorption)

Glucobay® (Bayer Schering) PoM

Tablets, acarbose 50 mg, net price 90-tab pack = £6.15; 100 mg (scored), 90-tab pack = £11.35. Counselling, administration

EXENATIDE

Indications see notes above

Cautions elderly; pancreatitis (see below); **interactions:** Appendix 1 (antidiabetics)

Pancreatitis Severe pancreatitis (sometimes fatal), including haemorrhagic or necrotising pancreatitis, has been reported rarely. Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek prompt medical attention if symptoms such as abdominal pain, nausea, and vomiting develop; discontinue permanently if pancreatitis is diagnosed

Contra-indications ketoacidosis; severe gastro-intestinal disease

Renal impairment use with caution if eGFR 30–50 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73m^2

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—no information available

Side-effects gastro-intestinal disturbances including nausea, vomiting, diarrhoea, dyspepsia, abdominal pain and distension, gastro-oesophageal reflux disease, decreased appetite; headache, dizziness, agitation, asthenia; hypoglycaemia; increased sweating, injection-site reactions; antibody formation; *less commonly* pancreatitis (see Cautions above); *very rarely* anaphylactic reactions; also reported constipation, flatulence, eructation, dehydration, taste disturbance, renal impairment, drowsiness, rash, pruritus, urticaria, and angioedema

Dose

- By subcutaneous injection, ADULT over 18 years, initially 5 micrograms twice daily within 1 hour before 2 main meals (at least 6 hours apart), increased if necessary after at least 1 month to max. 10 micrograms twice daily

  Counselling If a dose is missed, continue with the next scheduled dose—do not administer **after** a meal. Some oral medications should be taken at least 1 hour before or 4 hours after exenatide injection—consult product literature for details

Byetta® (Lilly) ▼ PoM

Injection, exenatide 250 micrograms/mL, net price 5 microgram/dose prefilled pen (60 doses) = £68.24, 10 microgram/dose prefilled pen (60 doses) = £68.24. Counselling, administration

LIRAGLUTIDE

Indications see notes above

Cautions discontinue if symptoms of acute pancreatitis (persistent, severe abdominal pain); **interactions:** Appendix 1 (antidiabetics)

Contra-indications ketoacidosis; inflammatory bowel disease; diabetic gastroparesis

Hepatic impairment avoid—limited experience

Renal impairment avoid if eGFR less than 60 mL/minute/1.73 m^2—limited experience

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—no information available

Side-effects gastro-intestinal disturbances including nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain and distension, flatulence, gastritis, gastro-oesophageal reflux disease, decreased appetite; headache, dizziness, fatigue; fever, bronchitis, nasopharyngitis; hypoglycaemia; injection site reactions; *also reported* acute pancreatitis, thyroid neoplasm, goitre, increased blood calcitonin, angioedema

Dose

- By subcutaneous injection, ADULT over 18 years, initially 0.6 mg once daily, increased after at least 1 week to 1.2 mg once daily, further increased if necessary after an interval of at least 1 week to max. 1.8 mg once daily
  Note Dose of concomitant sulfonylurea may need to be reduced

Victoza® (Novo Nordisk) ▼ PoM
Injection, liraglutide 6 mg/mL, net price 2 × 3-mL prefilled pens = £78.48, 3 × 3-mL prefilled pens = £117.72. Counselling, administration

NATEGLINIDE

Indications type 2 diabetes mellitus in combination with metformin (section 6.1.2.2) when metformin alone inadequate

Cautions substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit nateglinide on morning of surgery and recommence when eating and drinking normally); elderly, debilitated and malnourished patients; **interactions:** Appendix 1 (antidiabetics)

Contra-indications ketoacidosis

Hepatic impairment caution in moderate hepatic impairment; avoid in severe impairment—no information available

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects hypoglycaemia; hypersensitivity reactions including pruritus, rashes and urticaria

Dose

- ADULT over 18 years, initially 60 mg 3 times daily within 30 minutes before main meals, adjusted according to response up to max. 180 mg 3 times daily

Starlix® (Novartis) PoM
Tablets, f/c, nateglinide 60 mg (pink), net price 84-tab pack = £22.71; 120 mg (yellow), 84-tab pack = £25.88; 180 mg (red), 84-tab pack = £25.88

PIOGLITAZONE

Indications type 2 diabetes mellitus (alone or combined with metformin or a sulfonylurea, or with both, or with insulin—see also notes above)

Cautions monitor liver function (see below); cardiovascular disease or in combination with insulin (risk of heart failure—see MHRA/CHM advice p. 431); substitute insulin during peri-operative period (omit pioglitazone on morning of surgery and recommence when eating and drinking normally); increased risk of bone fractures, particularly in women; avoid in acute porphyria (but see section 9.8.2); **interactions:** Appendix 1 (antidiabetics)
Liver toxicity Rare reports of liver dysfunction; monitor liver function before treatment, and periodically thereafter; advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop; discontinue if jaundice occurs

Contra-indications history of heart failure

Hepatic impairment avoid; see also Cautions above

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances, weight gain, oedema, anaemia, headache, visual disturbances, dizziness, arthralgia, hypoaesthesia, haematuria, impotence; *less commonly* hypoglycaemia, fatigue, insomnia, vertigo, sweating, altered blood lipids, proteinuria; see also Liver Toxicity above

Dose

- ADULT over 18 years, initially 15–30 mg once daily increased to 45 mg once daily according to response
  Note Dose of concomitant sulfonylurea or insulin may need to be reduced

Actos® (Takeda) ▼ PoM
Tablets, pioglitazone (as hydrochloride) 15 mg, net price 28-tab pack = £25.83; 30 mg, 28-tab pack = £35.89; 45 mg, 28-tab pack = £39.55

With metformin

For prescribing information on metformin, see section 6.1.2.2

Competact® (Takeda) ▼ PoM
Tablets, f/c, pioglitazone (as hydrochloride) 15 mg, metformin hydrochloride 850 mg, net price 56-tab pack = £35.89. Label: 21
Dose ADULT over 18 years, type 2 diabetes not controlled by metformin alone, 1 tablet twice daily
Note Titration with the individual components (pioglitazone and metformin) desirable before initiating *Competact®*

REPAGLINIDE

Indications type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate)

Cautions substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit repaglinide on morning of surgery and recommence when eating and drinking normally); debilitated and malnourished patients; **interactions:** Appendix 1 (antidiabetics)

Contra-indications ketoacidosis

Hepatic impairment avoid in severe liver disease

Renal impairment use with caution

Pregnancy avoid

Breast-feeding avoid—present in milk in *animal* studies

Side-effects abdominal pain, diarrhoea, constipation, nausea, vomiting; *rarely* hypoglycaemia, hypersensitivity reactions including pruritus, rashes, vasculitis, urticaria, and visual disturbances

Dose

- ADULT over 18 years, initially 500 micrograms within 30 minutes before main meals (1 mg if transferring from another oral hypoglycaemic), adjusted according to response at intervals of 1–2 weeks; up to 4 mg may be given as a single dose, max. 16 mg daily; ELDERLY over 75 years, not recommended

Prandin® (Daiichi Sankyo) PoM

Tablets, repaglinide 500 micrograms, net price 30-tab pack = £3.92, 90-tab pack = £11.76; 1 mg (yellow), 30-tab pack = £3.92, 90-tab pack = £11.76; 2 mg (peach), 90-tab pack = £11.76

Formerly marketed as *NovoNorm®*

SAXAGLIPTIN

Indications see notes above

Cautions elderly; **interactions:** Appendix 1 (antidiabetics)

Hepatic impairment use with caution in moderate impairment; avoid in severe impairment

Renal impairment avoid if eGFR less than 50 mL/minute/1.73m^2

Pregnancy avoid unless essential—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects vomiting, dyspepsia, gastritis; peripheral oedema; headache, dizziness, fatigue; upper respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis, nasopharyngitis; hypoglycaemia, myalgia; *less commonly* dyslipidaemia, hypertriglyceridaemia, erectile dysfunction, arthralgia; *also reported* rash

Dose

- ADULT over 18 years, 5 mg once daily

Note Dose of concomitant sulfonylurea may need to be reduced

Onglyza® (Bristol-Myers Squibb) ▼ PoM

Tablets, pink, f/c, saxagliptin (as hydrochloride) 5 mg, net price 28-tab pack = £31.60

SITAGLIPTIN

Indications see notes above

Cautions **interactions:** Appendix 1 (antidiabetics)

Contra-indications ketoacidosis

Renal impairment avoid if eGFR less than 50 mL/minute/1.73 m^2

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects gastro-intestinal disturbances; peripheral oedema; upper respiratory tract infection, nasopharyngitis; pain; *less commonly* dry mouth, anorexia, headache, drowsiness, dizziness, hypoglycaemia, osteoarthritis; *also reported* pancreatitis, rash, cutaneous vasculitis, and Stevens-Johnson syndrome

Dose

- ADULT over 18 years, 100 mg once daily

Note Dose of concomitant sulfonylurea or insulin may need to be reduced

Januvia® (MSD) ▼ PoM

Tablets, beige, f/c, sitagliptin (as phosphate) 100 mg, net price 28-tab pack = £33.26

The *Scottish Medicines Consortium* (p. 4) has advised (June 2010) that *Januvia®* is accepted for restricted use within NHS Scotland as monotherapy, to improve glycaemic control in patients with type 2 diabetes mellitus, for whom both metformin and sulfonylureas are not appropriate

With metformin

For prescribing information on metformin, see section 6.1.2.2

Janumet® (MSD) ▼ PoM

Tablets, f/c, red, sitagliptin 50 mg, metformin hydrochloride 1 g, net price 56-tab pack = £34.56. Label: 21

Dose type 2 diabetes mellitus not controlled by metformin alone *or* by metformin in combination with either a sulfonylurea *or* pioglitazone *or* insulin, ADULT over 18 years, 1 tablet twice daily

Note Dose of concomitant sulfonylurea or insulin may need to be reduced

The *Scottish Medicines Consortium* (p. 4) has advised (July 2008) that *Janumet®* is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus when the addition of a sulfonylurea to metformin is not appropriate; it is also accepted for use in NHS Scotland in combination with a sulfonylurea in patients inadequately controlled on maximum tolerated doses of metformin and a sulfonylurea.

VILDAGLIPTIN

Indications type 2 diabetes mellitus (in combination with metformin *or* with a sulfonylurea *or* with pioglitazone—see also notes above)

Cautions elderly; monitor liver function (see below); heart failure (avoid if moderate or severe); **interactions:** Appendix 1 (antidiabetics)

Liver toxicity Rare reports of liver dysfunction; monitor liver function before treatment and every 3 months for first year and periodically thereafter; advise patients to seek prompt medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue, and dark urine develop; discontinue if jaundice or other signs of liver dysfunction occur

Contra-indications ketoacidosis

Hepatic impairment avoid; see also Cautions above

Renal impairment avoid if eGFR less than 50 mL/minute/1.73 m^2

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, peripheral oedema, headache, tremor, asthenia, dizziness; *less commonly* constipation, hypoglycaemia, arthralgia; *rarely* hepatic dysfunction (see also Liver Toxicity above); *very rarely* nasopharyngitis, upper respiratory tract infection; pancreatitis *also reported*

Dose

- ADULT over 18 years, in combination with metformin or pioglitazone, 50 mg twice daily; in combination with a sulfonylurea, 50 mg daily in the morning

Galvus® (Novartis) ▼ PoM

Tablets, pale yellow, vildagliptin 50 mg, net price 56-tab pack = £31.76

With metformin

For prescribing information on metformin, see section 6.1.2.2

Eucreas® (Novartis) ▼ PoM

Eucreas® 50 mg/850 mg tablets, f/c, yellow, vildagliptin 50 mg, metformin hydrochloride 850 mg, net price 60-tab pack = £31.76. Label: 21

Eucreas® 50 mg/1 g tablets, f/c, dark yellow, vildagliptin 50 mg, metformin hydrochloride 1 g, net price 60-tab pack = £31.76. Label: 21

Dose type 2 diabetes mellitus not controlled by metformin alone, ADULT over 18 years, 1 *Eucreas®* tablet twice daily (based on patient's current metformin dose)

The *Scottish Medicines Consortium* (p. 4) has advised (June 2008) that *Eucreas®* is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone or those already treated with vildagliptin and metformin as separate tablets

6.1.3 Diabetic ketoacidosis

The management of diabetic ketoacidosis involves the replacement of fluid and electrolytes and the administration of insulin. Guidelines for the Management of Diabetic Ketoacidosis in Adults, published by the Joint British Diabetes Societies Inpatient Care Group[1], should be followed.

- To restore circulating volume if systolic blood pressure is below 90 mmHg (adjusted for age, sex, and medication as appropriate), give 500 mL **sodium chloride 0.9%** by intravenous infusion over 10–15 minutes; repeat if blood pressure remains below 90 mmHg and seek senior medical advice.
- When blood pressure is over 90 mmHg, **sodium chloride 0.9%** should be given by intravenous infusion at a rate that replaces deficit and provides maintenance; see guideline for suggested regimen.
- Include **potassium chloride** in the fluids unless anuria is suspected; adjust according to plasma-potassium concentration (measure at 60 minutes, 2 hours, and 2 hourly thereafter; measure hourly if outside the normal range).
- Start an intravenous insulin infusion: **soluble insulin** should be diluted (and **mixed thoroughly**) with **sodium chloride 0.9%** intravenous infusion to a concentration of 1 unit/mL; infuse at a fixed rate of 0.1 units/kg/hour.
- Established subcutaneous therapy with long-acting insulin analogues (insulin detemir or insulin glargine) should be continued during treatment of diabetic ketoacidosis.
- Monitor blood-ketone and blood-glucose concentrations hourly and adjust the insulin infusion rate accordingly. Blood-ketone concentration should fall by at least 0.5 mmol/litre/hour and blood-glucose concentration should fall by at least 3 mmol/litre/hour.
- Once blood-glucose concentration falls below 14 mmol/litre, **glucose 10%** should be given by intravenous infusion (into a large vein through a large-gauge needle) at a rate of 125 mL/hour, in addition to the **sodium chloride 0.9%** infusion.
- Continue insulin infusion until blood-ketone concentration is below 0.3 mmol/litre, blood pH is above 7.3 *and* the patient is able to eat and drink; ideally give subcutaneous fast-acting insulin and a meal, and stop the insulin infusion 1 hour later.

For the management of diabetic ketoacidosis in children under 18 years, see *BNF for Children*.

The management of hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion are usually necessary and slower rehydration may be required.

1. Available at www.diabetes.nhs.uk

6.1.4 Treatment of hypoglycaemia

Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from non-diet versions of *Lucozade® Energy Original* 55 mL, *Coca-Cola®* 100 mL, *Ribena® Blackcurrant* 18 mL (to be diluted), 2 teaspoons of sugar, and also from 3 sugar lumps[2]. If necessary this may be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness is an emergency. **Glucagon**, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases plasma-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. Glucagon may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe on an 'if necessary' basis to hospitalised insulin-treated patients, so that it may be given rapidly by the nurses during an hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, 50 mL of **glucose intravenous infusion 20%** (section 9.2.2) may be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 10% may also be used but larger volumes are needed. Glucose intravenous infusion 50% is not recommended because of the higher risk of extravasation injury and because administration is difficult. Close monitoring is necessary in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Patients whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

For advice on the emergency management of hypoglycaemia in dental practice, see p. 28.

2. Proprietary products of quick-acting carbohydrate (e.g. *GlucoGel®*, *Dextrogel®*, *Hypo-Fit®*) are available on prescription for the patient to keep to hand in case of hypoglycaemia.

GLUCAGON

Indications see notes above and under Dose

Cautions see notes above, insulinoma, glucagonoma; ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency

Contra-indications phaeochromocytoma

Side-effects nausea, vomiting, abdominal pain, hypokalaemia, hypotension, rarely hypersensitivity reactions

Dose

- Insulin-induced hypoglycaemia, by subcutaneous, intramuscular, *or* intravenous injection, ADULT and CHILD over 8 years (or body-weight over 25 kg), 1 mg; CHILD under 8 years (or body-weight under 25 kg), 500 micrograms; if no response within 10 minutes intravenous glucose must be given
- Diagnostic aid, consult product literature
- Beta-blocker poisoning, see p. 37

Note 1 unit of glucagon = 1 mg of glucagon

[1]**GlucaGen® HypoKit** (Novo Nordisk) PoM
Injection, powder for reconstitution, glucagon (rys) as hydrochloride with lactose, net price 1-mg vial with prefilled syringe containing water for injection = £11.52

1. PoM restriction does not apply where administration is for saving life in emergency

Chronic hypoglycaemia

Diazoxide, administered by mouth, is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. It has no place in the management of acute hypoglycaemia.

DIAZOXIDE

Indications chronic intractable hypoglycaemia; hypertensive emergency—but no longer recommended, see section 2.5

Cautions ischaemic heart disease; monitor blood pressure; during prolonged use monitor white cell and platelet count, and in children, regularly assess growth, bone, and psychological development; **interactions:** Appendix 1 (diazoxide)

Renal impairment dose reduction may be required

Pregnancy prolonged use in second or third trimesters may produce alopecia and impaired glucose tolerance in neonate; inhibits uterine activity during labour

Side-effects anorexia, nausea, vomiting, hyperuricaemia, hypotension, oedema, tachycardia, arrhythmias, extrapyramidal effects; hypertrichosis on prolonged treatment

Dose

- By mouth, ADULT and CHILD, initially 5 mg/kg daily in 2–3 divided doses

Eudemine® (UCB Pharma) PoM
Tablets, diazoxide 50 mg. Net price 100 = £44.64
Injection, see section 2.5.1

6.1.5 Treatment of diabetic nephropathy and neuropathy

Diabetic nephropathy

Regular review of diabetic patients should include an annual test for urinary protein (using *Albustix®*) and serum creatinine measurement. If the urinary protein test is negative, the urine should be tested for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (*Micral-Test II®* NHS or *Microbumintest®* NHS) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Provided there are no contra-indications, all diabetic patients with nephropathy causing proteinuria or with established microalbuminuria (at least 3 positive tests) should be treated with an ACE inhibitor (section 2.5.5.1) or an angiotensin-II receptor antagonist (section 2.5.5.2) even if the blood pressure is normal; in any case, to minimise the risk of renal deterioration, blood pressure should be carefully controlled (section 2.5).

ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in patients with renal impairment.

For the treatment of hypertension in diabetes, see section 2.5.

Diabetic neuropathy

Optimal diabetic control is beneficial for the management of *painful neuropathy* in patients with type 1 diabetes (see also section 4.7.3). **Paracetamol** (p. 259) or a non-steroidal anti-inflammatory drug such as **ibuprofen** (p. 636) may relieve *mild to moderate pain*.

Duloxetine (p. 243) is effective for the treatment of painful diabetic neuropathy; **amitriptyline** (p. 235) [unlicensed use] can be used if duloxetine is ineffective or unsuitable. **Nortriptyline** (p. 236) [unlicensed] may be better tolerated than amitriptyline. If treatment with amitriptyline or duloxetine is inadequate, treatment with **pregabalin** (p. 284) should be tried. Combination therapy of duloxetine or amitriptyline with pregabalin can be used if monotherapy at the maximum tolerated dose does not control symptoms.

Neuropathic pain may respond to opioid analgesics. There is evidence of efficacy for **tramadol** (p. 271), **morphine** (p. 268), and **oxycodone** (p. 269); however, treatment with morphine or oxycodone should be initiated only under specialist supervision. Tramadol can be prescribed while the patient is waiting for assessment by a specialist if other treatments have been unsuccessful.

Gabapentin (p. 284) and **carbamazepine** (p. 281) are sometimes used for the treatment of neuropathic pain. **Capsaicin** cream 0.075% (p. 664) is licensed for painful diabetic neuropathy and may have some effect, but it produces an intense burning sensation during the initial treatment period.

In *autonomic neuropathy* diabetic diarrhoea can often be managed by 2 or 3 doses of **tetracycline** 250 mg [unlicensed use] (p. 347). Otherwise **codeine** (p. 58) is

the best drug, but other antidiarrhoeal preparations can be tried. An antiemetic which promotes gastric transit, such as **metoclopramide** (p. 253) or **domperidone** (p. 253), is helpful for gastroparesis. In rare cases when an antiemetic does not help, erythromycin (especially when given intravenously) may be beneficial but this needs confirmation.

In *neuropathic postural hypotension* increased salt intake and the use of the mineralocorticoid **fludrocortisone** 100–400 micrograms daily [unlicensed use] (p. 442) may help by increasing plasma volume, but uncomfortable oedema is a common side-effect. Fludrocortisone can also be combined with **flurbiprofen** (p. 636) and **ephedrine hydrochloride** (p. 179) [both unlicensed]. **Midodrine** [unlicensed], an alpha agonist, may also be useful in postural hypotension.

Gustatory sweating can be treated with an antimuscarinic such as **propantheline bromide** (p. 48); side-effects are common. For the management of hyperhidrosis, see section 13.12.

In some patients with *neuropathic oedema*, ephedrine hydrochloride [unlicensed use] 30–60 mg 3 times daily offers effective relief.

For the management of erectile dysfunction, see section 7.4.5.

6.1.6 Diagnostic and monitoring devices for diabetes mellitus

Blood monitoring

Blood **glucose** monitoring using a meter gives a direct measure of the glucose concentration at the time of the test and can detect hypoglycaemia as well as hyperglycaemia. Patients should be properly trained in the use of blood glucose monitoring systems and to take appropriate action on the results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

Patients using multiple injection regimens should understand how to adjust their insulin dose according to their carbohydrate intake. With fixed-dose insulin regimens, the carbohydrate intake needs to be regulated, and should be distributed throughout the day to match the insulin regimen.

Self-monitoring of blood-glucose concentration is appropriate for patients with type 2 diabetes:

- who are treated with insulin;
- who are treated with oral hypoglycaemic drugs e.g. sulfonylureas, to provide information on hypoglycaemia;
- to monitor changes in blood-glucose concentration resulting from changes in lifestyle or medication, and during intercurrent illness;
- to ensure safe blood-glucose concentration during activities, including driving.

Note In the UK blood-glucose concentration is expressed in mmol/litre and Diabetes UK advises that these units should be used for self-monitoring of blood glucose. In other European countries units of mg/100 mL (or mg/dL) are commonly used. It is advisable to check that the meter is pre-set in the correct units.

If the patient is unwell and diabetic ketoacidosis is suspected, blood **ketones** should be measured according to local guidelines (section 6.1.3). Patients and their carers should be trained in the use of blood ketone monitoring systems and to take appropriate action on the results obtained, including when to seek medical attention.

Urinalysis

Tests for glucose range from reagent strips specific to glucose to reagent tablets which detect all reducing sugars. Few patients still use *Clinitest®*; *Clinistix®* is suitable for screening purposes only. Tests for ketones by patients are rarely required unless they become unwell—see also Blood Monitoring, above.

Microalbuminuria can be detected with *Micral-Test II®* but this should be followed by confirmation in the laboratory, since false positive results are common.

Glucose

Clinistix® (Bayer Diabetes Care)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £3.27

Clinitest® (Bayer Diabetes Care)

Reagent tablets, for detection of glucose and other reducing substances in urine. Net price 36-tab pack = £2.00

Diabur-Test 5000® (Roche Diagnostics)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.87

Diastix® (Bayer Diabetes Care)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.78

Medi-Test® Glucose (BHR)

Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.33

Ketones

Ketostix® (Bayer Diabetes Care)

Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.95

Ketur Test® (Roche Diagnostics)

Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.76

Protein

Albustix® (Siemens)

Reagent strips, for detection of protein in urine. Net price 50-strip pack = £4.10

Medi-Test® Protein 2 (BHR)

Reagent strips, for detection of protein in urine. Net price 50-strip pack = £3.27

Other reagent strips available for urinalysis include:

Combur-3 Test® (glucose and protein—Roche Diagnostics), *Clinitek Microalbumin®* (albumin and creatinine—Siemens), *Ketodiastix®* (glucose and ketones—Bayer Diagnostics), *Medi-Test Combi 2®* (glucose and protein—BHR), *Micral-Test II®* (albumin—Roche Diagnostics), *Microalbustix®* (albumin and creatinine—Siemens), *Uristix®* (glucose and protein—Siemens)

Meters and test strips

Meter (all NHS)	Type of monitoring	Meter retail price	Compatible test strips	Test strip net price	Sensitivity range (mmol/litre)	Manufacturer
Accu-Chek® Active[1]	Blood glucose		**Active®**	50-strip pack = £15.16	0.6–33.3	Roche Diagnostics
Accu-Chek® Advantage[1]	Blood glucose		**Advantage Plus®**	50-strip pack = £15.17	0.6–33.3	Roche Diagnostics
Accu-Chek® Aviva	Blood glucose	£12.99	**Aviva®**	50-strip pack = £14.89	0.6–33.3	Roche Diagnostics
Accu-Chek® Compact[1]	Blood glucose		**Compact®**	3 × 17-strip pack = £15.29	0.6–33.3	Roche Diagnostics
Accu-Chek® Compact Plus	Blood glucose	£12.99	**Compact®**	3 × 17-strip pack = £15.29	0.6–33.3	Roche Diagnostics
Accu-Chek® Mobile	Blood glucose	£49.99	**Mobile®**	100 tests = £30.12	0.3–33.3	Roche Diagnostics
Accutrend®[1]	Blood glucose		**BM-Accutest®**	50-strip pack = £14.31	1.1–33.3	Roche Diagnostics
Ascensia Breeze®[1]	Blood glucose		**Ascensia® Autodisc**	5 × 10-disc pack = £14.62	0.6–33.3	Bayer Diabetes Care
Ascensia Esprit® 2[1]	Blood glucose		**Ascensia® Autodisc**	5 × 10-disc pack = £14.62	0.6–33.3	Bayer Diabetes Care
Breeze 2®	Blood glucose	£14.34	**Breeze 2®**	5 × 10-disc pack = £14.34	0.6–33.3	Bayer Diabetes Care
CareSens N®[2]	Blood glucose		**CareSens N®**	50-strip pack = £12.75	1.1–33.3	Spirit Healthcare
Contour®	Blood glucose	£10.80	**Contour®** Formerly *Ascensia® Microfill*	50-strip pack = £14.74	0.6–33.3	Bayer Diabetes Care
FreeStyle®[1]	Blood glucose		**FreeStyle®**	50-strip pack = £14.90	1.1–27.8	Abbott
FreeStyle Freedom®[1]	Blood glucose		**FreeStyle®**	50-strip pack = £14.90	1.1–27.8	Abbott
FreeStyle Freedom Lite®	Blood glucose	£11.49	**FreeStyle Lite®**	50-strip pack = £14.90	1.1–27.8	Abbott
FreeStyle Lite®	Blood glucose	£14.94	**FreeStyle Lite®**	50-strip pack = £14.90	1.1–27.8	Abbott
FreeStyle Mini®[1]	Blood glucose		**FreeStyle®**	50-strip pack = £14.90	1.1–27.8	Abbott
GlucoMen® Glycó[1]	Blood glucose		**GlucoMen®**	50-strip pack = £13.67	1.1–33.3	Menarini Diagnostics
GlucoMen® GM	Blood glucose	£15.26	**GlucoMen GM®**	50-strip pack = £14.67	0.6–33.3	Menarini Diagnostics
GlucoMen® LX	Blood glucose	£14.94	**GlucoMen® LX**	50-strip pack = £14.65	1.1–33.3	Menarini Diagnostics
GlucoMen® PC[1]	Blood glucose		**GlucoMen®**	50-strip pack = £13.67	1.1–33.3	Menarini Diagnostics
GlucoMen® Visio	Blood glucose	£10.34	**GlucoMen® Visio Sensor**	50-strip pack = £14.53	1.1–33.3	Menarini Diagnostics
Glucotrend®[1]	Blood glucose		**Active®**	50-strip pack = £14.76	0.6–33.3	Roche Diagnostics
One Touch® II[1]	Blood glucose		**One Touch®**	50-strip pack = £14.59	1.1–33.3	LifeScan
One Touch® Basic[1]	Blood glucose		**One Touch®**	50-strip pack = £14.59	1.1–33.3	LifeScan

1. Meter no longer available
2. Free of charge from diabetes healthcare professionals

Meter (all NHS)	Type of monitoring	Meter retail price	Compatible test strips	Test strip net price	Sensitivity range (mmol/litre)	Manufacturer
One Touch® Profile[1]	Blood glucose		**One Touch®**	50-strip pack = £14.59	1.1–33.3	LifeScan
One Touch Ultra®[1]	Blood glucose		**One Touch Ultra®**	50-strip pack = £14.75	1.1–33.3	LifeScan
One Touch Ultra 2®	Blood glucose	£25.98	**One Touch Ultra®**	50-strip pack = £14.75	1.1–33.3	LifeScan
One Touch UltraEasy®	Blood glucose	£25.98	**One Touch Ultra®**	50-strip pack = £14.75	1.1–33.3	LifeScan
One Touch UltraSmart®[2]	Blood glucose		**One Touch Ultra®**	50-strip pack = £14.75	1.1–33.3	LifeScan
One Touch® Vita[2]	Blood glucose		**One Touch® Vita**	50-strip pack = £14.81	1.1–33.3	LifeScan
Optium®[1]	Blood ketones		**Optium® β-ketone**	10-strip pack = £19.92	0–8.0	Abbott
Optium Xceed®	Blood glucose	£17.24	**Optium Plus®** Formerly *Medisense® Optium Plus*	50-strip pack = £14.80	1.1–27.8	Abbott
	Blood ketones		**Optium® β-ketone**	10-strip pack = £19.55	0–8.0	Abbott
PocketScan®[1]	Blood glucose		**PocketScan®**	50-strip pack = £14.41	1.1–33.3	LifeScan
Prestige®	Blood glucose	£8.62	**Prestige®**	50-strip pack = £14.51	1.4–33.3	Home Diagnostics
TRUEone®	Blood glucose	n/a	All-in-one test strips and meter	50-strip pack with meter = £14.36	1.1–33.3	Home Diagnostics
TRUEresult®[2]	Blood glucose	£11.74	**TRUEresult®**[2]	50-strip pack = £14.36	1.1–33.3	Home Diagnostics
TRUEresult twist®[2]	Blood glucose	£11.74	**TRUEresult®**	50-strip pack = £14.36	1.1–33.3	Home Diagnostics
TRUEtrack®	Blood glucose	£8.62	**TRUEtrack®**	50-strip pack = £14.25	1.1–33.3	Home Diagnostics
WaveSense Jazz®	Blood glucose	£24.99	**WaveSense Jazz®**	50-strip pack = £14.45	1.1–33.3	WaveSense

1. Meter no longer available
2. Free of charge from diabetes healthcare professionals

Oral glucose tolerance test

The oral glucose tolerance test is used mainly for diagnosis of impaired glucose tolerance; it is not recommended or necessary for routine diagnostic use when severe symptoms of hyperglycaemia are present. In patients who have less severe symptoms and blood glucose levels that do not establish or exclude diabetes (e.g. impaired fasting glycaemia), an oral glucose tolerance test may be required. It is also used to establish the presence of gestational diabetes. The oral glucose tolerance test generally involves giving anhydrous glucose 75 g (equivalent to Glucose BP 82.5 g) by mouth to the fasting patient, and measuring blood-glucose concentrations at intervals.

The appropriate amount of glucose should be given with 200–300 mL fluid. Anhydrous glucose 75 g may alternatively be given as 113 mL *Polycal®* (Nutricia Clinical) with extra fluid to administer a total volume of 200–300 mL.

6.2 Thyroid and antithyroid drugs

6.2.1 Thyroid hormones
6.2.2 Antithyroid drugs

6.2.1 Thyroid hormones

Thyroid hormones are used in hypothyroidism (myxoedema), and also in diffuse non-toxic goitre, Hashimoto's thyroiditis (lymphadenoid goitre), and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development. **Levothyroxine sodium** (thyroxine sodium) is the treatment of choice for *maintenance* therapy.

In infants and children with congenital hypothyroidism and juvenile myxoedema, the dose of levothyroxine should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone. See *BNF for Children* (section 6.2.1) for suitable dosage regimens.

Liothyronine sodium has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect; 20 micrograms is equivalent to 100 micrograms of levothyroxine. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in *severe hypothyroid states* when a rapid response is desired.

Liothyronine by intravenous injection is the treatment of choice in *hypothyroid coma*. Adjunctive therapy includes intravenous fluids, hydrocortisone, and treatment of infection; assisted ventilation is often required.

LEVOTHYROXINE SODIUM
(Thyroxine sodium)

Indications hypothyroidism; see also notes above

Cautions panhypopituitarism or predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine), elderly, cardiovascular disorders (including hypertension, myocardial insufficiency or myocardial infarction, see Initial Dosage below), long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased); **interactions:** Appendix 1 (thyroid hormones)

Initial dosage Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia. If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose

Contra-indications thyrotoxicosis

Pregnancy monitor maternal serum-thyrotrophin concentration—levothyroxine may cross the placenta and excessive maternal concentration can be detrimental to fetus

Breast-feeding amount too small to affect tests for neonatal hypothyroidism

Side-effects usually at excessive dosage (see Initial Dosage above) include diarrhoea, vomiting, anginal pain, arrhythmias, palpitation, tachycardia, tremor, restlessness, excitability, insomnia; headache, flushing, sweating, fever, heat intolerance, weight-loss, muscle cramp, and muscular weakness; transient hair loss in children; hypersensitivity reactions including rash, pruritus and oedema also reported

Dose

- ADULT over 18 years, initially 50–100 micrograms once daily, preferably before breakfast, adjusted in steps of 25–50 micrograms every 3–4 weeks according to response (usual maintenance dose 100–200 micrograms once daily); in cardiac disease, severe hypothyroidism, and patients over 50 years, initially 25 micrograms once daily, adjusted in steps of 25 micrograms every 4 weeks according to response; usual maintenance dose 50–200 micrograms once daily; CHILD under 18 years see *BNF for Children* (section 6.2.1)
- Congenital hypothyroidism and juvenile myxoedema, see *BNF for Children* (section 6.2.1)

Levothyroxine (Non-proprietary) PoM

Tablets, levothyroxine sodium 25 micrograms, net price 28-tab pack = £2.22; 50 micrograms, 28-tab pack = £1.09; 100 micrograms, 28-tab pack = £1.09

Brands include *Eltroxin*®

Oral solution, levothyroxine sodium 25 micrograms/5 mL, net price 100 mL = £42.75; 50 micrograms/5 mL, 100 mL = £44.90; 100 micrograms/5 mL, 100 mL = £52.75

Brands include *Evotrox*® (sugar-free)

Note All strengths of levothyroxine oral solution by Almus and branded as *Evotrox*®, have been reformulated (August 2010) leading to an increase in potency of approximately 10%; the manufacturer advises that the recommended dose has not changed, but recommends increased monitoring of patients on these preparations as dose adjustments may be necessary

LIOTHYRONINE SODIUM
(L-Tri-iodothyronine sodium)

Indications see notes above

Cautions see under Levothyroxine Sodium; **interactions:** Appendix 1 (thyroid hormones)

Contra-indications see under Levothyroxine Sodium

Pregnancy does not cross the placenta in significant amounts; monitor maternal thyroid function tests—dosage adjustment may be necessary

Breast-feeding amount too small to affect tests for neonatal hypothyroidism

Side-effects see under Levothyroxine Sodium

Dose

- By mouth, initially 10–20 micrograms daily gradually increased to 60 micrograms daily in 2–3 divided doses; ELDERLY smaller initial doses; CHILD, adult dose reduced in proportion to body-weight
- By slow intravenous injection, hypothyroid coma, 5–20 micrograms repeated every 12 hours or as often as every 4 hours if necessary; *alternatively* initially 50 micrograms then 25 micrograms every 8 hours reducing to 25 micrograms twice daily

Liothyronine sodium (Goldshield) PoM

Tablets, scored, liothyronine sodium 20 micrograms, net price 28-tab pack = £26.15

Triiodothyronine (Goldshield) PoM

Injection, powder for reconstitution, liothyronine sodium (with dextran). Net price 20-microgram amp = £37.92

6.2.2 Antithyroid drugs

Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management. In the UK carbimazole is the most commonly used drug. Propylthiouracil should be reserved for patients who are intolerant of carbimazole or for those who suffer sensitivity reactions to carbimazole, because sensitivity is not necessarily displayed to both drugs. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

Neutropenia and agranulocytosis

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

1. Patient should be asked to report symptoms and signs suggestive of infection, especially sore throat.
2. A white blood cell count should be performed if there is any clinical evidence of infection.
3. Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Carbimazole is given in a dose of 15 to 40 mg daily; higher doses should be prescribed under specialist supervision only. This dose is continued until the patient becomes euthyroid, usually after 4 to 8 weeks and the dose is then gradually reduced to a maintenance dose of 5 to 15 mg. Therapy is usually given for 12 to 18 months. Children may be given carbimazole in an initial dose of 250 micrograms/kg three times daily, adjusted according to response; treatment in children should be undertaken by a specialist. Rashes and pruritus are common but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted. All patients should be advised to report any sore throat immediately because of the rare complication of agranulocytosis (see Neutropenia and Agranulocytosis, above).

Propylthiouracil is given in a dose of 200 to 400 mg daily in divided doses in adults and this dose is maintained until the patient becomes euthyroid; the dose may then be gradually reduced to a maintenance dose of 50 to 150 mg daily in divided doses.

Over-treatment with antithyroid drugs can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.

A combination of carbimazole, 40 to 60 mg daily with levothyroxine, 50 to 150 micrograms daily, may be used in a *blocking-replacement regimen*; therapy is usually given for 18 months. The blocking-replacement regimen is **not** suitable during pregnancy.

Iodine has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (^{131}I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.

Propranolol is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism. Propranolol has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propranolol but **nadolol** is also used. For doses and preparations of beta-blockers see section 2.4.

Thyrotoxic crisis ('thyroid storm') requires emergency treatment with intravenous administration of fluids, propranolol (5 mg) and hydrocortisone (100 mg every 6 hours, as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

Pregnancy and breast-feeding Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen (see above) is **not** suitable. Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate—use carbimazole in pregnancy only if propylthiouracil is not suitable. Both propylthiouracil and carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves' disease tend to fall during pregnancy).

Carbimazole and propylthiouracil appear in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used.

CARBIMAZOLE

Indications hyperthyroidism

Contra-indications severe blood disorders

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment

Pregnancy neonatal goitre and hypothyroidism; has been associated with congenital defects including aplasia cutis of the neonate; see also notes above

Breast-feeding amount in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used; see also notes above

Side-effects nausea, mild gastro-intestinal disturbances, taste disturbance, headache; fever, malaise; rash, pruritus, arthralgia; *rarely* myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis, see Neutropenia and Agranulocytosis above), and jaundice

Counselling Warn patient to tell doctor **immediately** if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops

Dose

- See notes above

Carbimazole (Non-proprietary) PoM

Tablets, carbimazole 5 mg, net price 100-tab pack = £4.53; 20 mg, 100-tab pack = £16.83. Counselling, blood disorder symptoms

Neo-Mercazole® (Amdipharm) PoM

Tablets, both pink, carbimazole 5 mg, net price 100-tab pack = £3.85; 20 mg, 100-tab pack = £11.44. Counselling, blood disorder symptoms

IODINE AND IODIDE

Indications thyrotoxicosis (pre-operative)

Cautions children; not for long-term treatment

Pregnancy neonatal goitre and hypothyroidism; see also notes above

Breast-feeding stop breast-feeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk; see also notes above

Side-effects hypersensitivity reactions including coryza-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes; on prolonged treatment depression, insomnia, impotence; goitre in infants of mothers taking iodides

Dose

- See under preparation

Aqueous Iodine Oral Solution

Oral solution, iodine 5%, potassium iodide 10% in purified water, freshly boiled and cooled, total iodine 130 mg/mL, net price 500 mL = £6.24. Label: 27

Dose 0.1–0.3 mL 3 times daily well diluted with milk or water

PROPYLTHIOURACIL

Indications hyperthyroidism

Cautions monitor for hepatotoxicity

Hepatotoxicity Severe hepatic reactions have been reported, including fatal cases and cases requiring liver transplant—discontinue if significant liver-enzyme abnormalities develop

Counselling Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, dark urine, or pruritus develop

Hepatic impairment reduce dose (see also Hepatotoxicity above)

Renal impairment use three-quarters normal dose if eGFR 10–50 mL/minute/1.73 m^2; use half normal dose if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy neonatal goitre and hypothyroidism; see also notes above

Breast-feeding monitor infant's thyroid status but amount in milk probably too small to affect infant; high doses may affect neonatal thyroid function; see also notes above

Side-effects see under Carbimazole; leucopenia; rarely cutaneous vasculitis, thrombocytopenia, aplastic anaemia, hypoprothrombinaemia, hepatic disorders (including hepatitis, hepatic failure, encephalopathy, hepatic necrosis; see also Hepatotoxicity above), nephritis, lupus erythematous-like syndromes

Dose

- See notes above

Propylthiouracil (Non-proprietary) PoM

Tablets, propylthiouracil 50 mg. Net price 56-tab pack = £47.11, 100-tab pack = £67.38

6.3 Corticosteroids

6.3.1 Replacement therapy
6.3.2 Glucocorticoid therapy

6.3.1 Replacement therapy

The adrenal cortex normally secretes hydrocortisone (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of **hydrocortisone** (section 6.3.2) and the mineralocorticoid **fludrocortisone**; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In *Addison's disease* or following adrenalectomy, **hydrocortisone** 20 to 30 mg daily by mouth is usually required. This is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone 50 to 300 micrograms daily.

In *acute adrenocortical insufficiency*, **hydrocortisone** is given intravenously (preferably as sodium succinate) in doses of 100 mg every 6 to 8 hours in sodium chloride intravenous infusion 0.9%.

In *hypopituitarism* glucocorticoids should be given as in adrenocortical insufficiency, but since production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required. Additional replacement therapy with levothyroxine (section 6.2.1) and sex hormones (section 6.4) should be given as indicated by the pattern of hormone deficiency.

FLUDROCORTISONE ACETATE

Indications mineralocorticoid replacement in adrenocortical insufficiency

Cautions section 6.3.2; **interactions:** Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Hepatic impairment section 6.3.2

Renal impairment section 6.3.2

Pregnancy section 6.3.2

Breast-feeding section 6.3.2

Side-effects section 6.3.2

Dose

- 50–300 micrograms daily; CHILD 5 micrograms/kg daily

Florinef® (Squibb) PoM

Tablets, scored, fludrocortisone acetate 100 micrograms. Net price 100-tab pack = £5.05. Label: 10, steroid card

6.3.2 Glucocorticoid therapy

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids below). The mineralocorticoid activity of **fludrocortisone** (section 6.3.1) is so high that its anti-inflammatory activity is of no clinical relevance. The table below shows equivalent anti-inflammatory doses.

Equivalent anti-inflammatory doses of corticosteroids

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action

Prednisolone 5 mg
≡ Betamethasone 750 micrograms
≡ Cortisone acetate 25 mg
≡ Deflazacort 6 mg
≡ Dexamethasone 750 micrograms
≡ Hydrocortisone 20 mg
≡ Methylprednisolone 4 mg
≡ Prednisone 5 mg
≡ Triamcinolone 4 mg

The relatively high mineralocorticoid activity of **cortisone** and **hydrocortisone**, and the resulting fluid retention, make them unsuitable for disease suppression on a long-term basis. However, they can be used for adrenal replacement therapy (section 6.3.1); hydrocortisone is preferred because cortisone requires conversion in the

liver to hydrocortisone. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked (section 13.4); cortisone is not active topically.

Prednisolone and **prednisone** have predominantly glucocorticoid activity. Prednisolone is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone and **dexamethasone** have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia). Some esters of betamethasone and of **beclometasone** (beclomethasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

Deflazacort has a high glucocorticoid activity; it is derived from prednisolone.

Use of corticosteroids

Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin (section 13.4). Corticosteroids should be avoided or used only under specialist supervision in psoriasis (section 13.5).

Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn's disease (section 1.5). They are also included in locally applied creams for haemorrhoids (section 1.7.2).

Use can be made of the mineralocorticoid activity of fludrocortisone to treat postural hypotension in autonomic neuropathy (section 6.1.5).

High-dose corticosteroids should be avoided for the management of septic shock. However, there is evidence that administration of lower doses of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 micrograms daily by mouth) is of benefit in adrenocortical insufficiency resulting from septic shock.

Dexamethasone and betamethasone have little if any mineralocorticoid action and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17-hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamic-pituitary-adrenal axis is greatest and most prolonged when they are given at night. In most individuals a single dose of 1 mg of dexamethasone at night, is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the 'overnight dexamethasone suppression test' for diagnosing Cushing's syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

A corticosteroid may be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy (see also p. 22); high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should **not** be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylaxis, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline (epinephrine) (section 3.4.3). In such cases hydrocortisone (as sodium succinate) by intravenous injection in a dose of 100 to 300 mg may be required.

Corticosteroids are preferably used by inhalation in the management of asthma (section 3.2) but systemic therapy in association with bronchodilators is required for the emergency treatment of severe acute asthma (section 3.1.1).

Corticosteroids may also be useful in conditions such as autoimmune hepatitis, rheumatoid arthritis and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia (section 9.1.3), and some cases of the nephrotic syndrome (particularly in children) and thrombocytopenic purpura (section 9.1.4).

Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately remit. It is usual to begin therapy in these conditions at fairly high dose, such as 40 to 60 mg prednisolone daily, and then to reduce the dose to the lowest commensurate with disease control.

For other references to the use of corticosteroids see Prescribing in Palliative Care, section 8.2.2 (immunosuppression), section 10.1.2 (rheumatic diseases), section 11.4 (eye), section 12.1.1 (otitis externa), section 12.2.1 (allergic rhinitis), and section 12.3.1 (aphthous ulcers).

Administration

Whenever possible *local treatment* with creams, intra-articular injections, inhalations, eye-drops, or enemas should be used in preference to *systemic treatment*. The suppressive action of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. In an attempt to reduce pituitary-adrenal suppression further, the total dose for two days can

sometimes be taken as a single dose on alternate days; alternate-day administration has not been very successful in the management of asthma (section 3.2). Pituitary-adrenal suppression can also be reduced by means of intermittent therapy with short courses. In some conditions it may be possible to reduce the dose of corticosteroid by adding a small dose of an immunosuppressive drug (section 8.2.1).

Cautions and contra-indications of corticosteroids

Adrenal suppression

During prolonged therapy with corticosteroids, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Corticosteroids, below). Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists **must** know whether a patient is taking or has been taking a corticosteroid. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- *Minor surgery under general anaesthesia*—usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery
- *Moderate or major surgery*—usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by hydrocortisone 25–50 mg 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections

Patients on long-term corticosteroid treatment should carry a Steroid Treatment Card (see p. 445) which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

Infections

Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. *septicaemia* and *tuberculosis* may reach an advanced stage before being recognised, and *amoebiasis* or *strongyloidiasis* may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral *ocular infections* may also be exacerbated (see also section 11.4.1).

Chickenpox Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being *at risk of severe chickenpox* (see Steroid Treatment Card). Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature.

Passive immunisation with varicella–zoster immunoglobulin (section 14.5.2) is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment (section 5.3.2.1). Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

Measles Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin (section 14.5.1) may be needed.

Withdrawal of corticosteroids

The magnitude and speed of dose reduction in corticosteroid withdrawal should be determined on a case-by-case basis, taking into consideration the underlying condition that is being treated, and individual patient factors such as the likelihood of relapse and the duration of corticosteriod treatment. *Gradual* withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:

- received more than 40 mg prednisolone (or equivalent) daily for more than 1 week;
- been given repeat doses in the evening;
- received more than 3 weeks' treatment;
- recently received repeated courses (particularly if taken for longer than 3 weeks);
- taken a short course within 1 year of stopping long-term therapy;
- other possible causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse *and* who have received treatment for 3 weeks or less *and* who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

Psychiatric reactions

Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. A serious paranoid state or depression with risk of suicide can be induced, particularly in patients with a history of mental disorder. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be

alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment.

Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid-induced psychosis, or who have a personal or family history of psychiatric disorders.

Advice to patients

A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Patients should especially be advised of the following (for details, see Infections, Adrenal Suppression, Psychiatric Reactions, and Withdrawal of Corticosteroids above):

- **Immunosuppression** Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, patients are at risk of severe **chickenpox** and should avoid close contact with people who have chickenpox or shingles. Similarly, precautions should also be taken against contracting **measles**;
- **Adrenal suppression** If the corticosteroid is given for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the patient must mention the course of corticosteroid when receiving treatment for any illness or injury;
- **Mood and behaviour changes** Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the patient can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur;
- **Other serious effects** Serious gastro-intestinal, musculoskeletal, and ophthalmic effects which require medical help can also occur; for details see Side-effects of Corticosteroids, p. 446.

Steroid treatment cards (see below) should be issued where appropriate. Doctors and pharmacists can obtain supplies of the card from:

England and Wales
3M Security Printing and Systems Limited
Gorse Street, Chadderton
Oldham, OL9 9QH
Tel: (0161) 683 2189
Fax: (0161) 683 2188
nhsforms@spsl.uk.com

Scotland
R.R. Donnelley Global Document Solutions
20–22 South Gyle Crescent
Edinburgh, EH12 9EB
Tel: (0131) 334 1229
Fax: (0131) 334 5946
ian.fruish@rrd.com

Northern Ireland
Pharmaceutical Directorate
Business Services Organisation
2 Franklin Street
Belfast, BT2 8DQ
Tel: (028) 9053 5652

STEROID TREATMENT CARD

I am a patient on STEROID treatment which must not be stopped suddenly

- If you have been taking this medicine for more than three weeks, the dose should be reduced gradually when you stop taking steroids unless your doctor says otherwise.
- Read the patient information leaflet given with the medicine.
- Always carry this card with you and show it to anyone who treats you (for example a doctor, nurse, pharmacist or dentist). For one year after you stop the treatment, you must mention that you have taken steroids.
- If you become ill, or if you come into contact with anyone who has an infectious disease, consult your doctor promptly. If you have never had chickenpox, you should avoid close contact with people who have chickenpox or shingles. If you do come into contact with chickenpox, see your doctor urgently.
- Make sure that the information on the card is kept up to date.

Other cautions and contra-indications

Other cautions include: children and adolescents (growth restriction possibly irreversible), elderly (close supervision required particularly on long-term treatment); frequent monitoring required if history of tuberculosis (or X-ray changes), hypertension, recent myocardial infarction (rupture reported), congestive heart failure, diabetes mellitus including family history, osteoporosis (post-menopausal women at special risk), glaucoma (including family history), ocular herpes simplex—risk of corneal perforation, severe affective disorders (particularly if history of steroid-induced psychosis—see also Psychiatric Reactions, p. 444), epilepsy, peptic ulcer, hypothyroidism, history of steroid myopathy, ulcerative colitis, diverticulitis, recent intestinal anastomoses, thromboembolic disorders; myasthenia gravis; **interactions:** Appendix 1 (corticosteroids).

Other contra-indications include: systemic infection (unless specific therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished).

Hepatic impairment

When corticosteroids are administered orally or parenterally, the plasma-drug concentration may be increased in patients with hepatic impairment. Corticosteroids should be used with caution in hepatic impairment and the patient should be monitored closely.

Renal impairment

Oral and parenteral preparations of corticosteroids should be used with caution in patients with renal impairment.

Pregnancy and breast-feeding

The benefit of treatment with corticosteroids during pregnancy and breast-feeding outweighs the risk; pregnant women with fluid retention should be monitored closely. Corticosteroid cover is required during labour.

Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) has concluded:

- corticosteroids vary in their ability to cross the placenta; betamethasone and dexamethasone cross the placenta readily while 88% of prednisolone is inactivated as it crosses the placenta;
- there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip;
- when administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome);
- any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important;
- prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant; infants should be monitored for adrenal suppression if the mothers are taking a higher dose.

Side-effects of corticosteroids

Overdosage or prolonged use can exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.

Mineralocorticoid side-effects include hypertension, sodium and water retention, and potassium and calcium loss. They are most marked with fludrocortisone, but are significant with cortisone, hydrocortisone, corticotropin, and tetracosactide (tetracosactrin). Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

Glucocorticoid side-effects include diabetes and osteoporosis (section 6.6), which is a danger, particularly in the elderly, as it can result in osteoporotic fractures for example of the hip or vertebrae; in addition high doses are associated with avascular necrosis of the femoral head. Muscle wasting (proximal myopathy) can also occur. Corticosteroid therapy is also weakly linked with peptic ulceration and perforation (the potential advantage of soluble or enteric-coated preparations to reduce the risk is speculative only). See also Psychiatric Reactions, p. 444.

High doses of corticosteroids can cause Cushing's syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this must always be gradually tapered to avoid symptoms of acute adrenal insufficiency (**important:** see also Adrenal Suppression, p. 444).

In children, administration of corticosteroids may result in suppression of growth. For the effect of corticosteroids given in pregnancy, see Pregnancy and Breast-feeding, above.

Side-effects can be minimised by using lowest effective dose for minimum period possible.

Other side-effects include: *gastro-intestinal effects*: dyspepsia, abdominal distension, acute pancreatitis, oesophageal ulceration and candidiasis; *musculoskeletal effects*: muscle weakness, vertebral and long bone fractures, tendon rupture; *endocrine effects*: menstrual irregularities and amenorrhoea, hirsutism, weight gain, hypercholesterolaemia, hyperlipidaemia, negative nitrogen and calcium balance, increased appetite; increased susceptibility to and severity of infection, reactivation of dormant tuberculosis; *neuropsychiatric effects*: psychological dependence, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), aggravation of schizophrenia, aggravation of epilepsy; *ophthalmic effects*: glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease, increased intra-ocular pressure, exophthalmos; *also* impaired healing, petechiae, ecchymoses, facial erythema, suppression of skin test reactions, urticaria, hyperhidrosis, skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, congestive heart failure, leucocytosis, hyperglycaemia, thromboembolism, nausea, malaise, hiccups, headache, vertigo.

For other references to the side-effects of corticosteroids see section 3.2 (asthma), section 11.4 (eye) and section 13.4 (skin).

BETAMETHASONE

Indications suppression of inflammatory and allergic disorders; congenital adrenal hyperplasia; see also notes above; ear (section 12.1.1); eye (section 11.4.1); nose (section 12.2.1); oral ulceration (section 12.3.1)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above; transient effect on fetal movements and heart rate

Breast-feeding see notes above

Side-effects see notes above

Dose

- By mouth, usual range 0.5–5 mg daily; see also Administration (above)
- By intramuscular injection *or* slow intravenous injection *or* infusion, 4–20 mg, repeated up to 4 times in 24 hours; CHILD, by slow intravenous injection, up to 1 year 1 mg, 1–5 years 2 mg, 6–12 years 4 mg, repeated up to 4 times in 24 hours according to response

Betnelan® (UCB Pharma) PoM
Tablets, scored, betamethasone 500 micrograms. Net price 100-tab pack = £4.22. Label: 10, steroid card, 21

Betnesol® (UCB Pharma) PoM
Soluble tablets, pink, scored, betamethasone 500 micrograms (as sodium phosphate). Net price 100-tab pack = £4.97. Label: 10, steroid card, 13, 21

Injection, betamethasone 4 mg (as sodium phosphate) /mL. Net price 1-mL amp = £1.17. Label: 10, steroid card

CORTISONE ACETATE

Indications see under Dose but now superseded, see also notes above

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above; hepatic conversion to active metabolite hydrocortisone may be affected

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- For replacement therapy, 25–37.5 mg daily in divided doses

Cortisone (Non-proprietary) PoM
Tablets, cortisone acetate 25 mg, net price 56-tab pack = £10.54. Label: 10, steroid card, 21

DEFLAZACORT

Indications suppression of inflammatory and allergic disorders

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- Usual maintenance 3–18 mg daily (acute disorders, initially up to 120 mg daily); see also Administration (above)
  CHILD 0.25–1.5 mg/kg daily (or on alternate days); see also Administration (above)

Calcort® (Sanofi-Aventis) PoM
Tablets, deflazacort 6 mg, net price 60-tab pack = £15.82. Label: 5, 10, steroid card

DEXAMETHASONE

Indications suppression of inflammatory and allergic disorders; diagnosis of Cushing's disease, congenital adrenal hyperplasia; cerebral oedema associated with malignancy; croup (section 3.1); nausea and vomiting with chemotherapy (section 8.1); rheumatic disease (section 10.1.2); eye (section 11.4.1); see also notes above

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also perineal irritation may follow intravenous administration of the phosphate ester

Dose

- By mouth, usual range 0.5–10 mg daily; CHILD 10–100 micrograms/kg daily; see also Administration (above)
- By intramuscular injection *or* slow intravenous injection *or* infusion, see under preparations
  Note Dexamethasone 1 mg ≡ dexamethasone phosphate 1.2 mg ≡ dexamethasone sodium phosphate 1.3 mg

Dexamethasone (Non-proprietary) PoM
Tablets, dexamethasone 500 micrograms, net price 28-tab pack = £38.00; 2 mg, 50-tab pack = £7.46, 100-tab pack = £13.85. Label: 10, steroid card, 21

Oral solution, sugar-free, dexamethasone (as sodium phosphate) 2 mg/5 mL, net price 150-mL = £42.30. Label: 10, steroid card, 21
Brands include *Dexsol®*

Injection, dexamethasone (as sodium phosphate) 4 mg/mL, net price 1-mL amp = 83p. Label: 10, steroid card
Dose By intramuscular injection *or* slow intravenous injection *or* infusion, 0.4–20 mg; CHILD 200–400 micrograms/kg daily
Cerebral oedema, by intravenous injection 8–16 mg initially, then 5 mg by intramuscular injection *or* intravenous injection every 6 hours as required for 2–4 days then gradually reduced and stopped over 5–7 days
Adjunctive treatment of bacterial meningitis, (starting before or with first dose of antibacterial treatment), [unlicensed indication], by intravenous injection 8.3 mg every 6 hours for 4 days; CHILD 125 micrograms/kg every 6 hours for 4 days

Injection, dexamethasone (as sodium phosphate) 3.3 mg/mL, net price 1-mL amp = £1.00, 2-mL vial = £1.98. Label: 10, steroid card
Dose by intramuscular injection *or* slow intravenous injection *or* infusion, 0.4–20 mg; CHILD 167–333 micrograms/kg daily
Cerebral oedema associated with malignancy, by intravenous injection 8.3 mg initially, then 3.3 mg by intramuscular injection every 6 hours as required for 2–4 days then gradually reduced and stopped over 5–7 days
Adjunctive treatment of bacterial meningitis, (starting before or with first dose of antibacterial treatment), [unlicensed indication], by intravenous injection 8.3 mg every 6 hours for 4 days; CHILD 125 micrograms/kg every 6 hours for 4 days

HYDROCORTISONE

Indications adrenocortical insufficiency (section 6.3.1); shock; see also notes above; hypersensitivity reactions e.g. anaphylaxis and angioedema (section 3.4.3); asthma (section 3.1); severe inflammatory bowel disease (section 1.5); haemorrhoids (section 1.7.2); rheumatic disease (section 10.1.2); eye (section 11.4.1); skin (section 13.4)

Cautions see notes above

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also phosphate ester associated with paraesthesia and pain (particularly in the perineal region)

Dose

- By mouth, replacement therapy, 20–30 mg daily in divided doses—see section 6.3.1; CHILD 10–30 mg
- By intramuscular injection *or* slow intravenous injection *or* infusion, 100–500 mg, 3–4 times in 24 hours or

as required; CHILD by slow intravenous injection up to 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg

Hydrocortisone (Non-proprietary) PoM
Tablets, scored, hydrocortisone 10 mg, net price 30-tab pack = £44.25; 20 mg, 30-tab pack = £47.17. Label: 10, steroid card, 21

[1] **Efcortesol®** (Sovereign) PoM
Injection, hydrocortisone 100 mg (as sodium phosphate)/mL, net price 1-mL amp = £1.08, 5-mL amp = £4.89. Label: 10, steroid card
Note Paraesthesia and pain (particularly in the perineal region) may follow intravenous injection of the phosphate ester
1. PoM restriction does not apply where administration is for saving life in emergency

[1] **Solu-Cortef®** (Pharmacia) PoM
Injection, powder for reconstitution, hydrocortisone (as sodium succinate). Net price 100-mg vial = 92p, 100-mg vial with 2-mL amp water for injections = £1.16. Label: 10, steroid card
1. PoM restriction does not apply where administration is for saving life in emergency

METHYLPREDNISOLONE

Indications suppression of inflammatory and allergic disorders; severe inflammatory bowel disease (section 1.5); cerebral oedema associated with malignancy; see also notes above; rheumatic disease (section 10.1.2); skin (section 13.4)
Cautions see notes above; also rapid intravenous administration of large doses associated with cardiovascular collapse
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- By mouth, usual range 2–40 mg daily; see also Administration (above)
- By intramuscular injection *or* slow intravenous injection *or* infusion, initially 10–500 mg; graft rejection, up to 1 g daily by intravenous infusion for up to 3 days

Medrone® (Pharmacia) PoM
Tablets, scored, methylprednisolone 2 mg (pink), net price 30-tab pack = £3.88; 4 mg, 30-tab pack = £6.19; 16 mg, 30-tab pack = £17.17; 100 mg (blue), 20-tab pack = £48.32. Label: 10, steroid card, 21

Solu-Medrone® (Pharmacia) PoM
Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 40-mg vial = £1.58; 125-mg vial = £4.75; 500-mg vial = £9.60; 1-g vial = £17.30; 2-g vial = £32.86. Label: 10, steroid card

Intramuscular depot

Depo-Medrone® (Pharmacia) PoM
Injection (aqueous suspension), methylprednisolone acetate 40 mg/mL. Net price 1-mL vial = £2.87; 2-mL vial = £5.15; 3-mL vial = £7.47. Label: 10, steroid card
Dose by deep intramuscular injection into gluteal muscle, 40–120 mg, a second injection may be given after 2–3 weeks if required

PREDNISOLONE

Indications suppression of inflammatory and allergic disorders; see also notes above; inflammatory bowel disease (section 1.5); asthma (section 3.1 and section 3.2); croup (section 3.1); immunosuppression (section 8.2.2); rheumatic disease (section 10.1.2); eye (section 11.4.1); ear (section 12.1.1)
Cautions see notes above; also Duchenne's muscular dystrophy (possible transient rhabdomyolysis and myoglobinuria following strenuous physical activity)
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- By mouth, initially, up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; can often be reduced within a few days but may need to be continued for several weeks or months
  Maintenance, usual range, 2.5–15 mg daily, but higher doses may be needed; cushingoid side-effects increasingly likely with doses above 7.5 mg daily
- By intramuscular injection, prednisolone acetate (section 10.1.2.2), 25–100 mg once or twice weekly

Prednisolone (Non-proprietary) PoM
Tablets, prednisolone 1 mg, net price 28-tab pack = 93p; 5 mg, 28-tab pack = £1.03; 25 mg, 56-tab pack = £30.00. Label: 10, steroid card, 21
Tablets, e/c, prednisolone 2.5 mg (brown), net price 30-tab pack = £4.65, 100-tab pack = £30.79; 5 mg (red), 28-tab pack = £8.69, 100-tab pack = £31.04. Label: 5, 10, steroid card, 25
Brands include *Deltacortril®*
Soluble tablets, prednisolone 5 mg (as sodium phosphate), net price 30-tab pack = £8.95. Label: 10, steroid card, 13, 21
Injection, see section 10.1.2.2

PREDNISONE

Indications moderate to severe rheumatoid arthritis (section 10.1.2.1)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment see notes above
Renal impairment see notes above
Pregnancy see notes above
Breast-feeding see notes above
Side-effects see notes above
Dose
- ADULT over 18 years, initially 10–20 mg at bedtime, adjusted according to response

Lodotra® (Napp) PoM
Tablets, m/r, yellow, prednisone 1 mg, net price 30-tab pack = £26.70; 2 mg, 30-tab pack = £26.70, 100-tab pack = £89.00; 5 mg, 30-tab pack = £26.70, 100-tab pack = £89.00. Label: 10, steroid card, 21, 25

TRIAMCINOLONE

Indications suppression of inflammatory and allergic disorders; see also notes above; rheumatic disease (section 10.1.2); skin (section 13.4)

Cautions see notes above; also high dosage may cause proximal myopathy, avoid in chronic therapy

Contra-indications see notes above

Hepatic impairment see notes above

Renal impairment see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above

Dose

- By deep intramuscular injection, into gluteal muscle, 40 mg of acetonide for depot effect, repeated at intervals according to the patient's response; max. single dose 100 mg

Kenalog® Intra-articular/Intramuscular (Squibb) PoM
Injection (aqueous suspension), triamcinolone acetonide 40 mg/mL, net price 1-mL vial = £1.49. Label: 10, steroid card

6.4 Sex hormones

6.4.1 Female sex hormones
6.4.2 Male sex hormones and antagonists
6.4.3 Anabolic steroids

6.4.1 Female sex hormones

6.4.1.1 Oestrogens and HRT
6.4.1.2 Progestogens

6.4.1.1 Oestrogens and HRT

Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia.

In terms of oestrogenic activity *natural oestrogens* (estradiol (oestradiol), estrone (oestrone), and estriol (oestriol)) have a more appropriate profile for hormone replacement therapy (HRT) than *synthetic oestrogens* (ethinylestradiol (ethinyloestradiol) and mestranol). Tibolone has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a progestogen should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.

Hormone replacement therapy

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal osteoporosis (section 6.6.1) but other drugs (section 6.6) are preferred. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation (section 7.2.1) used for a few weeks and repeated if necessary.

Systemic therapy with an oestrogen or drugs with oestrogenic properties alleviates the symptoms of oestrogen deficiency such as vasomotor symptoms. Tibolone combines oestrogenic and progestogenic activity with weak androgenic activity; it is given continuously, without cyclical progestogen.

HRT may be used in women with early natural or surgical menopause (before age 45 years), since they are at high risk of osteoporosis. For early menopause, HRT can be given until the approximate age of natural menopause (i.e. until age 50 years). Alternatives to HRT should be considered if osteoporosis is the main concern (section 6.6).

Clonidine (section 2.5.2 and section 4.7.4.2) may be used to reduce vasomotor symptoms in women who cannot take an oestrogen, but clonidine may cause unacceptable side-effects.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. For details of these risks see HRT Risk table, p. 450.

The minimum effective dose of HRT should be used for the shortest duration. Treatment should be reviewed at least annually and for osteoporosis alternative treatments considered (section 6.6). HRT does not prevent coronary heart disease or protect against a decline in cognitive function and it should **not** be prescribed for these purposes. Experience of treating women over 65 years with HRT is limited.

For the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years.

Risk of breast cancer It is estimated that using *all* types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment, see HRT Risk table, p. 450 for details. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use; tibolone has only a limited effect on mammographic density.

Risk of endometrial cancer The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT, see HRT Risk table, p. 450 for details.

In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

Risk of ovarian cancer Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer, see HRT Risk table, below for details; this excess risk disappears within a few years of stopping.

Risk of venous thromboembolism Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use, see HRT Risk table, below for details.

In *women who have predisposing factors* (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it is prudent to review the need for HRT, as in some cases the risks of HRT may exceed the benefits. See below for advice on surgery.

Travel involving prolonged immobility further increases the risk of deep vein thrombosis, see under Travel in section 7.3.1.

Risk of stroke Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment, see HRT Risk table, below for details.

Risk of coronary heart disease HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause, see HRT Risk table, below for details. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

Choice The choice of HRT for an individual depends on an overall balance of indication, risk, and convenience. A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle *or* a preparation which involves continuous administration of an oestrogen and a progestogen (*or* one which provides both oestrogenic and progestogenic

HRT Risk

Risk	Age range (years)	Background incidence per 1000 women in Europe not using HRT		**Additional** cases per 1000 women using **oestrogen only HRT** (estimated)		**Additional** cases per 1000 women using **combined (oestrogen-progestogen) HRT** (estimated)	
		Over 5 years	Over 10 years	For 5 years' use	For 10 years' use	For 5 years' use	For 10 years' use
Breast cancer[1]	50–59	10	20	2	6	6	24
	60–69	15	30	3	9	9	36
Endometrial cancer[2,3]	50–59	2	4	4	32	NS	NS
	60–69	3	6	6	48	NS	NS
Ovarian cancer	50–59	2	4	<1	1	<1	1
	60–69	3	6	<1	2	<1	2
Venous thromboembolism[4,5]	50–59	5		2		7	
	60–69	8		2		10	
Stroke[6]	50–59	4		1		1	
	60–69	9		3		3	
Coronary heart disease[7,8]	70–79	29–44		NS		15	

Note Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference
Taken from MHRA/CHM (*Drug Safety Update* 2007; **1** (2): 2–6) available at www.mhra.gov.uk/drugsafetyupdate

1. Tibolone increases the risk of breast cancer but to a lesser extent than with combined HRT.
2. Evidence suggests an increased risk of endometrial cancer with tibolone. After 2.7 years of use (in women of average age 68 years), 1 extra case of endometrial hyperplasia and 4 extra cases of endometrial cancer were diagnosed compared with placebo users.
3. The risk of endometrial cancer cannot be reliably estimated in those using combined HRT because the addition of progestogen for at least 10 days per 28-day cycle greatly reduces the additional risk, and addition of a daily progestogen eliminates the additional risk. The risk of endometrial cancer in women who have not used HRT increases with body mass index (BMI); the increased risk of endometrial cancer in users of oestrogen-only HRT or tibolone is more apparent in women who are not overweight.
4. Limited data does not suggest an increased risk of thromboembolism with tibolone compared with combined HRT or women not taking HRT.
5. Although the level of risk of thromboembolism associated with non-oral routes of administration of HRT has not been established, it may be lower for the transdermal route.
6. Tibolone increases the risk of stroke about 2.2 times from the first year of treatment; risk of stroke is age-dependent and therefore the absolute risk of stroke with tibolone increases with age.
7. Increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause.
8. There is insufficient data to draw a conclusion on the risk of coronary heart disease with tibolone.

activity in a single preparation). Continuous combined preparations or tibolone are **not suitable** for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.

An oestrogen alone is suitable for continuous use in women without a uterus. However, in endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered in these circumstances.

An oestrogen may be given by mouth or it may be given by subcutaneous or transdermal administration, which avoids first-pass metabolism. In the case of subcutaneous implants, recurrence of vasomotor symptoms at supraphysiological plasma concentrations may occur; moreover, there is evidence of prolonged endometrial stimulation after discontinuation (calling for continued cyclical progestogen). For the use of topical HRT preparations see section 7.2.1.

Contraception HRT does **not** provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill (section 7.3.1) to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives. If any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary.

Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

Surgery Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery (see Risk of Venous Thromboembolism, above); it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective surgery), prophylaxis with unfractionated or low molecular weight heparin and graduated compression hosiery is advised. Oestrogenic activity may persist after removing an estradiol implant (see above).

Reasons to stop HRT For circumstances in which HRT should be stopped, see p. 496.

OESTROGENS FOR HRT

Note Relates only to small amounts of oestrogens given for hormone replacement therapy

Indications see notes above and under preparations

Cautions prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer (see notes above); migraine (or migraine-like headaches); diabetes (increased risk of heart disease); history of breast nodules or fibrocystic disease—closely monitor breast status (risk of breast cancer, see notes above); risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative); uterine fibroids may increase in size, symptoms of endometriosis may be exacerbated; history of endometrial hyperplasia; factors predisposing to thromboembolism (see notes above); presence of antiphospholipid antibodies (increased risk of thrombotic events); increased risk of gall-bladder disease reported; hypophyseal tumours; acute porphyria (see section 9.8.2); **interactions:** Appendix 1 (oestrogens)

Other conditions The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present, see above). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

Contra-indications oestrogen-dependent cancer, history of breast cancer, active thrombophlebitis, active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction), venous thromboembolism, or history of recurrent venous thromboembolism (unless already on anticoagulant treatment), liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor closely), untreated endometrial hyperplasia, undiagnosed vaginal bleeding

Hepatic impairment see Combined Hormonal Contraceptives, section 7.3.1

Renal impairment see Other Conditions, above

Pregnancy see Combined Hormonal Contraceptives, section 7.3.1

Breast-feeding see Combined Hormonal Contraceptives, section 7.3.1

Side-effects see notes above for risks of long-term use; nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, cholestatic jaundice, glucose intolerance, altered blood lipids—may lead to pancreatitis, rashes and chloasma, changes in libido, depression, mood changes, headache, migraine, dizziness, leg cramps (rule out venous thrombosis), vaginal candidiasis, contact lenses may irritate; transdermal delivery systems may cause contact sensitisation (possible severe hypersensitivity reaction on continued exposure), and headache has been reported on vigorous exercise

Withdrawal bleeding Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in *regular withdrawal bleeding* towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but *irregular bleeding* may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead)

Dose

- See under preparations

Counselling on patches Patch should be removed after 3–4 days (or once a week in case of 7-day patch) and replaced with fresh patch on slightly different site; recommended sites: clean, dry, unbroken areas of skin on trunk below waistline; not to be applied on or near breasts or under waistband. If patch falls off in bath allow skin to cool before applying new patch

Conjugated oestrogens with progestogen

For prescribing information on progestogens, see section 6.4.1.2

Premique® (Wyeth) PoM

Premique® Low Dose tablets, m/r, ivory, s/c, conjugated oestrogen (equine) 300 micrograms and medroxyprogesterone acetate 1.5 mg, net price 3 × 28-tab pack = £6.52

Dose menopausal symptoms in women with a uterus, 1 tablet daily continuously

Premique® tablets, s/c, blue, conjugated oestrogen (equine) 625 micrograms and medroxyprogesterone acetate 5 mg, net price 3 × 28-tab pack = £10.61

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously

Prempak-C® (Wyeth) PoM

Prempak C® 0.625 Calendar pack, s/c, 28 maroon tablets, conjugated oestrogens (equine) 625 micrograms; 12 light brown tablets, norgestrel 150 micrograms (≡ levonorgestrel 75 micrograms), net price 3 × 40-tab pack = £6.25

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 maroon tablet daily continuously, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), and 1 brown tablet daily on days 17–28 of each 28-day treatment cycle; subsequent courses are repeated without interval

Prempak C® 1.25 Calendar pack, s/c, 28 yellow tablets, conjugated oestrogens (equine) 1.25 mg; 12 light brown tablets, norgestrel 150 micrograms (≡ levonorgestrel 75 micrograms), net price 3 × 40-tab pack = £7.40

Dose see under 0.625 Calendar pack, but taking 1 yellow tablet daily continuously (instead of 1 maroon tablet) if symptoms not fully controlled with lower strength

Estradiol with progestogen

For prescribing information on progestogens, see section 6.4.1.2

Angeliq® (Bayer Schering) PoM

Tablets, f/c, red, estradiol 1 mg, drospirenone 2 mg, net price 3 × 28-tab pack = £24.32

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously (if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase)

Cautions use with care if an increased concentration of potassium might be hazardous

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Climagest® (Novartis) PoM

Climagest® 1-mg tablets, 16 grey-blue, estradiol valerate 1 mg; 12 white, estradiol valerate 1 mg and norethisterone 1 mg, net price 28-tab pack = £4.59; 3 × 28-tab pack = £13.35

Dose menopausal symptoms, 1 grey-blue tablet daily for 16 days, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) then 1 white tablet for 12 days; subsequent courses are repeated without interval

Climagest® 2-mg tablets, 16 blue, estradiol valerate 2 mg; 12 yellow, estradiol valerate 2 mg and norethisterone 1 mg, net price 28-tab pack = £4.59; 3 × 28-tab pack = £13.35

Dose see *Climagest® 1-mg*, but starting with 1 blue tablet daily (instead of 1 grey-blue tablet) if symptoms not controlled with lower strength

Climesse® (Novartis) PoM

Tablets, pink, estradiol valerate 2 mg, norethisterone 700 micrograms, net price 1 × 28-tab pack = £8.27; 3 × 28-tab pack = £24.82

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously

Clinorette® (ReSource Medical) PoM

Tablets, f/c, 16 white, estradiol 2 mg; 12 pink, estradiol 2 mg and norethisterone 1 mg, net price 3 × 28-tab pack = £9.23

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 16 days starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 pink tablet daily for 12 days; subsequent courses repeated without interval

Cyclo-Progynova® (Meda) PoM

Cyclo-Progynova® 2-mg tablets, s/c, 11 white, estradiol valerate 2 mg; 10 brown, estradiol valerate 2 mg and norgestrel 500 micrograms (≡ levonorgestrel 250 micrograms), net price per pack = £3.11

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus, 1 white tablet daily for 11 days, starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 brown tablet daily for 10 days, followed by a 7-day tablet-free interval

Elleste-Duet® (Meda) PoM

Elleste-Duet® 1-mg tablets, 16 white, estradiol 1 mg; 12 green, estradiol 1 mg and norethisterone acetate 1 mg, net price 3 × 28-tab pack = £9.16

Dose menopausal symptoms, 1 white tablet daily for 16 days starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 green tablet daily for 12 days; subsequent courses are repeated without interval

Elleste-Duet® 2-mg tablets, 16 orange, estradiol 2 mg; 12 grey, estradiol 2 mg, norethisterone acetate 1 mg, net price 3 × 28-tab pack = £9.72

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 orange tablet daily for 16 days, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) then 1 grey tablet daily for 12 days; subsequent courses are repeated without interval

Elleste-Duet Conti® tablets, f/c, grey, estradiol 2 mg, norethisterone acetate 1 mg, net price 3 × 28-tab pack = £16.93

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily on a continuous basis (if changing from cyclical HRT begin treatment at the end of scheduled bleed)

Evorel® (Janssen-Cilag) PoM

Evorel® Conti patches, self-adhesive, (releasing estradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours), net price 8-patch pack = £13.00, 24-patch pack = £37.22. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 patch to be applied twice weekly continuously

Evorel® Sequi combination pack, 4 self-adhesive patches of *Evorel® 50* (releasing estradiol approx. 50 micrograms/24 hours) and 4 self-adhesive patches of *Evorel® Conti* (releasing estradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours), net price 8-patch pack = £11.09. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 *Evorel® 50* patch to be applied twice weekly for 2 weeks, starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), followed by 1 *Evorel® Conti* patch twice weekly for 2 weeks; subsequent courses are repeated without interval

Femapak® (Abbott Healthcare) PoM

Femapak® 40 combination pack of 8 self-adhesive patches of *Fematrix® 40* (releasing estradiol approx. 40 micrograms/24 hours) and 14 tablets of dydrogesterone 10 mg, net price per pack = £7.61. Counselling, administration

Dose see under *Femapak® 80*

Femapak® 80 combination pack of 8 self-adhesive patches of *Fematrix® 80* (releasing estradiol approx. 80 micrograms/24 hours) and 14 tablets of dydrogesterone 10 mg, net price per pack = £8.06. Counselling, administration

Dose menopausal symptoms (and osteoporosis prophylaxis (see section 6.6) in case of *Femapak® 80* **only**), in women with a uterus, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), apply 1 patch twice weekly continuously and take 1 tablet daily on days 15–28 of each 28-day treatment cycle; therapy should be initiated with *Femapak® 40* in those with menopausal symptoms, prolonged oestrogen deficiency or anticipated intolerance to higher strengths, subsequently adjusted to lowest effective dose

Femoston® (Abbott Healthcare) PoM

Femoston® 1/10 tablets, f/c, 14 white, estradiol 1 mg; 14 grey, estradiol 1 mg, dydrogesterone 10 mg, net price 3 × 28-tab pack = £13.47

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 14 days, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent) then 1 grey tablet daily for 14 days; subsequent courses repeated without interval

Femoston® 2/10 tablets, f/c, 14 red, estradiol 2 mg; 14 yellow, estradiol 2 mg, dydrogesterone 10 mg, net price 3 × 28-tab pack = £13.47

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 red tablet daily for 14 days, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent) then 1 yellow tablet daily for 14 days; subsequent courses repeated without interval; where therapy required for menopausal symptoms alone, *Femoston® 1/10* given initially and *Femoston® 2/10* substituted if symptoms not controlled

Femoston®-conti tablets, f/c, salmon, estradiol 1 mg, dydrogesterone 5 mg, net price 3 × 28-tab pack = £22.44

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously (if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase)

FemSeven® Conti (Merck Serono) PoM

Patches, self-adhesive (releasing estradiol approx. 50 micrograms/24 hours and levonorgestrel approx. 7 micrograms/24 hours); net price 4-patch pack = £15.48, 12-patch pack = £ 44.12. Counselling, administration

Dose menopausal symptoms in women with a uterus whose last menstrual period occurred over 12 months previously, 1 patch to be applied once a week continuously

FemSeven® Sequi (Merck Serono) PoM

Combination pack, self-adhesive patches of *FemSeven® Sequi Phase 1* (releasing estradiol approx. 50 micrograms/24 hours) and of *FemSeven® Sequi Phase 2* (releasing estradiol approx. 50 micrograms/24 hours and levonorgestrel approx. 10 micrograms/24 hours); net price 1-month pack (2 of each) = £13.18, 3-month pack (6 of each) = £37.54. Counselling, administration

Dose menopausal symptoms in women with a uterus, 1 *Phase 1* patch applied once a week for 2 weeks followed by 1 *Phase 2* patch once a week for 2 weeks; subsequent courses are repeated without interval

Indivina® (Orion) PoM

Indivina® 1 mg/2.5 mg tablets, estradiol valerate 1 mg, medroxyprogesterone acetate 2.5 mg, net price 3 × 28-tab pack = £20.58

Indivina® 1 mg/5 mg tablets, estradiol valerate 1 mg, medroxyprogesterone acetate 5 mg, net price 3 × 28-tab pack = £20.58

Indivina® 2 mg/5 mg tablets, estradiol valerate 2 mg, medroxyprogesterone acetate 5 mg, net price 3 × 28-tab pack = £20.58

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 3 years previously, 1 tablet daily continuously; initiate therapy with *Indivina® 1 mg/2.5 mg* tablets and adjust according to response; start at end of scheduled bleed if changing from cyclical HRT

Kliofem® (Novo Nordisk) PoM

Tablets, f/c yellow, estradiol 2 mg, norethisterone acetate 1 mg, net price 3 × 28-tab pack = £11.43

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT

Kliovance® (Novo Nordisk) PoM

Tablets, f/c, estradiol 1 mg, norethisterone acetate 500 micrograms, net price 3 × 28-tab pack = £13.20

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT

Novofem® (Novo Nordisk) PoM

Tablets, f/c, 16 red, estradiol 1 mg; 12 white, estradiol 1 mg, norethisterone acetate 1 mg, net price 3 × 28-tab pack = £13.50

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 red tablet daily for 16 days then 1 white tablet daily for 12 days; subsequent courses are repeated without interval; start treatment with red tablet at any time or if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase

Nuvelle® Continuous (Bayer Schering) PoM

Tablets, f/c, pink, estradiol 2 mg, norethisterone acetate 1 mg, net price 3 × 28-tab pack = £15.89

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in women with a uterus whose last menstrual period occurred over 12 months previously, 1 tablet daily continuously; if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase

Tridestra® (Orion) PoM

Tablets, 70 white, estradiol valerate 2 mg; 14 blue, estradiol valerate 2 mg and medroxyprogesterone acetate 20 mg; 7 yellow, inactive, net price 91-tab pack = £20.49

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 70 days, then 1 blue tablet daily for 14 days, then 1 yellow tablet daily for 7 days; subsequent courses are repeated without interval

Trisequens® (Novo Nordisk) PoM

Tablets, 12 blue, estradiol 2 mg; 10 white, estradiol 2 mg, norethisterone acetate 1 mg; 6 red, estradiol 1 mg, net price 3 × 28-tab pack = £11.10

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 blue tablet daily, starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily in sequence (without interruption)

Conjugated oestrogens only

Premarin® (Wyeth) PoM

Tablets, all s/c, conjugated oestrogens (equine) 300 micrograms (green) net price 3 × 28-tab pack = £6.07; 625 micrograms (maroon), 3 × 28-tab pack = £4.02; 1.25 mg (yellow), 3 × 28-tab pack = £3.58

Dose menopausal symptoms, 0.3–1.25 mg daily continuously; osteoporosis prophylaxis (see section 6.6), 0.625–1.25 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus

Estradiol only

Estradiol Implants (Organon) PoM

Implant, estradiol 25 mg, net price each = £12.47; 50 mg, each = £20.29

Dose *by implantation*, oestrogen replacement, and osteoporosis prophylaxis (see section 6.6) (with cyclical progestogen for 12–14 days of each cycle in women with a uterus, see notes above), 25–100 mg as required (usually every 4–8 months) according to oestrogen levels—check before each implant

Note On cessation of treatment or if implants are removed from those with a uterus, cyclical progestogen should be continued until withdrawal bleed stops

Bedol® (ReSource Medical) PoM

Tablets, f/c, estradiol 2 mg, net price 3 × 28-tab pack = £5.07

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), with cyclical progestogen for 12–14 days of each cycle in women with a uterus, 2 mg daily starting on day 1–5 of menstruation (or at any time if cycles have ceased or are infrequent)

Climaval® (Novartis) PoM

Tablets, estradiol valerate 1 mg (grey-blue), net price 1 × 28-tab pack = £2.45, 3 × 28-tab pack = £7.35; 2 mg (blue), 1 × 28-tab pack = £2.45, 3 × 28-tab pack = £7.35

Dose menopausal symptoms (if patient has had a hysterectomy), 1–2 mg daily

Elleste-Solo® (Meda) PoM

Elleste-Solo® 1-mg tablets, estradiol 1 mg, net price 3 × 28-tab pack = £5.03

Dose menopausal symptoms, with cyclical progestogen for 12–14 days of each cycle in women with a uterus, 1 mg daily starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent)

Elleste-Solo® 2-mg tablets, orange, estradiol 2 mg, net price 3 × 28-tab pack = £5.34

Dose menopausal symptoms not controlled with lower strength and osteoporosis prophylaxis (see section 6.6), with cyclical progestogen for 12–14 days of each cycle in women with a uterus, 2 mg daily starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent)

Elleste Solo® MX (Meda) PoM

Patches, self-adhesive, estradiol, *MX 40 patch* (releasing approx. 40 micrograms/24 hours), net price 8-patch pack = £5.19; *MX 80 patch* (releasing approx. 80 micrograms/24 hours), 8-patch pack = £5.99. Counselling, administration.

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent); with cyclical progestogen for 12–14 days of each cycle in women with a uterus; for menopausal symptoms initiate therapy with *MX 40*, subsequently adjust according to response; for osteoporosis prophylaxis, initiate therapy with *MX 80*

Estraderm MX® (Novartis) PoM

Patches, self-adhesive, estradiol, *MX 25 patch* (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £4.58, 24-patch pack = £13.72; *MX 50 patch* (releasing approx. 50 micrograms/24 hours), 8-patch pack = £4.59, 24-patch pack = £13.72, 20-patch pack (hosp. only) = £13.04; *MX 75 patch* (releasing approx. 75 micrograms/24 hours), 8-patch pack = £5.35, 24-patch pack = £16.06; *MX 100 patch* (releasing approx. 100 micrograms/24 hours), 8-patch pack = £5.55, 24-patch pack = £16.66. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), with cyclical progestogen for at least 12 days of each cycle in women with a uterus; for menopausal symptoms, initiate therapy with *MX25* for first 3 months; for osteoporosis prophylaxis, initiate therapy with *MX50*; subsequently adjust according to response

Estraderm TTS® (Novartis) PoM

Patches, self-adhesive, estradiol, *TTS 25 patch* (releasing approx. 25 micrograms/24 hours), net price, 8-patch pack = £5.96, 24-patch pack = £17.88; *TTS 100 patch* (releasing approx. 100 micrograms/24 hours), 8-patch pack = £7.22, 24-patch pack = £21.72, 20-patch pack (hosp. only) = £16.76. Counselling, administration

Dose menopausal symptoms, 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), with cyclical progestogen for at least 12 days of each cycle in women with a uterus; initiate therapy with *TTS 25* for first 3 months, subsequently adjust according to response

Estradot® (Novartis) PoM

Patches, self-adhesive, estradiol, *'25' patch* (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £4.16; *'37.5' patch* (releasing approx. 37.5 micrograms/24 hours), 8-patch pack = £4.17; *'50' patch* (releasing approx. 50 micrograms/24 hours), 8-patch pack = £4.18; *'75' patch* (releasing approx. 75 micrograms/24 hours), 8-patch pack = £4.86; *'100' patch* (releasing approx. 100 micrograms/24 hours), 8-patch pack = £5.05. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied twice weekly continuously, with cyclical progestogen for 12–14 days of each cycle in women with a uterus; for menopausal symptoms, initiate therapy with *25 patch* for 3 months; for osteoporosis prophylaxis initiate therapy with *50 patch*; subsequently adjust according to response

Evorel® (Janssen-Cilag) PoM

Patches, self-adhesive, estradiol, *'25' patch* (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £3.42; *'50' patch* (releasing approx. 50 micrograms/24 hours), 8-patch pack = £3.88, 24-patch pack = £11.66; *'75' patch* (releasing approx. 75 micrograms/24 hours), 8-patch pack = £4.12; *'100' patch* (releasing approx. 100 micrograms/24 hours), 8-patch pack = £4.28. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), with cyclical progestogen for 12–14 days of each cycle in women with a uterus; therapy should be initiated with *Evorel 50* patch; subsequently adjust according to response; dose may be reduced to *Evorel 25* patch after first month if necessary for menopausal symptoms **only**

Fematrix® (Abbott Healthcare) PoM

Patches, self-adhesive, estradiol, *'40' patch* (releasing approx. 40 micrograms/24 hours), net price 8-patch pack = £4.95; *'80' patch* (releasing approx. 80 micrograms/24 hours), 8-patch pack = £5.40. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if

cycles have ceased or are infrequent), with cyclical progestogen for 12–14 days of each cycle in women with a uterus; for menopausal symptoms, initiate therapy with *Fematrix 40*, subsequently adjust according to response; for osteoporosis prophylaxis, initiate therapy with *Fematrix 80*

FemSeven® (Merck Serono) PoM

Patches, self-adhesive, estradiol, *'50' patch* (releasing approx. 50 micrograms/24 hours), net price 4-patch pack = £6.04, 12-patch pack = £18.02; *'75' patch* (releasing approx. 75 micrograms/24 hours), net price 4-patch pack = £6.98; *'100' patch* (releasing approx. 100 micrograms/24 hours), net price 4-patch pack = £7.28. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied once a week continuously, with cyclical progestogen for 12–14 days of each cycle in women with a uterus; initiate therapy with *FemSeven 50* patches for the first few months, subsequently adjust according to response

Oestrogel® (Ferring) PoM

Gel, estradiol 0.06%, net price 64-dose pump pack = £4.80. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 2 measures (estradiol 1.5 mg) to be applied over an area twice that of the template provided once daily continuously, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), with cyclical progestogen for at least 12 days of each cycle in women with a uterus; for menopausal symptoms may be increased if necessary after 1 month to max. 4 measures daily

Counselling Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 5 minutes before covering with clothing. Not to be applied on or near breasts or on vulval region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application

Progynova® (Bayer Schering) PoM

Tablets, s/c, estradiol valerate 1 mg (beige), net price 3 × 28-tab pack = £6.18; 2 mg (blue), 3 × 28-tab pack = £6.18

Dose menopausal symptoms, 1–2 mg daily continuously starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent); osteoporosis prophylaxis (see section 6.6), 2 mg daily continuously; with cyclical progestogen for 12–14 days of each cycle in women with a uterus

Progynova® TS (Bayer Schering) PoM

Patches, self-adhesive, *Progynova® TS 50* (releasing estradiol approx. 50 micrograms/24 hours), net price 12-patch pack = £15.75; *Progynova® TS 100* (releasing estradiol approx. 100 micrograms/24 hours), 12-patch pack = £17.34. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied once a week continuously *or* 1 patch per week for 3 weeks followed by a 7-day patch-free interval (cyclical); with cyclical progestogen for 12–14 days of each cycle in women with a uterus; initiate therapy with *Progynova TS 50*, subsequently adjust according to response

Note Women receiving *Progynova TS 100* patches for menopausal symptoms may continue with this strength for osteoporosis prophylaxis (see section 6.6)

Sandrena® (Orion) PoM

Gel, estradiol (0.1%), 500 microgram/500 mg sachet, net price 28-sachet pack = £5.08, 1 mg/1 g sachet, 28-sachet pack = £5.85. Counselling, administration

Excipients include propylene glycol (see section 13.1.3)

Dose menopausal symptoms, estradiol 1 mg (1 g gel) to be applied once daily over area 1–2 times size of hand; with cyclical progestogen for 12–14 days of each cycle in women with a uterus; dose may be adjusted after 2–3 cycles to lowest effective dose (usual dose of estradiol 0.5–1.5 mg (0.5–1.5 g gel) daily)

Counselling Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour

Zumenon® (Abbott Healthcare) PoM

Tablets, f/c, estradiol 1 mg, net price 84-tab pack = £6.89; 2 mg (red), 84-tab pack = £6.89

Dose menopausal symptoms, initially 1 mg daily starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent) increased to 2 mg daily if required; osteoporosis prophylaxis (see section 6.6), 2 mg daily; with cyclical progestogen for 12–14 days of each cycle in women with a uterus

Estradiol, estriol and estrone

Hormonin® (Amdipharm) PoM

Tablets, pink, estradiol 600 micrograms, estriol 270 micrograms, estrone 1.4 mg, net price 84-tab pack = £6.94

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1–2 tablets daily starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), with cyclical progestogen for 12–14 days of each cycle in women with a uterus

Note *Hormonin* tablets can be given continuously or cyclically (21 days out of 28)

TIBOLONE

Indications short-term treatment of symptoms of oestrogen deficiency (including women being treated with gonadotrophin releasing hormone analogues); osteoporosis prophylaxis in women at risk of fractures (second-line)

Cautions see Hormone Replacement Therapy, p. 449 and under Oestrogens for HRT; vaginal bleeding (investigate for endometrial cancer if bleeding continues beyond 6 months or after stopping treatment); history of liver disease, epilepsy, migraine, diabetes mellitus, hypercholesterolaemia; withdraw if signs of thromboembolic disease, abnormal liver function tests or cholestatic jaundice; see also Note below; **interactions:** Appendix 1 (tibolone)

Contra-indications see notes above and under Oestrogens for HRT; hormone-dependent tumours, history of cardiovascular or cerebrovascular disease (e.g. thrombophlebitis, thromboembolism), uninvestigated vaginal bleeding

Hepatic impairment avoid in severe impairment

Renal impairment risk of fluid retention—patients with renal impairment should be closely monitored

Pregnancy avoid; toxicity in *animal* studies

Breast-feeding avoid

Side-effects see notes above; also abdominal pain, weight changes, vaginal bleeding, leucorrhoea, facial hair, and *rarely* amnesia; gastro-intestinal disturbances, oedema, dizziness, headache, migraine, depression, breast cancer (see notes above and section 6.4.1.1), arthralgia, myalgia, visual disturbances, seborrhoeic dermatitis, rash and pruritus also reported

Dose

- 2.5 mg daily

Note Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogue) and as (or with) an oral contraceptive; also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding); induce withdrawal bleed with progestogen if transferring from another form of HRT

Livial® (Organon) PoM

Tablets, tibolone 2.5 mg, net price 28-tab pack = £10.36; 3 × 28-tab pack = £31.08

Ethinylestradiol

Ethinylestradiol (ethinyloestradiol) is licensed for short-term treatment of symptoms of oestrogen deficiency, for osteoporosis prophylaxis if other drugs (section 6.6) cannot be used and for the treatment of female hypogonadism and menstrual disorders.

Ethinylestradiol is occasionally used under **specialist supervision** for the management of *hereditary haemorrhagic telangiectasia* (but evidence of benefit is limited). Side-effects include nausea, fluid retention, and thrombosis. Impotence and gynaecomastia have been reported in men.

For use in prostate cancer, see section 8.3.1.

ETHINYLESTRADIOL
(Ethinyloestradiol)

Indications see notes above

Cautions cardiovascular disease (sodium retention with oedema, thromboembolism); see also under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 451)

Contra-indications see under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 451)

Hepatic impairment avoid; see also Combined Hormonal Contraceptives, section 7.3.1

Pregnancy see Combined Hormonal Contraceptives, section 7.3.1

Breast-feeding see Combined Hormonal Contraceptives, section 7.3.1

Side-effects feminising effects in men; see also under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 451)

Dose

- Menopausal symptoms and osteoporosis prophylaxis, (with progestogen for 12–14 days per cycle in women with intact uterus), 10–50 micrograms daily for 21 days, repeated after 7-day tablet-free period
- Female hypogonadism, 10–50 micrograms daily, usually on cyclical basis; initial oestrogen therapy should be followed by combined oestrogen and progestogen therapy
- Menstrual disorders, 20–50 micrograms daily from day 5 to 25 of each cycle, with progestogen added either throughout the cycle or from day 15 to 25

Ethinylestradiol (Non-proprietary) PoM
Tablets, ethinylestradiol 10 micrograms, net price 21-tab pack = £29.95; 50 micrograms, 21-tab pack = £38.20; 1 mg, 28-tab pack = £49.50

Raloxifene

Raloxifene is licensed for the treatment and prevention of *postmenopausal osteoporosis*; unlike hormone replacement therapy, raloxifene does not reduce menopausal vasomotor symptoms.

Raloxifene may reduce the incidence of oestrogen-receptor-positive breast cancer but its role in established breast cancer is not yet clear. The manufacturer advises avoiding its use during treatment for breast cancer.

RALOXIFENE HYDROCHLORIDE

Indications treatment and prevention of postmenopausal osteoporosis

Cautions risk factors for venous thromboembolism (discontinue if prolonged immobilisation); risk factors for stroke; breast cancer (see notes above); history of oestrogen-induced hypertriglyceridaemia (monitor serum triglycerides); **interactions:** Appendix 1 (raloxifene)

Contra-indications history of venous thromboembolism, undiagnosed uterine bleeding, endometrial cancer, cholestasis

Hepatic impairment avoid

Renal impairment caution in mild to moderate impairment; avoid in severe impairment

Side-effects hot flushes, leg cramps, peripheral oedema, influenza-like symptoms; *less commonly* venous thromboembolism, thrombophlebitis; *rarely* rashes, gastro-intestinal disturbances, hypertension, arterial thromboembolism, headache (including migraine), breast discomfort, thrombocytopenia

Dose

- 60 mg once daily

Evista® (Daiichi Sankyo) PoM
Tablets, f/c, raloxifene hydrochloride 60 mg, net price 28-tab pack = £17.06; 84-tab pack = £59.59

6.4.1.2 Progestogens

There are two main groups of progestogen, progesterone and its analogues (dydrogesterone and medroxyprogesterone) and testosterone analogues (norethisterone and norgestrel). The newer progestogens (desogestrel, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel is the active isomer of norgestrel and has twice its potency. Progesterone and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

Where endometriosis requires drug treatment, it may respond to a progestogen, e.g. norethisterone, administered on a continuous basis. Danazol and gonadorelin analogues are also available (section 6.7.2).

Although oral progestogens have been used widely for menorrhagia they are relatively ineffective compared with tranexamic acid (section 2.11) or, particularly where dysmenorrhoea is also a factor, mefenamic acid (section 10.1.1); the levonorgestrel-releasing intrauterine system (section 7.3.2.3) may be particularly useful for women also requiring contraception. Oral progestogens have also been used for severe dysmenorrhoea, but where contraception is also required in younger women the best choice is a combined oral contraceptive (section 7.3.1).

Progestogens have also been advocated for the alleviation of premenstrual symptoms, but no convincing physiological basis for such treatment has been shown.

Progestogens have been used for the prevention of spontaneous abortion in women with a history of recurrent miscarriage (habitual abortion) but there is no evidence of benefit and they are **not** recommended for this purpose. In pregnant women with antiphospholipid antibody syndrome who have suffered recurrent miscarriage, administration of low-dose

aspirin (section 2.9) and a prophylactic dose of a low molecular weight heparin (section 2.8.1) may decrease the risk of fetal loss (use under specialist supervision only).

Hormone replacement therapy In women with a uterus a progestogen needs to be added to long-term oestrogen therapy for hormone replacement, to prevent cystic hyperplasia of the endometrium and possible transformation to cancer; it can be added on a cyclical or a continuous basis (see section 6.4.1.1). Combined packs incorporating suitable progestogen tablets are available, see p. 452.

Oral contraception Desogestrel, etynodiol (ethynodiol), gestodene, levonorgestrel, norethisterone, and norgestimate are used in combined oral contraceptives and in progestogen-only contraceptives (section 7.3.1 and section 7.3.2).

Cancer Progestogens also have a role in neoplastic disease (section 8.3.2).

Cautions Progestogens should be used with caution in conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, asthma, or cardiac dysfunction, and in those susceptible to thromboembolism (particular caution with high dose). Care is also required in those with a history of depression. Progestogens can decrease glucose tolerance and patients with diabetes should be monitored closely. For **interactions** see Appendix 1 (progestogens).

Contra-indications Progestogens should be avoided in patients with a history of liver tumours. They are also contra-indicated in those with genital or breast cancer (unless progestogens are being used in the management of these conditions), severe arterial disease, undiagnosed vaginal bleeding and acute porphyria (section 9.8.2). Progestogens should not be used if there is a history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis.

Side-effects Side-effects of progestogens include menstrual disturbances, premenstrual-like syndrome (including bloating, fluid retention, breast tenderness), weight change, nausea, headache, dizziness, insomnia, drowsiness, depression, change in libido; also skin reactions (including urticaria, pruritus, rash, and acne), hirsutism and alopecia. Jaundice and anaphylactoid reactions have also been reported.

DYDROGESTERONE

Indications HRT (section 6.4.1.1)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment avoid; see also Combined Hormonal Contraceptives, section 7.3.1
Renal impairment use with caution
Pregnancy not known to be harmful
Breast-feeding present in milk—no adverse effects reported
Side-effects see notes above
Dose

- See under combined preparations (section 6.4.1.1)

MEDROXYPROGESTERONE ACETATE

Indications see under Dose; contraception (section 7.3.2.2); malignant disease (section 8.3.2)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment section 8.3.2
Renal impairment use with caution
Pregnancy section 8.3.2
Breast-feeding section 8.3.2
Side-effects see notes above; indigestion
Dose

- By mouth, 2.5–10 mg daily for 5–10 days beginning on day 16 to 21 of cycle, repeated for 2 cycles in dysfunctional uterine bleeding and 3 cycles in secondary amenorrhoea
- Mild to moderate endometriosis, 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle
- Progestogenic opposition of oestrogen HRT, 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

Provera® (Pharmacia) PoM
Tablets, all scored, medroxyprogesterone acetate 2.5 mg (orange), net price 30-tab pack = £1.84; 5 mg (blue), 10-tab pack = £1.23; 10 mg (white), 10-tab pack = £2.47, 90-tab pack = £22.16

Climanor® (ReSource Medical) PoM
Tablets, f/c, medroxyprogesterone acetate 5 mg, net price 28-tab pack = £3.27

Combined preparations
Section 6.4.1.1

NORETHISTERONE

Indications see under Dose; HRT (section 6.4.1.1); contraception (section 7.3.1 and section 7.3.2); malignant disease (section 8.3.2)
Cautions see notes above
Contra-indications see notes above
Hepatic impairment section 8.3.2
Renal impairment use with caution
Pregnancy section 8.3.2
Breast-feeding section 8.3.2
Side-effects see notes above
Dose

- Endometriosis, by mouth, 10–15 mg daily for 4–6 months or longer, starting on day 5 of cycle (if spotting occurs increase dose to 20–25 mg daily, reduced once bleeding has stopped)
- Dysfunctional uterine bleeding, menorrhagia (but see notes above), by mouth, 5 mg 3 times daily for 10 days to arrest bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26
- Dysmenorrhoea (but see notes above), by mouth, 5 mg 3 times daily from day 5 to 24 for 3–4 cycles
- Premenstrual syndrome (but not recommended, see notes above), by mouth, 5 mg 2–3 times daily from day 19 to 26 for several cycles
- Postponement of menstruation, by mouth, 5 mg 3 times daily starting 3 days before expected onset (menstruation occurs 2–3 days after stopping)

Norethisterone (Non-proprietary) PoM
Tablets, norethisterone 5 mg, net price 30-tab pack = £2.18

Primolut N® (Bayer Schering) PoM
Tablets, norethisterone 5 mg, net price 30-tab pack = £1.89

Utovlan® (Pharmacia) PoM
Tablets, norethisterone 5 mg, net price 30-tab pack = £1.40, 90-tab pack = £4.21

Combined preparations

Section 6.4.1.1

PROGESTERONE

Indications see under preparations
Cautions see notes above
Contra-indications see notes above; missed or incomplete abortion
Hepatic impairment avoid; see also Combined Hormonal Contraceptives, section 7.3.1
Renal impairment use with caution
Pregnancy not known to be harmful
Breast-feeding avoid—present in milk
Side-effects see notes above; injection-site reactions; pain, diarrhoea and flatulence can occur with rectal administration
Dose
- See under preparations

Crinone® (Merck Serono) PoM
Vaginal gel, progesterone 90 mg/application (8%), 15 = £30.83
Dose by vagina, infertility due to inadequate luteal phase, insert 1 applicatorful daily starting either after documented ovulation or on day 18–21 of cycle. *In vitro* fertilisation, daily application continued for 30 days after laboratory evidence of pregnancy

Cyclogest® (Actavis) PoM
Pessaries, progesterone 200 mg, net price 15 = £7.03; 400 mg, 15 = £10.18
Dose by vagina *or* rectum, premenstrual syndrome and postnatal depression, 200 mg daily to 400 mg twice daily; for premenstrual syndrome start on day 12–14 and continue until onset of menstruation (but not recommended, see notes above); rectally if barrier methods of contraception are used, in patients who have recently given birth or in those who suffer from vaginal infection or recurrent cystitis

Gestone® (Nordic) PoM
Injection, progesterone 50 mg/mL, net price 1-mL amp = £4.50, 2-mL amp = £4.50
Dose by deep intramuscular injection into buttock, dysfunctional uterine bleeding, 5–10 mg daily for 5–10 days until 2 days before expected onset of menstruation
Recurrent miscarriage due to inadequate luteal phase (but not recommended, see notes above) or following *in vitro* fertilisation *or* gamete intra-fallopian transfer, 25–100 mg 2–7 times a week from day 15, or day of embryo *or* gamete transfer, until 8–16 weeks of pregnancy; max. 200 mg daily

Utrogestan® (Ferring) PoM
Capsules, progesterone (micronised) 100 mg, net price 30-cap pack = £5.13; 200 mg 15-cap pack = £5.13. Counselling, administration
Excipients include arachis (peanut) oil
Counselling Capsules should be taken at bedtime on an empty stomach
Dose progestogenic opposition of oestrogen HRT 200 mg once daily on days 15–26, *or* 100 mg once daily on days 1–25, of each 28-day oestrogen HRT cycle

6.4.2 Male sex hormones and antagonists

Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids (section 6.4.3).

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone (section 6.5.1) which will stimulate spermatogenesis as well as androgen production.

Caution should be used when androgens or chorionic gonadotrophin are used in treating boys with delayed puberty since the fusion of epiphyses is hastened and may result in short stature; skeletal maturation should be monitored.

Intramuscular depot preparations of **testosterone esters** are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively *Sustanon®*, which consists of a mixture of testosterone esters and has a longer duration of action, may be used. Satisfactory replacement therapy can sometimes be obtained with 1 mL of *Sustanon 250®*, given by intramuscular injection once a month, although more frequent dose intervals are often necessary. Implants of testosterone can be used for hypogonadism; the implants are replaced every 4 to 5 months.

Testosterone implants can be used in postmenopausal women as an adjunct to hormone replacement therapy. A testosterone patch is also licensed to improve libido in *surgically induced* menopausal women (receiving concomitant oestrogen therapy).

TESTOSTERONE AND ESTERS

Indications see under preparations
Cautions cardiac impairment, elderly, ischaemic heart disease, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia), undertake regular examination of the prostate and breast during treatment; monitor full blood count, lipid profile and liver function; pre-pubertal boys (see notes above and under Side-effects); **interactions:** Appendix 1 (testosterone)
Women Regularly assess for androgenic side-effects; women should be advised to report any signs of virilisation e.g. deepening of the voice or hirsutism
Contra-indications breast cancer in men, prostate cancer, history of primary liver tumours, hypercalcaemia, nephrotic syndrome
Hepatic impairment avoid if possible—fluid retention and dose-related toxicity
Renal impairment caution—potential for fluid retention

Pregnancy avoid; causes masculinisation of female fetus

Breast-feeding avoid; may cause masculinisation in the female infant or precocious development in the male infant; high doses suppress lactation

Side-effects prostate abnormalities and prostate cancer, headache, depression, gastro-intestinal bleeding, nausea, vomiting, cholestatic jaundice, changes in libido, gynaecomastia, polycythaemia, anxiety, irritability, nervousness, asthenia, paraesthesia, hypertension, electrolyte disturbances including sodium retention with oedema and hypercalcaemia, weight gain; increased bone growth, muscle cramps, arthralgia; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, pruritus, excessive frequency and duration of penile erection, precocious sexual development and premature closure of epiphyses in pre-pubertal males, suppression of spermatogenesis in men and virilism in women; *rarely* liver tumours; sleep apnoea also reported; *with patches, buccal tablets, and gel*, local irritation and allergic reactions (including burn-like lesions with *patches*), and taste disturbances

Dose

- See under preparations

Oral

Restandol® Testocaps (Organon) PoM

Capsules, orange, testosterone undecanoate 40 mg in oily solution, net price 30-cap pack = £8.55; 60-cap pack = £17.10. Label: 21, 25

Dose androgen deficiency, 120–160 mg daily for 2–3 weeks; maintenance 40–120 mg daily

Buccal

Striant® SR (The Urology Co.) PoM

Mucoadhesive buccal tablets, m/r, testosterone 30 mg, net price 60-tab pack = £45.84. Counselling, see under Dose below

Dose hypogonadism, 30 mg every 12 hours; CHILD and ADOLESCENT under 18 years not recommended

Counselling Place rounded side of tablet on gum above front teeth and hold lip firmly over the gum for 30 seconds. If tablet detaches within 4 hours of next dose, replace with new tablet which is considered the second dose for the day.

Intramuscular

Testosterone Enantate (Non-proprietary) PoM

Injection (oily), testosterone enantate 250 mg/mL, net price 1-mL amp = £13.33

Dose by slow intramuscular injection, hypogonadism, initially 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks

Breast cancer, 250 mg every 2–3 weeks

Nebido® (Bayer Schering) ▼ PoM

Injection (oily), testosterone undecanoate 250 mg/mL, net price 4-mL amp = £76.70

Dose by deep intramuscular injection, hypogonadism in men over 18 years, 1 g every 10–14 weeks; if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks

Sustanon 250® (Organon) PoM

Injection (oily), testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL, net price 1-mL amp = £2.45

Excipients include arachis (peanut) oil, benzyl alcohol (see Excipients p. 2)

Dose by deep intramuscular injection, androgen deficiency, 1 mL usually every 3 weeks

Virormone® (Nordic) PoM

Injection, testosterone propionate 50 mg/mL, net price 2-mL amp = £4.50

Dose by intramuscular injection, androgen deficiency, 50 mg 2–3 times weekly

Delayed puberty, 50 mg weekly

Breast cancer in women, 100 mg 2–3 times weekly

Implant

Testosterone (Organon) PoM

Implant, testosterone 100 mg, net price = £7.40; 200 mg = £13.79

Dose by implantation, male hypogonadism, 100–600 mg; 600 mg usually maintains plasma-testosterone concentration within the normal range for 4–5 months

Postmenopausal women, 50–100 mg every 4–8 months, as an adjunct to oestrogen replacement therapy

Transdermal preparations

Intrinsa® (Warner Chilcott) ▼ PoM

Patches, self-adhesive, releasing testosterone approx. 300 micrograms/24 hours, net price 8-patch pack = £26.91. Counselling, administration

Dose hypoactive sexual desire disorder associated with surgically induced menopause (in women receiving concomitant oestrogen therapy (section 6.4.1.1)), apply 1 patch twice weekly continuously to clean, dry, unbroken skin on lower abdomen below waistline; site replacement patch on a different area (avoid using same area for 7 days); assess treatment after 3–6 months, discontinue if no benefit

Note Not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of use beyond 1 year not established

Testim® (Ferring) PoM

Gel, testosterone 50 mg/5 g tube, net price 30-tube pack = £32.00. Counselling, administration

Excipients include propylene glycol (see section 13.1.3)

Dose hypogonadism due to testosterone deficiency in men (over 18 years), 50 mg testosterone (5 g gel) applied once daily; subsequent application adjusted according to response; max. 100 mg (10 g gel) daily

Counselling Squeeze entire content of tube on to one palm and apply as a thin layer on clean, dry, healthy skin of shoulder or upper arm, preferably in the morning after washing or bathing (if 2 tubes required use 1 per shoulder or upper arm); rub in and allow to dry before putting on clothing to cover site; wash hands with soap after application; avoid washing application site for at least 6 hours

Avoid skin contact with application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature

Testogel® (Bayer Schering) PoM

Gel, testosterone 50 mg/5 g sachet, net price 30-sachet pack = £31.11. Counselling, administration

Dose hypogonadism due to androgen deficiency in men (over 18 years), 50 mg testosterone (5 g gel) to be applied once daily; subsequent application adjusted according to response in 25-mg (2.5 g gel) increments to max. 100 mg (10 g gel) daily

Counselling Apply thin layer of gel on clean, dry, healthy skin such as shoulders, arms or abdomen, immediately after sachet is opened. Not to be applied on genital area as high alcohol content may cause local irritation. Allow to dry for 3–5 minutes before dressing. Wash hands with soap and water after applying gel, avoid shower or bath for at least 6 hours

Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature

Tostran® (ProStrakan) PoM

Gel, testosterone 2% (10 mg/metered application), net price 60-g multidose dispenser = £26.67. Counselling, administration

Excipients include butylhydroxytoluene, propylene glycol (see section 13.1.3)

Dose hypogonadism due to testosterone deficiency in men (over 18 years), initially 60 mg testosterone (3 g gel) applied

once daily; subsequent applications adjusted according to response; max. 80 mg (4 g gel) daily

Counselling Apply gel on clean, dry, intact skin of abdomen or both inner thighs, preferably in the morning. Gently rub in with a finger until dry before dressing. Wash hands with soap and water after applying gel; avoid washing application site for at least 2 hours. Not to be applied on genital area.

Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature

MESTEROLONE

Indications see under Dose

Cautions see under Testosterone and Esters

Contra-indications see under Testosterone and Esters

Hepatic impairment see under Testosterone and Esters

Renal impairment see under Testosterone and Esters

Pregnancy see under Testosterone and Esters

Breast-feeding see under Testosterone and Esters

Side-effects see under Testosterone and Esters but spermatogenesis unimpaired

Dose

- Androgen deficiency and male infertility associated with hypogonadism, 25 mg 3–4 times daily for several months, reduced to 50–75 mg daily in divided doses for maintenance; CHILD not recommended

Pro-Viron® (Bayer Schering) PoM

Tablets, scored, mesterolone 25 mg. Net price 30-tab pack = £4.19

Anti-androgens

Cyproterone acetate

Cyproterone acetate is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertility (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermatogram. As hepatic tumours have been produced in *animal* studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also used as an adjunct in prostatic cancer (section 8.3.4.2) and in the treatment of acne and hirsutism in women (section 13.6.2).

CYPROTERONE ACETATE

Indications see notes above; prostate cancer (section 8.3.4.2)

Cautions ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known); blood counts initially and throughout treatment; monitor hepatic function regularly (liver function tests should be performed before treatment, see also under Side-effects below); monitor adrenocortical function regularly; diabetes mellitus (see also Contra-indications)

Driving Fatigue and lassitude may impair performance of skilled tasks (e.g. driving)

Contra-indications (do not apply in prostate cancer), severe diabetes (with vascular changes), sickle-cell anaemia, liver-disease including Dubin-Johnson and Rotor syndromes, previous or existing liver tumours, malignant or wasting diseases, meningioma or history of meningioma, severe depression, history of thromboembolic disorders; youths under 18 years (may arrest bone maturation and testicular development)

Hepatic impairment dose-related toxicity; see also side-effects, p. 573

Side-effects fatigue and lassitude, breathlessness, weight changes, reduced sebum production (may clear acne), changes in hair pattern, gynaecomastia (rarely leading to galactorrhoea and benign breast nodules); rarely hypersensitivity reactions, rash and osteoporosis; inhibition of spermatogenesis (see notes above); hepatotoxicity reported (including jaundice, hepatitis and hepatic failure usually in men given 200–300 mg daily for prostatic cancer, see section 8.3.4.2 for details and warnings)

Dose

- ADULT over 18 years, male hypersexuality, 50 mg twice daily after food

Cyproterone Acetate (Non-proprietary) PoM

Tablets, cyproterone acetate 50 mg, net price 56-tab pack = £31.54. Label: 21 counselling, driving

Androcur® (Bayer Schering) PoM

Tablets, scored, cyproterone acetate 50 mg, net price 56-tab pack = £24.41. Label: 21 counselling, driving

Dutasteride and finasteride

Dutasteride and **finasteride** are specific inhibitors of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone. This inhibition of testosterone metabolism leads to reduction in prostate size, with improvement in urinary flow rate and in obstructive symptoms. Dutasteride and finasteride are alternatives to alpha-blockers (section 7.4.1) particularly in men with a significantly enlarged prostate. Finasteride is also licensed for use with doxazosin in the management of benign prostatic hyperplasia.

A low strength of finasteride is licensed for treating male-pattern baldness in men (section 13.9).

Cautions Dutasteride and finasteride decrease serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment. Both dutasteride and finasteride are excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant. Women of childbearing potential should avoid handling crushed or broken tablets of finasteride and leaking capsules of dutasteride.

Side-effects The side-effects of dutasteride and finasteride include impotence, decreased libido, ejaculation disorders, and breast tenderness and enlargement.

DUTASTERIDE

Indications benign prostatic hyperplasia

Cautions see notes above; **interactions:** Appendix 1 (dutasteride)

Hepatic impairment avoid in severe impairment—no information available

Side-effects see notes above

Dose

- 500 micrograms daily, review treatment at 3–6 months and then every 6–12 months (may require several months treatment before benefit is obtained)

Avodart® (GSK) PoM

Capsules, yellow, dutasteride 500 micrograms, net price 30-cap pack = £19.80. Label: 25

With tamsulosin

Section 7.4.1

FINASTERIDE

Indications benign prostatic hyperplasia; male-pattern baldness in men (section 13.9)

Cautions see notes above; also obstructive uropathy

Male breast cancer Cases of male breast cancer have been reported. Patients or their carers should be told to promptly report to their doctor any changes in breast tissue such as lumps, pain, or nipple discharge

Side-effects see notes above; also testicular pain, hypersensitivity reactions (including lip and face swelling, pruritus and rash); male breast cancer also reported (see Cautions above)

Dose

- 5 mg daily, review treatment at 3–6 months and then every 6–12 months (may require several months' treatment before benefit is obtained)

Finasteride (Non-proprietary) PoM

Tablets, finasteride 5 mg, net price 28-tab pack = £2.19

Proscar® (MSD) PoM

Tablets, blue, f/c, finasteride 5 mg, net price 28-tab pack = £13.94

6.4.3 Anabolic steroids

Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They are used in the treatment of some *aplastic anaemias* (section 9.1.3). Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is unjustified; some athletes abuse them.

NANDROLONE

Indications osteoporosis in postmenopausal women (but not recommended, see notes above); aplastic anaemia (section 9.1.3)

Cautions cardiac impairment, hypertension, diabetes mellitus, epilepsy, migraine; monitor skeletal maturation in young patients; skeletal metastases (risk of hypercalcaemia); **interactions:** Appendix 1 (anabolic steroids)

Contra-indications prostate cancer, male breast cancer, acute porphyria (section 9.8.2)

Hepatic impairment use in severe hepatic impairment only if benefit outweighs risk

Renal impairment use with caution—may cause sodium and water retention

Side-effects acne, sodium retention with oedema, virilisation with high doses including voice changes (sometimes irreversible), amenorrhoea, inhibition of spermatogenesis, premature epiphyseal closure; abnormal liver-function tests reported with high doses; liver tumours reported occasionally on prolonged treatment with anabolic steroids

Dose

- See below

Deca-Durabolin® (Organon) PoM

Injection (oily), nandrolone decanoate 50 mg/mL, net price 1-mL amp = £3.17

Excipients include arachis (peanut) oil, benzyl alcohol (see Excipients, p. 2)

Dose by deep intramuscular injection, 50 mg every 3 weeks

6.5 Hypothalamic and pituitary hormones and anti-oestrogens

6.5.1 Hypothalamic and anterior pituitary hormones and anti-oestrogens
6.5.2 Posterior pituitary hormones and antagonists

Use of preparations in these sections requires detailed prior investigation of the patient and *should be reserved for specialist centres.*

6.5.1 Hypothalamic and anterior pituitary hormones and anti-oestrogens

Anti-oestrogens

The anti-oestrogens **clomifene** (clomiphene) and **tamoxifen** (section 8.3.4.1) are used in the treatment of female infertility due to oligomenorrhoea or secondary amenorrhoea (e.g. associated with polycystic ovarian disease). They induce gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used as an adjunct. Patients should be warned that there is a risk of multiple pregnancy (*rarely* more than twins).

CLOMIFENE CITRATE
(Clomiphene Citrate)

Indications anovulatory infertility—see notes above

Cautions see notes above; polycystic ovary syndrome (cysts may enlarge during treatment, also risk of exaggerated response to usual doses), ovarian hyperstimulation syndrome, uterine fibroids, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring), visual symptoms (discontinue and initiate ophthalmological examination)

CSM Advice The CSM has recommended that clomifene should not normally be used for longer than 6 cycles (possibly increased risk of ovarian cancer)

Contra-indications ovarian cysts, hormone-dependent tumours or abnormal uterine bleeding of undetermined cause

Hepatic impairment avoid in severe liver disease

Pregnancy exclude pregnancy before treatment; possible effects on fetal development

Breast-feeding may inhibit lactation

Side-effects visual disturbances (withdraw), ovarian hyperstimulation (withdraw), hot flushes, abdominal discomfort, occasionally nausea, vomiting, depression, insomnia, breast tenderness, headache, intermenstrual spotting, menorrhagia, endometriosis, convulsions, weight gain, rashes, dizziness, hair loss

Dose

- 50 mg daily for 5 days, starting within about 5 days of onset of menstruation (preferably on 2nd day) or at any time (normally preceded by a progestogen-induced withdrawal bleed) if cycles have ceased; second course of 100 mg daily for 5 days may be given in absence of ovulation; most patients who are going to respond will do so to first course; 3 courses should constitute adequate therapeutic trial; long-term cyclical therapy not recommended—see CSM advice, above

Clomifene (Non-proprietary) PoM

Tablets, clomifene citrate 50 mg, net price 30-tab pack = £15.94

Clomid® (Sanofi-Aventis) PoM

Tablets, yellow, scored, clomifene citrate 50 mg. Net price 30-tab pack = £8.46

Anterior pituitary hormones

Corticotrophins

Tetracosactide (tetracosactrin), an analogue of corticotropin (ACTH), is used to test adrenocortical function; failure of the plasma cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency.

Both corticotropin and tetracosactide were formerly used as alternatives to corticosteroids in conditions such as Crohn's disease or rheumatoid arthritis; their value was limited by the variable and unpredictable therapeutic response and by the waning of their effect with time.

TETRACOSACTIDE
(Tetracosactrin)

Indications see notes above

Cautions as for corticosteroids, section 6.3.2; **important:** risk of anaphylaxis (medical supervision; consult product literature); **interactions:** Appendix 1 (corticosteroids)

Contra-indications as for corticosteroids, section 6.3.2; avoid injections containing benzyl alcohol in neonates (see under preparations)

Hepatic impairment see section 6.3.2

Renal impairment see section 6.3.2

Pregnancy avoid (but may be used diagnostically if essential)

Breast-feeding avoid (but may be used diagnostically if essential)

Side-effects as for corticosteroids, section 6.3.2

Dose

- See under preparations below

Synacthen® (Alliance) PoM

Injection, tetracosactide 250 micrograms (as acetate)/mL. Net price 1-mL amp = £2.70

Dose diagnostic (30-minute test), by intramuscular *or* intravenous injection, 250 micrograms as a single dose

Synacthen Depot® (Alliance) PoM

Injection (aqueous suspension), tetracosactide acetate 1 mg/mL, with zinc phosphate complex. Net price 1-mL amp = £3.87

Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)

Dose diagnostic (5-hour test), by intramuscular injection, 1 mg as a single dose

Note Formerly used therapeutically by intramuscular injection, in an initial dose of 1 mg daily (or every 12 hours in acute cases); reduced to 1 mg every 2–3 days, then 1 mg weekly (or 500 micrograms every 2–3 days) but value was limited (see notes above)

Gonadotrophins

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) together (as in **human menopausal gonadotrophin**), follicle-stimulating hormone alone (as in **follitropin**), or chorionic gonadotrophin, are used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene, or in superovulation treatment for assisted conception (such as *in vitro* fertilisation).

The gonadotrophins are also occasionally used in the treatment of hypogonadotrophic hypogonadism and associated oligospermia. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone (section 6.4.2).

CHORIONIC GONADOTROPHIN
(Human Chorionic Gonadotrophin; HCG)

A preparation of a glycoprotein fraction secreted by the placenta and obtained from the urine of pregnant women having the action of the pituitary luteinising hormone

Indications see notes above

Cautions cardiac impairment, asthma, epilepsy, migraine; prepubertal boys (risk of premature epiphyseal closure or precocious puberty); acute porphyria (section 9.8.2)

Contra-indications androgen-dependent tumours

Renal impairment use with caution

Side-effects oedema (particularly in males—reduce dose), headache, tiredness, mood changes, gynaecomastia, local reactions; may aggravate ovarian hyperstimulation, multiple pregnancy

Dose

- By subcutaneous *or* intramuscular injection, according to patient's response

Choragon® (Ferring) PoM

Injection, powder for reconstitution, chorionic gonadotrophin. Net price 5000-unit amp (with solvent) = £3.26. For intramuscular injection

Pregnyl® (Organon) PoM

Injection, powder for reconstitution, chorionic gonadotrophin. Net price 1500-unit amp = £2.12; 5000-unit amp = £3.15 (both with solvent). For subcutaneous or intramuscular injection

CHORIOGONADOTROPIN ALFA
(Human chorionic gonadotropin)

Indications see notes above

Cautions acute porphyria (section 9.8.2)

Contra-indications ovarian enlargement or cyst (unless caused by polycystic ovarian disease); ectopic pregnancy in previous 3 months; active thromboembolic disorders; hypothalamus, pituitary, ovarian, uterine or mammary malignancy

Side-effects nausea, vomiting, abdominal pain; headache, tiredness; injection-site reactions; ovarian hyperstimulation syndrome; rarely diarrhoea, depression, irritability, breast pain; ectopic pregnancy and ovarian torsion reported

Dose

- By subcutaneous injection, according to patient's response

Ovitrelle® (Merck Serono) PoM

Injection, choriogonadotropin alfa, net price 6500-unit/0.5 mL (250-micrograms/0.5 mL) prefilled syringe = £31.38

CORIFOLLITROPIN ALFA

Indications controlled ovarian stimulation in combination with a gonadotrophin-releasing hormone antagonist

Cautions risk factors for thromboembolism; risk of ovarian hyperstimulation syndrome; acute porphyria (section 9.8.2)

Contra-indications ovarian enlargement or cyst; polycystic ovarian syndrome; tumours of hypothalamus, pituitary, ovaries, uterus, or breast; vaginal bleeding of unknown cause; history of ovarian hyperstimulation syndrome

Renal impairment avoid

Breast-feeding avoid

Side-effects nausea; headache, fatigue; ovarian hyperstimulation, pelvic pain, breast pain; *less commonly* vomiting, abdominal distension and pain, diarrhoea, constipation, dizziness, ovarian torsion; *also reported* ectopic pregnancy, miscarriage, and multiple pregnancies

Dose

- By subcutaneous injection, body-weight under 60 kg, 100 micrograms; body-weight over 60 kg, 150 micrograms

Elonva® (Organon) ▼ PoM

Injection, prefilled syringe, corifollitropin alfa, net price 100 micrograms/0.5 mL = £638.00; 150 micrograms/0.5 mL = £638.00

FOLLITROPIN ALFA and BETA
(Recombinant human follicle stimulating hormone)

Indications see notes above

Cautions acute porphyria (section 9.8.2)

Contra-indications see under Human Menopausal Gonadotrophins

Pregnancy avoid

Breast-feeding avoid

Side-effects see under Human Menopausal Gonadotrophins

Dose

- By subcutaneous *or* intramuscular injection, according to patient's response

Follitropin alfa

Gonal-F® (Merck Serono) PoM

Injection, powder for reconstitution, follitropin alfa. Net price 75-unit amp = £21.02; 450 units/0.75 mL, multidose vial = £126.10; 1050 units/1.75 mL, multidose vial = £294.22 (all with solvent). For subcutaneous injection

Injection, prefilled pen, follitropin alfa 600 units/mL, net price 0.5 mL (300 units) = £94.00, 0.75 mL (450 units) = £141.00, 1.5 mL (900 units) = £282.00. For subcutaneous injection

Follitropin alfa with lutropin alfa

Pergoveris® (Merck Serono) PoM

Injection, powder for reconstitution, follitropin alfa 150 units (11 micrograms), lutropin alfa 75 units (3 micrograms), net price per vial (with solvent) = £60.29. For subcutaneous injection

Electrolytes $Na^+ < 1$ mmol/vial

Follitropin beta

Puregon® (Organon) PoM

Injection, follitropin beta 100 units/mL, net price 0.5-mL (50-unit) vial = £18.03; 200 units/mL, 0.5-mL (100-unit) vial = £36.06; 300 units/mL, 0.5-mL (150-unit) vial = £50.62; 400 units/mL, 0.5-mL (200-unit) vial = £67.49; 0.36-mL (300-unit) cartridge = £97.41, 0.72-mL (600-unit) cartridge = £194.82, 1.08-mL (900-unit) cartridge = £292.23, (cartridges for use with *Puregon®* pen). For subcutaneous (cartridges and vials) or intramuscular injection (vials)

Excipients may include neomycin and streptomycin

HUMAN MENOPAUSAL GONADOTROPHINS

Indications see notes above

Cautions acute porphyria (section 9.8.2)

Contra-indications ovarian cysts (not caused by polycystic ovarian syndrome); tumours of pituitary, hypothalamus, breast, uterus, ovaries, testes or prostate; vaginal bleeding of unknown cause

Pregnancy avoid

Breast-feeding avoid

Side-effects ovarian hyperstimulation, increased risk of multiple pregnancy and miscarriage, hypersensitivity reactions, gastro-intestinal disturbances, headache, joint pain, fever, injection site reactions, *very rarely* thromboembolism; gynaecomastia, acne, and weight gain reported in men

Dose

- By deep intramuscular *or* subcutaneous injection, according to patient's response

Menotrophin

Purified extract of human post-menopausal urine containing follicle-stimulating hormone (FSH) and luteinising hormone (LH) in a ratio of 1:1

Merional® (Pharmasure) PoM

Injection, powder for reconstitution, menotrophin as follicle-stimulating hormone 75 units and luteinising hormone 75 units, net price per vial (with solvent) = £13.95; follicle-stimulating hormone 150 units, luteinising hormone 150 units, net price per vial (with solvent) = £27.90. For intramuscular injection

Menopur® (Ferring) PoM
Injection, powder for reconstitution, menotrophin as follicle-stimulating hormone 75 units and luteinising hormone 75 units, net price per vial (with solvent) = £13.38. For intramuscular or subcutaneous injection

Urofollitropin

Purified extract of human post-menopausal urine containing follicle-stimulating hormone (FSH)

Fostimon® (Pharmasure) PoM
Injection, powder for reconstitution, urofollitropin as follicle-stimulating hormone 75 units, net price per vial (with solvent) = £27.90; follicle-stimulating hormone 150 units, net price per vial (with solvent) = £55.80. For intramuscular or subcutaneous injection

LUTROPIN ALFA

(Recombinant human luteinising hormone)

Indications see notes above

Cautions acute porphyria (section 9.8.2)

Contra-indications ovarian enlargement or cyst (unless caused by polycystic ovarian disease); undiagnosed vaginal bleeding; tumours of hypothalamus and pituitary; ovarian, uterine or mammary carcinoma

Side-effects nausea, vomiting, abdominal and pelvic pain; headache, somnolence; injection-site reactions; ovarian hyperstimulation syndrome, ovarian cyst, breast pain, ectopic pregnancy; thromboembolism, adnexal torsion, and haemoperitoneum

Dose

- By subcutaneous injection, in conjunction with follicle-stimulating hormone, according to response

Luveris® (Merck Serono) PoM
Injection, powder for reconstitution, lutropin alfa, net price 75-unit vial = £31.38 (with solvent)

Growth hormone

Growth hormone is used to treat deficiency of the hormone in children and in adults (see NICE guidance below). In children it is used in Prader-Willi syndrome, Turner syndrome, chronic renal insufficiency, short children considered small for gestational age at birth, and short stature homeobox-containing gene (SHOX) deficiency.

Growth hormone of human origin (HGH; somatotrophin) has been replaced by a growth hormone of human sequence, **somatropin**, produced using recombinant DNA technology.

NICE guidance

Somatropin for the treatment of growth failure in children (May 2010)

Somatropin is recommended for children with growth failure who:

- have growth-hormone deficiency;
- have Turner syndrome;
- have Prader-Willi syndrome;
- have chronic renal insufficiency;
- are born small for gestational age with subsequent growth failure at 4 years of age or later;
- have short stature homeobox-containing gene (SHOX) deficiency.

Treatment should be discontinued if growth velocity increases by less than 50% from baseline in the first year of treatment.

NICE guidance

Somatropin for adults with growth hormone deficiency (August 2003)

Somatropin is recommended in adults **only** if the following 3 criteria are fulfilled:

- Severe growth hormone deficiency, established by an appropriate method,
- Impaired quality of life, measured by means of a specific questionnaire,
- Already receiving treatment for another pituitary hormone deficiency.

Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months.

Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved. Treatment for adult-onset growth hormone deficiency should be stopped only when the patient and the patient's physician consider it appropriate.

Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone disorders; maintenance treatment can be prescribed in the community under a shared-care protocol.

Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is licensed to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency (section 6.7.4).

SOMATROPIN

(Recombinant Human Growth Hormone)

Indications see under Dose

Cautions diabetes mellitus (adjustment of antidiabetic therapy may be necessary), papilloedema (see under Side-effects), relative deficiencies of other pituitary hormones (notably hypothyroidism—manufacturers recommend periodic thyroid function tests but limited evidence of clinical value), history of malignant disease, disorders of the epiphysis of the hip (monitor for limping), resolved intracranial hypertension (monitor closely), initiation of treatment close to puberty not recommended in child born small for gestational age; Silver-Russell syndrome; rotate subcutaneous injection sites to prevent lipoatrophy; **interactions:** Appendix 1 (somatropin)

Contra-indications evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting); not to be used after renal transplantation or for growth promotion in children with closed epiphyses (or near closure in Prader-Willi syndrome); severe obesity or severe respiratory impairment in Prader-Willi syndrome

Pregnancy discontinue if pregnancy occurs—no information available

Breast-feeding no information available

Side-effects headache, funduscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); fluid retention (peripheral oedema), arthralgia, myalgia, carpal tunnel syndrome, paraesthesia, antibody formation, hypothyroidism, insulin resistance, hyperglycaemia, hypo-

glycaemia, reactions at injection site; leukaemia in children with growth hormone deficiency also reported

Dose

- Gonadal dysgenesis (Turner syndrome), by subcutaneous injection, 45–50 micrograms/kg daily *or* 1.4 mg/m^2 daily
- Deficiency of growth hormone in children, by subcutaneous *or* intramuscular injection, 23–39 micrograms/kg daily *or* 0.7–1 mg/m^2 daily
- Growth disturbance in short children born small for gestational age whose growth has not caught up by 4 years or later, by subcutaneous injection, 35 micrograms/kg daily or 1 mg/m^2 daily
- Prader-Willi syndrome, by subcutaneous injection in children with growth velocity greater than 1 cm/year, in combination with energy-restricted diet, 35 micrograms/kg daily *or* 1 mg/m^2 daily; max. 2.7 mg daily
- Chronic renal insufficiency in children (renal function decreased to less than 50%), by subcutaneous injection, 45–50 micrograms/kg daily *or* 1.4 mg/m^2 daily (higher doses may be needed) adjusted if necessary after 6 months
- Adult growth hormone deficiency, by subcutaneous injection, initially 150–300 micrograms daily, gradually increased if required to max. 1 mg daily; use minimum effective dose (requirements may decrease with age)
- SHOX deficiency in children, by subcutaneous injection, 45–50 micrograms/kg daily

Note Dose formerly expressed in units; somatropin 1 mg ≡ 3 units

Genotropin® (Pharmacia) PoM

Injection, two-compartment cartridge containing powder for reconstitution, somatropin (rbe) and diluent, net price 5.3-mg (16-unit) cartridge = £122.87, 12-mg (36-unit) cartridge = £278.20. For use with *Genotropin® Pen* NHS device (available free of charge from clinics). For subcutaneous injection

GoQuick® injection, two-compartment, multi-dose disposable, prefilled pen containing powder for reconstitution, somatropin (rbe) and diluent, net price 5.3-mg (16-unit) prefilled pen = £122.87; 12-mg (36-unit) prefilled pen = £278.20. For subcutaneous injection

MiniQuick injection, two-compartment single-dose syringe containing powder for reconstitution, somatropin (rbe) and diluent, net price 0.2-mg (0.6-unit) syringe = £4.64; 0.4-mg (1.2-unit) syringe = £9.27; 0.6-mg (1.8-unit) syringe = £13.91; 0.8-mg (2.4-unit) syringe = £18.55; 1-mg (3-unit) syringe = £23.18; 1.2-mg (3.6-unit) syringe = £27.82; 1.4-mg (4.2-unit) syringe = £32.46; 1.6-mg (4.8-unit) syringe = £37.09; 1.8-mg (5.4-unit) syringe = £41.73; 2-mg (6-unit) syringe = £46.37. For subcutaneous injection

Humatrope® (Lilly) PoM

Injection, powder for reconstitution, somatropin (rbe), net price 6-mg (18-unit) cartridge = £108.00; 12-mg (36-unit) cartridge = £216.00; 24-mg (72-unit) cartridge = £432.00; all supplied with diluent. For subcutaneous or intramuscular injection; cartridges for subcutaneous injection

Norditropin® (Novo Nordisk) PoM

SimpleXx injection, somatropin (epr) 3.3 mg (10 units)/mL, net price 1.5-mL (5-mg, 15-unit) cartridge = £106.35; 6.7 mg (20 units)/mL, 1.5-mL (10-mg, 30-unit) cartridge = £212.70; 10 mg (30 units)/mL, 1.5-mL (15-mg, 45-unit) cartridge = £319.05. For use with appropriate *NordiPen®* NHS device (available free of charge from clinics). For subcutaneous injection

NutropinAq® (Ipsen) PoM

Injection, somatropin (rbe), net price 10 mg (30 units) 2-ml cartridge = £203.00. For use with *NutropinAq® Pen* NHS device (available free of charge from clinics). For subcutaneous injection

Omnitrope® (Sandoz) PoM

Injection, somatropin (rbe) 3.3 mg (10 units)/mL, net price 1.5 mL (5-mg, 15-unit) cartridge = £86.77; 6.7 mg (20 units)/mL, 1.5 mL (10-mg, 30-unit) cartridge = £173.50. For use with *Omnitrope Pen 5®* NHS and *Omnitrope Pen 10®* NHS devices respectively (available free of charge from clinics). For subcutaneous injection

Excipients include benzyl alcohol (in 5-mg cartridge) (avoid in neonates, see Excipients, p. 2)

Note Biosimilar medicine, see p. 1

Saizen® (Merck Serono) PoM

Injection, powder for reconstitution, somatropin (rmc), net price 1.33-mg (4-unit) vial (with diluent) = £29.28; 3.33-mg (10-unit) vial (with diluent) = £73.20. For subcutaneous or intramuscular injection

Click.easy®, powder for reconstitution, somatropin (rmc), net price 8-mg (24-unit) vial (in *Click.easy®* device with diluent) = £185.44. For use with *One.click®* NHS autoinjector device *or Cool.Click®* NHS needle-free device (both available free of charge from clinics). For subcutaneous injection

Excipients include benzyl alcohol (in diluent for 3.33 mg vial) (avoid in neonates, see Excipients p. 2)

Note *Saizen®* 3.33 mg vial may be reconstituted with sodium chloride intravenous infusion or water for injections for immediate use when administering to children under 3 years of age

Zomacton® (Ferring) PoM

Injection, powder for reconstitution, somatropin (rbe), net price 4-mg (12-unit) vial (with diluent) = £79.69, for use with *ZomaJet 2® Vision* NHS needle-free device (available free of charge from clinics) or with needles and syringes; 10 mg (30-unit) vial (with diluent) = £199.23, for use with *ZomaJet Vision X ®* NHS needle-free device (available free of charge from clinics) or with needles and syringes. For subcutaneous injection

Excipients include benzyl alcohol (in 4-mg vial) (avoid in neonates, see Excipients p. 2)

Growth hormone receptor antagonists

Pegvisomant is a genetically modified analogue of human growth hormone and is a highly selective growth hormone receptor antagonist. Pegvisomant is licensed for the treatment of acromegaly in patients with inadequate response to surgery, radiation, or both, and to treatment with somatostatin analogues. Pegvisomant should be initiated only by physicians experienced in the treatment of acromegaly.

PEGVISOMANT

Indications see notes above

Cautions liver disease (monitor liver enzymes every 4–6 weeks for 6 months or if symptoms of hepatitis develop); diabetes mellitus (adjustment of antidiabetic therapy may be necessary); possible increase in female fertility

Pregnancy avoid

Breast-feeding avoid

Side-effects diarrhoea, constipation, nausea, vomiting, abdominal distension, dyspepsia, flatulence, elevated liver enzymes; hypertension; headache, asthenia, dizziness, drowsiness, tremor, sleep disturbances; influenza-like syndrome, weight gain, hyperglycaemia, hypoglycaemia; arthralgia, myalgia; injection-site reactions, sweating, pruritus, rash; fatigue; hypercholesterolaemia; less commonly thrombocytopenia, leucopenia, leucocytosis, bleeding tendency

Dose

- By subcutaneous injection, initially 80 mg, then 10 mg daily, increased in steps of 5 mg daily according to response; max. 30 mg daily; CHILD not recommended

Somavert® (Pfizer) PoM

Injection, powder for reconstitution, pegvisomant, net price 10-mg vial = £50.00; 15-mg vial = £75.00; 20-mg vial = £100.00 (all with solvent)

Thyrotrophin

Thyrotropin alfa is a recombinant form of thyrotrophin (thyroid stimulating hormone). It is licensed for use with or without radioiodine imaging, together with serum thyroglobulin testing, for the detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients. It is also licensed to increase radio-iodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients.

THYROTROPIN ALFA

(Recombinant human thyroid stimulating hormone, rhTSH)

Indications see notes above and product literature

Cautions presence of thyroglobulin autoantibodies may give false negative results

Contra-indications hypersensitivity to bovine or human thyrotrophin

Pregnancy avoid

Breast-feeding avoid

Side-effects nausea, vomiting; headache, dizziness, fatigue; *less commonly* asthenia, paraesthesia, back pain, influenza-like symptoms, rash, urticaria; *rarely* diarrhoea; *very rarely* palpitation, flushing, dyspnoea, pain at site of metastases, tremor, arthralgia, myalgia, hyperhidrosis, and injection-site reactions including pain, pruritus, and rash

Dose

- By intramuscular injection into the gluteal muscle, 900 micrograms every 24 hours for 2 doses, consult product literature

Thyrogen® (Genzyme) PoM

Injection, powder for reconstitution, thyrotropin alfa 900 micrograms/vial, net price = £291.52

Hypothalamic hormones

Gonadorelin when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating hormone (FSH). It has not proved to be very helpful, however, in distinguishing hypothalamic from pituitary lesions. **Gonadorelin analogues** are indicated in endometriosis and infertility (section 6.7.2) and in breast and prostate cancer (section 8.3.4).

GONADORELIN

(Gonadotrophin-releasing hormone; GnRH; LH–RH)

Indications see preparations below

Cautions pituitary adenoma

Pregnancy avoid

Breast-feeding avoid

Side-effects rarely, nausea, headache, abdominal pain, increased menstrual bleeding; rarely, hypersensitivity reaction on repeated administration of large doses; irritation at injection site

Dose

- See under preparations

HRF® (Intrapharm) PoM

Injection, powder for reconstitution, gonadorelin. Net price 100-microgram vial (with diluent) = £13.72 (hosp. only)

Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)

Dose for assessment of pituitary function (adults), by subcutaneous *or* intravenous injection, 100 micrograms

6.5.2 Posterior pituitary hormones and antagonists

Posterior pituitary hormones

Diabetes insipidus **Vasopressin** (antidiuretic hormone, ADH) is used in the treatment of *pituitary* ('cranial') *diabetes insipidus* as is its analogue **desmopressin**. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose of 2 micrograms intramuscularly or 20 micrograms intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In *nephrogenic* and *partial pituitary diabetes insipidus* benefit may be gained from the paradoxical antidiuretic effect of thiazides (section 2.2.1) e.g. chlortalidone 100 mg twice daily reduced to maintenance dose of 50 mg daily.

Carbamazepine (section 4.8.1) is sometimes useful in partial pituitary diabetes insipidus (in a dose of 200 mg once or twice daily) [unlicensed]; it may act by sensitising the renal tubules to the action of remaining endogenous vasopressin.

Other uses Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand's disease; it is also used to test fibrinolytic response. For a comment on use of desmopressin in nocturnal enuresis see section 7.4.2.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. **Terlipressin**, a derivative of vasopressin, is used similarly.

Oxytocin, another posterior pituitary hormone, is indicated in obstetrics (section 7.1.1).

DESMOPRESSIN

Indications see under Dose

Cautions see under Vasopressin; less pressor activity, but still considerable caution in cardiovascular disease and in hypertension (not indicated for nocturnal enuresis or nocturia in these circumstances); elderly (avoid for nocturnal enuresis and nocturia in those over 65 years); also considerable caution in cystic fibrosis; in nocturia and nocturnal enuresis limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards; in nocturia periodic blood pressure and weight checks needed to monitor for fluid overload; **interactions:** Appendix 1 (desmopressin)

Hyponatraemic convulsions Patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal). The risk of hyponatraemic convulsions can also be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants)

Contra-indications cardiac insufficiency and other conditions treated with diuretics; psychogenic polydipsia and polydipsia in alcohol dependence

Renal impairment use with caution; antidiuretic effect may be reduced

Pregnancy small oxytocic effect in third trimester; increased risk of pre-eclampsia

Breast-feeding not known to be harmful

Side-effects fluid retention, and hyponatraemia (in more serious cases with convulsions) on administration without restricting fluid intake; stomach pain, headache, nausea, vomiting, allergic reactions, and emotional disturbance in children also reported; epistaxis, nasal congestion, rhinitis with nasal spray

Dose

- By mouth (as desmopressin acetate)

  Diabetes insipidus, treatment, ADULT and CHILD initially 300 micrograms daily (in 3 divided doses); maintenance, 300–600 micrograms daily in 3 divided doses; range 0.2–1.2 mg daily

  Primary nocturnal enuresis, ADULT (under 65 years) and CHILD over 5 years (preferably over 7 years) 200 micrograms at bedtime, only increased to 400 micrograms if lower dose not effective (**important:** see also Cautions); withdraw for at least 1 week for reassessment after 3 months

  Postoperative polyuria or polydipsia, adjust dose according to urine osmolality

- Sublingually (as desmopressin base)

  Diabetes insipidus, treatment, ADULT and CHILD initially 180 micrograms daily in 3 divided doses; range 120–720 micrograms daily

  Primary nocturnal enuresis, ADULT (under 65 years) and CHILD over 5 years (preferably over 7 years) 120 micrograms at bedtime, only increased to 240 micrograms if lower dose not effective (**important:** see also Cautions); withdraw for at least 1 week for reassessment after 3 months

  Polyuria or polydipsia after hypophysectomy, adjust dose according to urine osmolality

- Intranasally (as desmopressin acetate)

  Diabetes insipidus, diagnosis, ADULT and CHILD 20 micrograms (limit fluid intake to 500 mL from 1 hour before to 8 hours after administration)

  Diabetes insipidus, treatment, ADULT 10–40 micrograms daily (in 1–2 divided doses); CHILD 5–20 micrograms daily; infants may require lower doses

  Nocturia associated with multiple sclerosis (when other treatments have failed), ADULT (under 65 years) 10–20 micrograms at bedtime (**important:** see also Cautions), dose not to be repeated within 24 hours

  Renal function testing (empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration), ADULT 40 micrograms; INFANT under 1 year 10 micrograms (restrict fluid intake to 50% at next 2 feeds to avoid fluid overload), CHILD 1–15 years 20 micrograms

  Mild to moderate haemophilia and von Willebrand's disease, ADULT 300 micrograms (one 150-microgram spray into each nostril) 30 minutes before surgery or when bleeding; may be repeated at intervals of 12 hours (or at intervals of at least 3 days if self-administered)

  Fibrinolytic response testing, ADULT 300 micrograms (one 150-microgram spray into each nostril); blood sampled after 1 hour for fibrinolytic activity

- By injection (as desmopressin acetate)

  Diabetes insipidus, diagnosis (subcutaneous *or* intramuscular), ADULT and CHILD 2 micrograms (limit fluid intake to 500 mL from 1 hour before to 8 hours after administration)

  Diabetes insipidus, treatment (subcutaneous, intramuscular *or* intravenous), ADULT 1–4 micrograms daily; INFANT and CHILD 400 nanograms

  Renal function testing (empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration) (subcutaneous *or* intramuscular), ADULT and CHILD 2 micrograms; INFANT 400 nanograms (restrict fluid intake to 50% at next 2 feeds)

  Mild to moderate haemophilia and von Willebrand's disease, (subcutaneous *or* intravenous), ADULT and CHILD over 1 month 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours

  Fibrinolytic response testing, (subcutaneous *or* intravenous), ADULT and CHILD 300 nanograms/kg; blood sampled after 20 minutes for fibrinolytic activity

  Lumbar-puncture-associated headache, consult product literature

Desmopressin acetate (Non-proprietary) PoM

Tablets, desmopressin acetate 100 micrograms, net price 90-tab pack = £50.57; 200 micrograms, 30-tab pack = £24.36, 90-tab pack = 69.82

Nasal spray, desmopressin acetate 10 micrograms/metered spray, net price 6-mL unit (60 metered sprays) = £18.74. Counselling, fluid intake, see above

Brands include *Presinex®*

Note Children requiring dose of less than 10 micrograms should be given *DDAVP®* intranasal solution

DDAVP® (Ferring) ▼ PoM

Tablets, both scored, desmopressin acetate 100 micrograms, net price 90-tab pack = £44.12; 200 micrograms, 90-tab pack = £88.23. Counselling, fluid intake, see above

Oral lyophilisates (DDAVP® Melt), desmopressin (as acetate) 60 micrograms, net price 100-tab pack =

£50.53; 120 micrograms, 100-tab pack = £101.07; 240 micrograms, 100-tab pack = £202.14. Label: 26, counselling, fluid intake, see above

Intranasal solution, desmopressin acetate 100 micrograms/mL. Net price 2.5-mL dropper bottle and catheter = £9.72. Counselling, fluid intake, see above

Injection, desmopressin acetate 4 micrograms/mL. Net price 1-mL amp = £1.10

Desmotabs® (Ferring) PoM

Tablets, scored, desmopressin acetate 200 micrograms, net price 30-tab pack = £29.43. Counselling, fluid intake, see above

DesmoMelt® (Ferring) ▼ PoM

Oral lyophilisates, desmopressin (as acetate) 120 micrograms, net price 30-tab pack = £30.34; 240 micrograms, 30-tab pack = £60.68. Label: 26, counselling, fluid intake, see above

Desmospray® (Ferring) PoM

Nasal spray, desmopressin acetate 10 micrograms/metered spray. Net price 6-mL unit (60 metered sprays) = £25.02. Counselling, fluid intake, see above

Note Children requiring dose of less than 10 micrograms should be given *DDAVP® intranasal solution*

Octim® (Ferring) PoM

Nasal spray, desmopressin acetate 150 micrograms/metered spray, net price 2.5-mL unit (25 metered sprays) = £576.60. Counselling, fluid intake, see above

Injection, desmopressin acetate 15 micrograms/mL, net price 1-mL amp = £19.22

TERLIPRESSIN

Indications bleeding from oesophageal varices

Cautions see under Vasopressin

Contra-indications see under Vasopressin

Breast-feeding see under Vasopressin

Side-effects see under Vasopressin, but effects milder

Dose

- By intravenous injection, 2 mg followed by 1 or 2 mg every 4 to 6 hours until bleeding is controlled, for up to 72 hours

Glypressin® (Ferring) PoM

Injection, terlipressin, powder for reconstitution, net price 1-mg vial with 5 mL diluent = £18.47

Injection, terlipressin 0.12 mg/mL, solution for injection, net price 1-mg (8.5 mL) vial = £19.39

VASOPRESSIN

Indications pituitary diabetes insipidus; bleeding from oesophageal varices

Cautions heart failure, hypertension, asthma, epilepsy, migraine or other conditions which might be aggravated by water retention; avoid fluid overload

Contra-indications vascular disease (especially disease of coronary arteries) unless extreme caution, chronic nephritis (until reasonable blood nitrogen concentrations attained)

Renal impairment see Contra-indications

Pregnancy oxytocic effect in third trimester

Breast-feeding not known to be harmful

Side-effects fluid retention, pallor, tremor, sweating, vertigo, headache, nausea, vomiting, belching, abdominal cramps, desire to defaecate, hypersensitivity reactions (including anaphylaxis), constriction of coronary arteries (may cause anginal attacks and myocardial ischaemia), peripheral ischaemia and rarely gangrene

Dose

- By subcutaneous *or* intramuscular injection, diabetes insipidus, 5–20 units every four hours
- By intravenous infusion, initial control of variceal bleeding, 20 units over 15 minutes

Synthetic vasopressin

Pitressin® (Goldshield) PoM

Injection, argipressin (synthetic vasopressin) 20 units/mL. Net price 1-mL amp = £17.14 (hosp. only)

Antidiuretic hormone antagonists

Demeclocycline (section 5.1.3) can be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable. Demeclocycline is thought to act by directly blocking the renal tubular effect of antidiuretic hormone. Initially 0.9–1.2 g is given daily in divided doses, reduced to 600–900 mg daily for maintenance.

Tolvaptan

Tolvaptan is a vasopressin V_2-receptor antagonist licensed for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion; treatment duration with tolvaptan is determined by the underlying disease and its treatment.

TOLVAPTAN

Indications see notes above

Cautions ensure adequate fluid intake (monitor for dehydration in patients who are fluid-restricted); discontinue if rapid rise in serum sodium (greater than 12 mmol/litre in 24 hours); diabetes mellitus; pseudohyponatraemia associated with diabetes mellitus (exclude before treatment); **interactions:** Appendix 1 (tolvaptan)

Contra-indications anuria; volume depletion; hypovolaemic hyponatraemia; hypernatraemia; impaired perception of thirst

Hepatic impairment use with caution in severe impairment—no information available

Renal impairment no information available in severe impairment

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—present in milk in *animal* studies

Side-effects nausea, constipation, dry mouth; postural hypotension; thirst, decreased appetite, fever, asthenia; hyperglycaemia; urinary frequency;

hyperkalaemia, dehydration, ecchymosis, increased blood creatinine; pruritus; *less commonly* taste disturbance; *also reported* hypernatraemia, hyperuricaemia, hypoglycaemia, syncope, and dizziness

Dose

- ADULT over 18 years, 15 mg once daily, increased as required to max. 60 mg daily

Samsca® (Otsuka) ▼ PoM

Tablets, blue, tolvaptan 15 mg, net price 10-tab pack = £746.80; 30 mg, 10-tab pack = £746.80

6.6 Drugs affecting bone metabolism

6.6.1 Calcitonin and parathyroid hormone
6.6.2 Bisphosphonates and other drugs affecting bone metabolism

See also calcium (section 9.5.1.1), phosphorus (section 9.5.2), vitamin D (section 9.6.4), and oestrogens in postmenopausal osteoporosis (section 6.4.1.1).

Osteoporosis

Osteoporosis occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids (glucocorticosteroids). Other risk factors for osteoporosis include low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause.

Those at risk of osteoporosis should maintain an adequate intake of **calcium and vitamin D** and any deficiency should be corrected by increasing dietary intake or taking supplements.

Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements (section 9.5.1.1 and section 9.6.4). Reversible secondary causes of osteoporosis such as hyperthyroidism, hyperparathyroidism, osteomalacia or hypogonadism should be excluded, in both men and women, before treatment for osteoporosis is initiated.

Postmenopausal osteoporosis The **bisphosphonates** (alendronic acid, disodium etidronate, and risedronate, section 6.6.2) are effective for preventing postmenopausal osteoporosis. **Hormone replacement therapy** (HRT section 6.4.1.1) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The CSM has advised that HRT should **not** be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT. **Calcitonin** (section 6.6.1) may be considered for those at high risk of osteoporosis for whom a bisphosphonate is unsuitable. Women of Afro-Caribbean origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

Postmenopausal osteoporosis may be *treated* with a **bisphosphonate** (section 6.6.2). The bisphosphonates (such as alendronate, etidronate, and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures. If bisphosphonates are unsuitable **calcitriol** (section 9.6.4), **calcitonin** or **strontium ranelate** (section 6.6.2) may be considered. Calcitonin [unlicensed indication] may also be useful for pain relief for up to 3 months after a vertebral fracture if other analgesics are ineffective. **Parathyroid hormone**, and **teriparatide** (section 6.6.1) have been introduced for the treatment of postmenopausal osteoporosis.

Raloxifene (section 6.4.1.1) is licensed for the *prophylaxis* and *treatment* of vertebral fractures in postmenopausal women.

NICE guidance

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008)

Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fractures in the following susceptible postmenopausal women:

- Women over 70 years who have an independent risk factor for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis) *or* an indicator of low bone mineral density (body mass index under 22 kg/m^2, ankylosing spondylitis, Crohn's disease, prolonged immobility, untreated premature menopause, or rheumatoid arthritis) **and** confirmed osteoporosis
- Women aged 65–69 years who have an independent risk factor for fracture **and** confirmed osteoporosis
- Women under 65 years who have an independent risk factor for fracture **and** at least one additional indicator of low bone mineral density **and** confirmed osteoporosis

Risedronate or **etidronate** are recommended as alternatives for women:

- in whom alendronate is contra-indicated or not tolerated **and**
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance[1]

Strontium ranelate is recommended as an alternative for women:

- in whom alendronate and either risedronate or editronate are contra-indicated or not tolerated **and**
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance[1]

Raloxifene is **not** recommended as a treatment option in postmenopausal women for primary prevention of osteoporotic fractures.

1. Available at www.nice.org.uk/TA160

NICE guidance

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate, and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (October 2008)

This guideline recommends treatment options for the secondary prevention of osteoporotic fractures in postmenopausal women with confirmed osteoporosis who have also sustained a clinically apparent osteoporotic fracture.

Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fractures in susceptible postmenupausal women.

Risedronate or **etidronate** are recommended as alternatives for women:

- in whom alendronate is contra-indicated or not tolerated **and**
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis, as indicated in the full NICE guidance[1]

Strontium ranelate or **raloxifene** are recommended as alternatives for women:

- in whom alendronate and either risedronate or editronate are contra-indicated or not tolerated **and**
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance[1]

Teriparatide is recommended as an alternative for women:

- in whom alendronate and either risedronate or editronate, *or* strontium ranelate are contra-indicated or not tolerated, **or** where treatment with alendronate, risedronate or editronate has been unsatisfactory (indicated by another fragility fracture and a decline in bone mineral density despite treatment for 1 year) **and**
- who comply with particular combinations of bone mineral density measurement, age, and number of fractures, as indicated in the full NICE guidance[1]

Corticosteroid-induced osteoporosis To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis (section 3.2).

Patients taking (or who are likely to take) an oral corticosteroid for 3 months or longer should be assessed and where necessary given prophylactic treatment; those aged over 65 years are at greater risk. Patients taking oral corticosteroids who have sustained a low-trauma fracture should receive treatment for osteoporosis. The therapeutic options for *prophylaxis* and *treatment* of corticosteroid-induced osteoporosis are the same:

- a bisphosphonate (section 6.6.2);
- calcitriol [unlicensed indication] (section 9.6.4);
- hormone replacement (HRT in women (section 6.4.1), testosterone in men [unlicensed indication] (section 6.4.2)).

1. Available at www.nice.org.uk/TA161

6.6.1 Calcitonin and parathyroid hormone

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. **Calcitonin (salmon)** (**salcatonin**, synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in some patients with hypercalcaemia (notably when associated with malignant disease). Calcitonin is licensed for treatment of Paget's disease of bone. It can also be used in the prevention and treatment of postmenopausal osteoporosis (see section 6.6).

Recombinant **parathyroid hormone** is used for the treatment of postmenopausal osteoporosis. **Teriparatide** (a recombinant fragment of parathyroid hormone) is used for the treatment of postmenopausal osteoporosis, osteoporosis in men at increased risk of fracture, and corticosteroid-induced osteoporosis. *The Scottish Medicines Consortium*, p. 4 has advised (February 2007) that parathyroid hormone (*Preotact®*) should be initiated by specialists experienced in the treatment of osteoporosis; also that the use of teriparatide (*Forsteo®*) (December 2003) in postmenopausal women should be restricted to the treatment of established (severe) osteoporosis and should be initiated by specialists experienced in the treatment of osteoporosis.

Cinacalcet (section 9.5.1.2) is licensed for the treatment of hypercalcaemia in parathyroid carcinoma.

CALCITONIN (SALMON)/ SALCATONIN

Indications see under Dose

Cautions history of allergy (skin test advised); heart failure

Contra-indications hypocalcaemia

Renal impairment use with caution

Pregnancy avoid unless potential benefit outweighs risk (toxicity in *animal* studies)

Breast-feeding avoid; inhibits lactation in *animals*

Side-effects nausea, vomiting, diarrhoea, abdominal pain; flushing; dizziness, headache, taste disturbances; musculoskeletal pain; with nasal spray nose and throat irritation, rhinitis, sinusitis and epistaxis; *less commonly* diuresis, oedema, cough, visual disturbances, injection-site reactions, rash, hypersensitivity reactions including pruritus

Dose

- Hypercalcaemia of malignancy (see also section 9.5.1.2), ADULT over 18 years, by subcutaneous *or* intramuscular injection, 100 units every 6–8 hours adjusted according to response; max. 400 units every 6–8 hours; in severe or emergency cases, by intravenous infusion, up to 10 units/kg over at least 6 hours
- Paget's disease of bone, ADULT over 18 years, by subcutaneous *or* intramuscular injection, 50 units 3 times weekly to 100 units daily adjusted according to response
- Postmenopausal osteoporosis to reduce risk of vertebral fractures, intranasally, 200 units (1 spray) into one nostril daily, with dietary calcium and vitamin D supplements (section 9.5.1.1 and section 9.6.4)
- Prevention of acute bone loss due to sudden immobility, ADULT over 18 years, by subcutaneous *or* intramuscular injection, 100 units daily in 1–2 divided doses for 2–4 weeks, reduced to 50 units daily at start of mobilisation and continued until fully mobile

Miacalcic® (Novartis) PoM

Nasal spray ▼, calcitonin (salmon) 200 units/metered spray, net price 2-mL unit (approx. 14 metered sprays) = £16.79

Injection, calcitonin (salmon) 50 units/mL, net price 1-mL amp = £3.42; 100 units/mL, 1-mL amp = £6.85; 200 units/mL, 2-mL vial = £30.75

For subcutaneous or intramuscular injection and for dilution and use as an intravenous infusion

PARATHYROID HORMONE

(Human recombinant parathyroid hormone)

Indications treatment of osteoporosis in postmenopausal women at high risk of fractures (to reduce the risk of vertebral fractures) (see also notes above)

Cautions monitor serum or urinary calcium concentration at 1, 3 and 6 months after initiation of treatment (consult product literature for guidance if serum-calcium concentration raised); active or previous urolithiasis; concomitant cardiac glycosides

Contra-indications previous radiation therapy to skeleton, pre-existing hypercalcaemia, metabolic bone disease (including hyperparathyroidism and Paget's disease), unexplained raised levels of alkaline phosphatase

Hepatic impairment avoid

Renal impairment avoid if eGFR less than 30 mL/minute/1.73m^2

Pregnancy avoid

Breast-feeding avoid

Side-effects nausea, vomiting, dyspepsia, constipation, diarrhoea; palpitation; headache, dizziness, fatigue, asthenia; transient hypercalcaemia, hypercalciuria; muscle cramp, pain in extremities, back pain; injection-site reactions; *less commonly* abdominal pain, altered sense of smell, taste disturbance, anorexia, influenza, hyperuricaemia

Dose

- By subcutaneous injection, 100 micrograms daily, max. duration of treatment 24 months

Preotact® (Nycomed) PoM

Injection, dual-chamber cartridge containing powder for reconstitution, parathyroid hormone (rdna) and diluent, net price 1.61-mg (14-dose) cartridge = £156.24. For use with *Preotact®* pen device.

TERIPARATIDE

Indications treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures; treatment of corticosteroid-induced osteoporosis; see also notes above

Contra-indications pre-existing hypercalcaemia, skeletal malignancies or bone metastases, metabolic bone diseases, including Paget's disease and hyperparathyroidism, unexplained raised alkaline phosphatase, previous radiation therapy to the skeleton

Renal impairment caution in moderate impairment; avoid if severe

Pregnancy avoid

Breast-feeding avoid

Side-effects gastro-intestinal disorders (including nausea, reflux and haemorrhoids); palpitation; dyspnoea; headache, fatigue, asthenia, depression, dizziness, vertigo; anaemia, increased sweating, muscle cramps, sciatica, myalgia, arthralgia; *less commonly* urinary disorders, hypercalcaemia; injection-site reactions; *rarely* hypersensitivity reactions

Dose

- By subcutaneous injection, 20 micrograms daily; max. duration of treatment 18 months (course not to be repeated)

Forsteo® (Lilly) PoM

Injection, teriparatide 250 micrograms/mL, net price 2.4-mL prefilled pen = £271.88, 3-mL prefilled pen = £271.88

Note 3-ml prefilled pen intended for 28 doses

6.6.2 Bisphosphonates and other drugs affecting bone metabolism

Bisphosphonates

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover. Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; **alendronic acid** or **risedronate sodium** are considered the drugs of choice for these conditions, but **disodium etidronate** may be considered if these drugs are unsuitable or not tolerated (see also section 6.6).

Bisphosphonates are also used in the treatment of *Paget's disease*, hypercalcaemia of malignancy (section 9.5.1.2), and in bone metastases in breast cancer (section 8.3.4.1). Disodium etidronate can impair bone

mineralisation when used continuously or in high doses (such as in the treatment of *Paget's disease*).

MHRA/CHM advice

Bisphosphonates: osteonecrosis of the jaw (October 2007 and November 2009)

The risk of osteonecrosis of the jaw is substantially greater for patients receiving intravenous bisphosphonates in the treatment of cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.

Risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zolendronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease.

All patients receiving bisphosphonates for cancer should have a dental check-up (and any necessary remedial work should be performed) before bisphosphonate treatment. However, urgent bisphosphonate treatment should not be delayed, and a dental check-up should be carried out as soon as possible in these patients. All other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health.

During bisphosphonate treatment patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms.

ALENDRONIC ACID

Indications see under Dose

Cautions upper gastro-intestinal disorders (dysphagia, symptomatic oesophageal disease, gastritis, duodenitis, or ulcers—see also under Contra-indications and Side-effects); history (within 1 year) of ulcers, active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract; correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting and monitor serum-calcium concentration during treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, above); exclude other causes of osteoporosis; atypical stress fractures reported (discontinue unless benefits of continued treatment clearly outweigh risks); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications abnormalities of oesophagus and other factors which delay emptying (e.g. stricture or achalasia), hypocalcaemia

Renal impairment avoid if eGFR less than 35 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding no information available

Side-effects oesophageal reactions (see below), abdominal pain and distension, dyspepsia, regurgitation, melaena, diarrhoea or constipation, flatulence, musculoskeletal pain, headache; *rarely* rash, pruritus, erythema, photosensitivity, uveitis, scleritis, transient decrease in serum calcium and phosphate; nausea, vomiting, gastritis, peptic ulceration, hypersensitivity reactions (including urticaria and angioedema), and atypical stress fractures with long-term use also reported; myalgia, malaise, and fever at initiation of treatment; *very rarely* severe skin reactions (including Stevens-Johnson syndrome), osteonecrosis of the jaw (see MHRA/CHM advice, above)

Oesophageal reactions Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain

Dose

- Treatment of postmenopausal osteoporosis, 10 mg daily *or* 70 mg once weekly
- Treatment of osteoporosis in men, 10 mg daily
- Prevention and treatment of corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy, 10 mg daily

Counselling Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet

Alendronic acid (Non-proprietary) PoM

Tablets, alendronic acid (as sodium alendronate) 10 mg, net price 28-tab pack = £1.65.Counselling, administration

Fosamax® (MSD) PoM

Tablets, alendronic acid (as sodium alendronate) 10 mg, 28-tab pack = £23.12. Counselling, administration

Alendronic Acid Once-Weekly (Non-proprietary) PoM

Tablets, alendronic acid (as sodium alendronate) 70 mg, net price 4-tab pack = £1.05.Counselling, administration

Fosamax® Once Weekly (MSD) PoM

Tablets, alendronic acid (as sodium alendronate) 70 mg, net price 4-tab pack = £22.80. Counselling, administration

With colecalciferol

For prescribing information on colecalciferol, see section 9.6.4

Fosavance® (MSD) PoM

Tablets, alendronic acid (as sodium alendronate) 70 mg, colecalciferol 70 micrograms (2 800 units), net price 4-tab pack = £22.80. Counselling, administration

Dose treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency, 1 tablet once weekly

Counselling Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet

DISODIUM ETIDRONATE

Indications see under Dose

Cautions consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, above); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications not indicated for osteoporosis in presence of hypercalcaemia or hypercalciuria or for osteomalacia

Renal impairment reduce dose in mild impairment; avoid in moderate to severe renal impairment

Pregnancy avoid

Breast-feeding no information available

Side-effects nausea, diarrhoea or constipation, abdominal pain; increased bone pain in Paget's disease, also increased risk of fractures with high doses in Paget's disease (discontinue if fractures occur); rarely exacerbation of asthma, skin reactions (including angioedema, rash, urticaria and pruritus), transient hyperphosphataemia, headache, paraesthesia, peripheral neuropathy reported; blood disorders (including leucopenia, agranulocytosis and pancytopenia) also reported; *very rarely* osteonecrosis of the jaw (see MHRA/CHM advice, p. 472)

Dose

- Paget's disease of bone, by mouth, 5 mg/kg as a single daily dose for up to 6 months; doses above 10 mg/kg daily for up to 3 months may be used with caution but doses above 20 mg/kg daily are not recommended; after interval of not less than 3 months may be repeated where evidence of reactivation—including biochemical indices (avoid premature retreatment)
  Monitoring Serum phosphate, serum alkaline phosphatase and (if possible) urinary hydroxyproline should be measured before starting and at intervals of 3 months—consult product literature for further details
- Osteoporosis, see under *Didronel PMO®*
  Counselling Avoid food for at least 2 hours before and after oral treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids

Didronel® (Warner Chilcott) PoM

Tablets, disodium etidronate 200 mg. Net price 60-tab pack = £19.48. Counselling, food and calcium (see above)

With calcium carbonate

For prescribing information on calcium carbonate see section 9.5.1.1

Didronel PMO® (Warner Chilcott) PoM

Tablets, 14 white, disodium etidronate 400 mg; 76 pink, effervescent, calcium carbonate 1.25 g (*Cacit®*). Net price per pack = £19.89. Label: 10, patient information leaflet, counselling, food and calcium (see above)

Dose treatment of osteoporosis, prevention of bone loss in postmenopausal women (particularly if hormone replacement therapy inappropriate), and prevention and treatment of corticosteroid-induced osteoporosis, given in 90-day cycles, 1 *Didronel®* tablet daily for 14 days, then 1 *Cacit®* tablet daily for 76 days

DISODIUM PAMIDRONATE

Disodium pamidronate was formerly called aminohydroxypropylidenediphosphonate disodium (APD)

Indications see under Dose

Cautions assess renal function before each dose; ensure adequate hydration; cardiac disease (especially in elderly); previous thyroid surgery (risk of hypocalcaemia); monitor serum electrolytes, calcium and phosphate—possibility of convulsions due to electrolyte changes; avoid concurrent use with other bisphosphonates; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); **interactions:** Appendix 1 (bisphosphonates)

Driving Patients should be warned against driving or operating machinery immediately after treatment (somnolence or dizziness can occur)

Hepatic impairment caution in severe hepatic impairment—no information available

Renal impairment max. infusion rate 20 mg/hour; avoid if eGFR less than 30 mL/minute/1.73 m^2, except in life-threatening hypercalcaemia if benefit outweighs risk; if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value

Pregnancy avoid

Breast-feeding avoid

Side-effects hypophosphataemia, fever and influenza-like symptoms (sometimes accompanied by malaise, rigors, fatigue and flushes); nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation; symptomatic hypocalcaemia (paraesthesia, tetany), hypomagnesaemia, headache, insomnia, drowsiness; hypertension; anaemia, thrombocytopenia, lymphocytopenia; rash; arthralgia, myalgia, bone pain; *rarely* muscle cramps, dyspepsia, agitation, confusion, dizziness, lethargy; leucopenia, hypotension, pruritus, hyperkalaemia or hypokalaemia, and hypernatraemia; osteonecrosis of the jaw (see also MHRA/CHM advice, p. 472), isolated cases of seizures, hallucinations, haematuria, acute renal failure, deterioration of renal disease, conjunctivitis and other ocular symptoms; atrial fibrillation, and reactivation of herpes simplex and zoster also reported; also injection-site reactions

Dose

- By slow intravenous infusion (via cannula in a relatively large vein), see also Appendix 6

  Hypercalcaemia of malignancy, according to serum calcium concentration 15–60 mg in single infusion or in divided doses over 2–4 days; max. 90 mg per treatment course

  Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma, 90 mg every 4 weeks (or every 3 weeks to coincide with chemotherapy in breast cancer)

  Paget's disease of bone, 30 mg once a week for 6 weeks (total dose 180 mg) *or* 30 mg in first week then 60 mg every other week (total dose 210 mg); max. total 360 mg (in divided doses of 60 mg) per treatment course; may be repeated every 6 months
- CHILD not recommended

Calcium and vitamin D supplements Oral supplements are advised to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases or multiple myeloma at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and in those with Paget's disease

Disodium pamidronate (Non-proprietary) PoM

Concentrate for intravenous infusion, disodium pamidronate 3 mg/mL, net price 5-mL vial = £27.50, 10-mL vial = £55.00; 6 mg/mL, 10-mL vial = £95.00; 9 mg/mL, 10-mL vial = £165.00; 15 mg/mL, 1-mL vial = £29.83, 2-mL vial = £59.66, 4-mL vial = £119.32, 6-mL vial £170.46

Aredia Dry Powder® (Novartis) PoM

Injection, powder for reconstitution, disodium pamidronate, for use as an infusion. Net price 15-mg vial = £29.83; 30-mg vial = £59.66; 90-mg vial = £170.45 (all with diluent)

IBANDRONIC ACID

Indications see under Dose

Cautions consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); monitor renal function and serum calcium, phosphate and magnesium; cardiac disease (avoid fluid overload); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications hypocalcaemia; *oral route* abnormalities of the oesophagus and other factors which delay emptying (e.g. stricture or achalasia)

Renal impairment for treatment of osteoporosis, avoid if eGFR less than 30 mL/minute/1.73 m^2; for reduction of bone damage in bone metastases, if eGFR 30–50 mL/minute/1.73 m^2 reduce *intravenous dose* to 4 mg and infuse over 1 hour, reduce *oral dose* to 50 mg on alternative days, if eGFR less than 30 mL/minute/1.73 m^2 reduce *intravenous dose* to 2 mg and infuse over 1 hour, reduce *oral dose* to 50 mg once weekly

Pregnancy avoid

Breast-feeding avoid—present in milk in *animal* studies

Side-effects hypocalcaemia, hypophosphataemia, influenza-like symptoms (including fever, chills, and muscle pain), bone pain; oesophageal reactions (see below), diarrhoea, nausea, vomiting, gastritis, abdominal pain, dyspepsia, pharyngitis; headache, asthenia, rash; *rarely* anaemia, hypersensitivity reactions (pruritus, bronchospasm and angioedema reported); urticaria; injection-site reactions; *very rarely* osteonecrosis of the jaw (see MHRA/CHM advice, p. 472)

Oesophageal reactions Severe oesophageal reactions reported with all **oral** bisphosphonates; patients should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn

Dose

- Reduction of bone damage in bone metastases in breast cancer, by mouth, 50 mg daily, *or* by intravenous infusion, 6 mg every 3–4 weeks
- Hypercalcaemia of malignancy by intravenous infusion, according to serum calcium concentration, 2–4 mg in single infusion
- Treatment of postmenopausal osteoporosis, by mouth, 150 mg once a month *or* by intravenous injection over 15–30 seconds, 3 mg every 3 months
- CHILD not recommended

Counselling Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes (*Bondronat*® tablets, 50 mg) or 1 hour (*Bonviva*® tablets, 150 mg) before first food or drink (other than water) of the day, or another oral medicine; patient should stand or sit upright for at least 1 hour after taking tablet

Bondronat® (Roche) PoM

Tablets, f/c, ibandronic acid 50 mg, net price 28-tab pack = £183.69. Counselling, administration

Concentrate for intravenous infusion, ibandronic acid 1 mg/mL, net price 2-mL amp = £89.36, 6-mL vial = £183.69

Bonviva® (Roche) PoM

Tablets, f/c, ibandronic acid 150 mg, net price 1-tab pack = £18.40, 3-tab pack = £55.21. Counselling, administration

Injection, ibandronic acid 1 mg/mL, net price 3-mL prefilled syringe = £68.64

RISEDRONATE SODIUM

Indications see under Dose

Cautions oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia—see also under Side-effects); correct hypocalcaemia before starting, correct other disturbances of bone and mineral metabolism (e.g. vitamin-D deficiency) at onset of treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications hypocalcaemia (see Cautions above)

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding avoid

Side-effects abdominal pain, dyspepsia, nausea, diarrhoea, constipation, headache, musculoskeletal pain; *less commonly* oesophagitis, oesophageal ulcer, dysphagia, gastritis, duodenitis, uveitis; *rarely* glossitis, oesophageal stricture; *also reported* gastroduodenal ulceration, hepatic disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, hair loss, osteonecrosis of the jaw (see MHRA/CHM advice, p. 472)

Oesophageal reactions Patients should be advised to stop taking the tablets and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn

Dose

- Paget's disease of bone, 30 mg daily for 2 months; may be repeated if necessary after at least 2 months
- Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, 5 mg daily *or* 35 mg once weekly
- Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, 5 mg daily
- Treatment of osteoporosis in men at high risk of fractures, 35 mg once weekly
- CHILD see *BNF for Children*

Counselling Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day **or**, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising

Actonel® (Warner Chilcott) PoM

Tablets, f/c, risedronate sodium 5 mg (yellow), net price 28-tab pack = £17.99; 30 mg (white), 28-tab pack = £143.95. Counselling, administration, food and calcium (see above)

Actonel Once a Week® (Warner Chilcott) PoM

Tablets, f/c, orange, risedronate sodium 35 mg, net price 4-tab pack = £19.12. Counselling, administration, food and calcium (see above)

With calcium carbonate and colecalciferol

For cautions, contra-indications, and side-effects of calcium carbonate, see section 9.5.1.1 and of colecalciferol, see section 9.6.4

Actonel® Combi (Warner Chilcott) PoM

Tablets, f/c, orange, risedronate sodium 35 mg (*Actonel Once a Week*®);

Granules, effervescent, lemon flavour, calcium carbonate 2.5 g (calcium 1 g or Ca^{2+} 25 mmol) and colecalciferol 22 micrograms (880 units)/sachet, net price 24-sachet plus 4-tab pack = £19.12. Counselling, administration, food and calcium (see above)

Dose treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, given in weekly cycles, 1 *Actonel Once a Week®* tablet on the first day followed by 1 calcium and colecalciferol sachet daily for 6 days

Counselling Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet. Granules should be stirred into a glass of water and after dissolution complete taken immediately

SODIUM CLODRONATE

Indications see under Dose

Cautions monitor renal and hepatic function and white cell count; also monitor serum calcium and phosphate periodically; renal dysfunction reported in patients receiving concomitant NSAIDs; maintain adequate fluid intake during treatment; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications acute gastro-intestinal inflammatory conditions

Renal impairment use half normal dose if eGFR 10–30 mL/minute/1.73 m^2; avoid if eGFR less than 10 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding no information available

Side-effects nausea, diarrhoea; skin reactions; bronchospasm; *very rarely* osteonecrosis of the jaw (see MHRA/CHM advice, p. 472)

Dose

- Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma, by mouth, 1.6 g daily in single or 2 divided doses increased if necessary to a max. of 3.2 g daily

  Counselling Avoid food for 1 hour before and after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake

Bonefos® (Bayer Schering) PoM

Capsules, yellow, sodium clodronate 400 mg, net price 120-cap pack = £139.83. Counselling, food and calcium

Tablets, f/c, scored, sodium clodronate 800 mg, net price 60-tab pack = £146.43. Counselling, food and calcium

Clasteon® (Beacon) PoM

Capsules, blue/white, sodium clodronate 400 mg, net price 30-cap pack = £34.96, 120-cap pack = £139.83. Counselling, food and calcium

Loron 520® (Roche) PoM

Tablets, f/c, scored, sodium clodronate 520 mg, net price 60-tab pack = £152.59. Label: 10, patient information leaflet, counselling, food and calcium

Dose 2 tablets daily in single or two divided doses; may be increased to max. 4 tablets daily

TILUDRONIC ACID

Indications Paget's disease of bone

Cautions correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting; avoid concomitant use of indometacin; consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); **interactions:** Appendix 1 (bisphosphonates)

Contra-indications juvenile Paget's disease

Renal impairment use with caution and monitor renal function regularly if eGFR 30–90 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid

Breast-feeding avoid—no information available

Side-effects stomach pain, nausea, diarrhoea; rarely asthenia, dizziness, headache and skin reactions; *very rarely* osteonecrosis of the jaw (see MHRA/CHM advice, p. 472)

Dose

- 400 mg daily as a single dose for 12 weeks; may be repeated if necessary after 6 months

  Counselling Avoid food for 2 hours before and after treatment, particularly calcium-containing products e.g. milk; also avoid antacids

Skelid® (Sanofi-Aventis) PoM

Tablets, tiludronic acid (as tiludronate disodium) 200 mg. Net price 28-tab pack = £95.14. Counselling, food and calcium

ZOLEDRONIC ACID

Indications see under preparations

Cautions correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting; monitor serum electrolytes, calcium, phosphate and magnesium; cardiac disease (avoid fluid overload); consider dental check-up before initiating bisphosphonate (risk of osteonecrosis of the jaw, see MHRA/CHM advice, p. 472); **interactions:** Appendix 1 (bisphosphonates)

Renal function Renal impairment and renal failure have been reported. Before each dose ensure patient is hydrated and assess renal function. Continue to monitor renal function in patients at risk, such as those with pre-existing renal impairment, those of advanced age, those taking concomitant nephrotoxic drugs or diuretics, or those who are dehydrated. Use with caution with concomitant medicines that affect renal function

Contra-indications women of child-bearing potential

Hepatic impairment caution in severe hepatic impairment—limited information available

Renal impairment avoid if serum creatinine above 400 micromol/litre in tumour-induced hypercalcaemia; in advanced malignancies involving bone, if eGFR 50–60 mL/minute/1.73 m^2 reduce dose to 3.5 mg every 3–4 weeks, if eGFR 40–50 mL/minute/1.73 m^2 reduce dose to 3.3 mg every 3–4 weeks, if eGFR 30–40 mL/minute/1.73 m^2 reduce dose to 3 mg every 3–4 weeks, avoid if eGFR less than 30 mL/minute/1.73 m^2 (or if serum creatinine greater than 265 micromol/litre); if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value; avoid in Paget's disease, treatment of postmenopausal osteoporosis and osteoporosis in men if

eGFR less than 35 mL/minute/1.73 m^2; see also Cautions above

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid—no information available

Side-effects hypophosphataemia, anaemia, influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors; gastro-intestinal disturbances; atrial fibrillation; headache, dizziness, conjunctivitis, renal impairment (rarely acute renal failure); *less commonly* anorexia, taste disturbance, dry mouth, stomatitis, chest pain, hypertension, hypotension, dyspnoea, cough, paraesthesia, tremor, anxiety, lethargy, sleep disturbance, blurred vision, weight gain, pruritus, rash, sweating, muscle cramps, haematuria, proteinuria, urinary frequency, hypersensitivity reactions (including angioedema), asthenia, peripheral oedema, thrombocytopenia, leucopenia, hypomagnesaemia, hypokalaemia, also injection-site reactions; *rarely* bradycardia, confusion, hyperkalaemia, hypernatraemia, pancytopenia, osteonecrosis of the jaw (see also MHRA/CHM advice, p. 472); *very rarely* uveitis and episcleritis

Dose

- See under preparations

Aclasta® (Novartis) ▼ PoM

Intravenous infusion, zoledronic acid 50 micrograms/mL, net price 100-mL bottle = £266.72

Dose treatment of Paget's disease of bone, by intravenous infusion, 5 mg as a single dose over at least 15 minutes

Note At least 500 mg elemental calcium twice daily (with vitamin D, section 9.6.4) for at least 10 days is recommended following infusion

Treatment of postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis), by intravenous infusion, 5 mg over at least 15 minutes once a year

Note In patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair; before first infusion give 50 000–125 000 units of vitamin D (section 9.6.4)

Note The *Scottish Medicines Consortium* (p. 4) has advised (February 2008) that in postmenopausal women *Aclasta®* is accepted for restricted use within the NHS Scotland for the treatment of osteoporosis in those for whom oral treatment options for osteoporosis are inappropriate and when initiated by a specialist

Zometa® (Novartis) PoM

Concentrate for intravenous infusion, zoledronic acid, 800 micrograms/mL, net price 5-mL (4-mg) vial = £183.30

Dose reduction of bone damage in advanced malignancies involving bone, by intravenous infusion, 4 mg over at least 15 minutes every 3–4 weeks; CHILD not recommended

Note Calcium 500 mg daily and vitamin D 400 units daily should also be taken

Hypercalcaemia of malignancy, by intravenous infusion, 4 mg as a single dose over at least 15 minutes; CHILD not recommended

Note The *Scottish Medicines Consortium* (p. 4) has advised (May 2003) that for the prevention of skeletal related events *Zometa®* is accepted for restricted use within NHS Scotland for the treatment of patients with breast cancer and multiple myeloma if prescribed by an oncologist

Denosumab

Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption. It is licensed for the treatment of postmenopausal osteoporosis in women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer.

NICE guidance

Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010)

Denosumab is recommended as a treatment option for the *primary prevention* of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures:

- who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contra-indication to, those treatments **and**
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance (available at www.nice.org.uk/TA204).

Denosumab is recommended as a treatment option for the *secondary prevention* of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contra-indication to, those treatments.

DENOSUMAB

Indications see notes above

Cautions correct hypocalcaemia and vitamin D deficiency before starting (monitor plasma-calcium concentration during therapy); consider dental check-up and carry out invasive procedures before initiating treatment (risk of osteoneocrosis of the jaw)

Renal impairment increased risk of hypocalcaemia if eGFR less than 30 mL/minute/1.73 m^2—monitor plasma-calcium concentration

Pregnancy avoid

Breast-feeding avoid

Side-effects constipation; urinary tract infection, upper respiratory tract infection; pain in extremity, sciatica; cataracts, rash; *less commonly* diverticulitis, cellulitis (seek prompt medical attention), ear infection, eczema; *rarely* osteonecrosis of the jaw; *very rarely* hypocalcaemia

Dose

- By subcutaneous injection, 60 mg every 6 months
  Note Supplement with calcium and vitamin D

Prolia® (Amgen) ▼ PoM

Injection, denosumab 60 mg/mL, net price 1-mL prefilled syringe = £183.00

Strontium ranelate

Strontium ranelate stimulates bone formation and reduces bone resorption. It is licensed for the treatment of postmenopausal osteoporosis. The *Scottish Medicines Consortium* (p. 4) has advised (July 2005) that treatment with strontium ranelate should be restricted to those patients in whom bisphosphonates are contra-indicated or not tolerated, and then only in women aged over 75 years with a previous fracture and low bone mineral density or in other women at equivalent risk.

STRONTIUM RANELATE

Indications see notes above

Cautions predisposition to thromboembolism; interferes with colorimetric measurements of calcium in blood and urine; **interactions**: Appendix 1 (strontium ranelate)

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy avoid—toxicity in *animal* studies

Breast-feeding avoid

Side-effects nausea, diarrhoea; venous thromboembolism; headache; dermatitis, eczema; *very rarely* vomiting, abdominal pain, stomatitis, and hypersensitivity reactions, including rash, pruritus, urticaria and angioedema—see Severe Allergic Reactions, below

Severe allergic reactions

Severe allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), have been reported in patients taking strontium ranelate. DRESS starts with rash, fever, swollen glands, and increased white cell count, and it can affect the liver, kidneys and lungs; DRESS can also be fatal.

Patients should be advised to stop taking strontium ranelate and consult their doctor immediately if skin rash develops. Treatment with strontium ranelate should not be restarted.

Dose

- 2 g once daily in water, preferably at bedtime

  Counselling Avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules

Protelos® (Servier) PoM

Granules, yellow, strontium ranelate, 2 g/sachet, net price 28-sachets = £25.60. Label: 5, 13, counselling, food and calcium

Excipients include aspartame (section 9.4.1)

6.7 Other endocrine drugs

6.7.1 Bromocriptine and other dopaminergic drugs
6.7.2 Drugs affecting gonadotrophins
6.7.3 Metyrapone and trilostane
6.7.4 Somatomedins

6.7.1 Bromocriptine and other dopaminergic drugs

Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary. Bromocriptine is used for the treatment of galactorrhoea, and for the treatment of prolactinomas (when it reduces both plasma prolactin concentration and tumour size). Bromocriptine also inhibits the release of growth hormone and is sometimes used in the treatment of acromegaly, but somatostatin analogues (such as octreotide, section 8.3.4.3) are more effective.

Cabergoline has actions and uses similar to those of bromocriptine, but its duration of action is longer. It has similar side-effects to bromocriptine, however patients intolerant of bromocriptine may be able to tolerate cabergoline (and *vice versa*).

Quinagolide is a non-ergot dopamine D_2 agonist; it has actions and uses similar to those of ergot-derived dopamine agonists, but its side-effects differ slightly.

Cautions see notes below; also bromocriptine and cabergoline should be used with caution in patients with a history of peptic ulcer, particularly in acromegalic patients. Treatment should be withdrawn if gastro-intestinal bleeding occurs. In hyperprolactinaemic patients, the source of the hyperprolactinaemia should be established (i.e. exclude pituitary tumour before treatment). Bromocriptine and cabergoline should be used with caution in patients with Raynaud's syndrome and cardiovascular disease (see also Contra-indications under Bromocriptine, below). Monitor for fibrotic disease (see Fibrotic Reactions, below). Caution is also advised in patients with a history of serious mental disorders (especially psychotic disorders) and in those with acute porphyria (see section 9.8.2). Tolerance may be reduced by alcohol.

Contra-indications Bromocriptine and cabergoline should not be used in patients with hypersensitivity to ergot alkaloids. They are contra-indicated in those with cardiac valvulopathy (exclude before treatment, see Fibrotic Reactions, below). They should also be avoided in pre-eclampsia (see also Contra-indications under Bromocriptine, below).

Side-effects Nausea, constipation, and headache are common side-effects of bromocriptine and cabergoline. Paraesthesia has been reported rarely. Other reported side-effects include hypotension (see also Hypotensive Reactions, below), dyskinesia, pathological gambling, increased libido, hypersexuality, leg cramps, allergic skin reactions, alopecia, and peripheral oedema. Bromocriptine and cabergoline have been associated with pleuritis, pleural effusion, cardiac valvulopathy, pericardial effusion, constrictive pericarditis, and retroperitoneal, pleural, and pulmonary fibrosis (see Fibrotic Reactions).

Fibrotic reactions

Ergot-derived dopamine-receptor agonists, bromocriptine, cabergoline, lisuride [discontinued], and pergolide have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions.

Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for chronic endocrine disorders (excludes suppression of lactation) or Parkinson's disease; it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline or pergolide should be regularly monitored for cardiac fibrosis, by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

Driving

Sudden onset of sleep Excessive daytime sleepiness and sudden onset of sleep can occur with dopaminergic drugs.

Patients starting treatment with these drugs should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery.

Patients who have suffered excessive sedation or sudden onset of sleep should refrain from driving or operating machines until those effects have stopped recurring.

Hypotensive reactions Hypotensive reactions can be disturbing in some patients during the first few days of treatment with bromocriptine, cabergoline, or quinagolide—monitor blood pressure for a few days after starting treatment and following dosage increases; particular care should be exercised when driving or operating machinery.

Suppression of lactation Although bromocriptine and cabergoline are licensed to suppress lactation, they are **not** recommended for routine suppression (or for the relief of symptoms of postpartum pain and engorgement) that can be adequately treated with simple analgesics and breast support. If a dopamine-receptor agonist is required, cabergoline is preferred. Quinagolide is not licensed for the suppression of lactation.

BROMOCRIPTINE

Indications see notes above and under Dose; Parkinson's disease (section 4.9.1)

Cautions see notes above; also specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinoma; contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration); **interactions:** Appendix 1 (bromocriptine)

Contra-indications see notes above; also hypertension in postpartum women or in puerperium (see also below)

Postpartum or puerperium Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression—caution with antihypertensive therapy and avoid other ergot alkaloids. Discontinue immediately if hypertension, unremitting headache, or signs of CNS toxicity develop

Hepatic impairment dose reduction may be necessary

Pregnancy see Cautions above

Breast-feeding suppresses lactation; avoid breast feeding for about 5 days if lactation prevention fails

Side-effects see notes above; also drowsiness (see also Driving, above), nasal congestion; *less commonly* vomiting, postural hypotension, fatigue, dizziness, dry mouth; also, particularly with *high doses*, confusion, psychomotor excitation, hallucinations; *rarely* diarrhoea, gastro-intestinal bleeding, gastric ulcer, abdominal pain, tachycardia, bradycardia, arrhythmia, insomnia, psychosis, visual disturbances, tinnitus; *very rarely* vasospasm of fingers and toes particularly in patients with Raynaud's syndrome, and effects like neuroleptic malignant syndrome on withdrawal; urinary incontinence, leucopenia, thrombocytopenia, hyponatraemia, reversible hearing loss, increased libido, and hypersexuality also reported

Dose

- Prevention or suppression of lactation (but see notes above and under Cautions), 2.5 mg on day 1 (prevention) or daily for 2–3 days (suppression); then 2.5 mg twice daily for 14 days
- Hypogonadism, galactorrhoea, infertility, initially 1–1.25 mg at bedtime, increased gradually; usual dose 7.5 mg daily in divided doses, increased if necessary to max. 30 mg daily, usual dose in infertility without hyperprolactinaemia, 2.5 mg twice daily
- Acromegaly, initially 1–1.25 mg at bedtime, increase gradually to 5 mg every 6 hours
- Prolactinoma, initially 1–1.25 mg at bedtime; increased gradually to 5 mg every 6 hours (occasional patients may require up to 30 mg daily)
- CHILD under 15 years, not recommended

Bromocriptine (Non-proprietary) PoM

Tablets, bromocriptine (as mesilate) 2.5 mg, net price 30-tab pack = £22.92. Label: 10, 21, counselling, driving, see notes above

Parlodel® (Meda) PoM

Tablets, both scored, bromocriptine (as mesilate) 1 mg, net price 100-tab pack = £9.90; 2.5 mg, 30-tab pack = £5.78. Label: 10, 21, counselling, driving, see notes above

Capsules, bromocriptine (as mesilate) 5 mg (blue/white), net price 100-cap pack = £37.57; 10 mg (white), 100-cap pack = £69.50. Label: 10, 21, counselling, driving, see notes above

CABERGOLINE

Indications see notes above and under Dose

Cautions see notes above; also monthly pregnancy tests during the amenorrhoeic period; advise non-hormonal contraception if pregnancy not desired (see also Pregnancy, below); **interactions:** Appendix 1 (cabergoline)

Contra-indications see notes above; history of puerperal psychosis; history of pulmonary, pericardial, or retroperitoneal fibrotic disorders (see Fibrotic Reactions in notes above); cardiac valvulopathy

Hepatic impairment reduce dose in severe hepatic impairment

Pregnancy no evidence of harm; exclude pregnancy before starting and discontinue 1 month before intended conception (ovulatory cycles persist for 6 months)—discontinue if pregnancy occurs during treatment (specialist advice needed)

Breast-feeding suppresses lactation; avoid breast-feeding if lactation prevention fails

Side-effects see notes above; also cardiac valvulopathy, drowsiness (see also Driving, above), dyspepsia, gastritis, epigastric and abdominal pain, angina, syncope, depression, confusion, hallucinations, breast pain; *rarely* vomiting, palpitation, epistaxis, digital vasospasm, hot flushes, transient hemianopia, muscle weakness; *also reported* erythromelalgia

Dose

- Prevention of lactation (but see notes above and under Contra-indications), during first day postpartum, 1 mg as a single dose; suppression of established lactation (but see notes above) 250 micrograms every 12 hours for 2 days; CHILD under 16 years, not recommended
- Hyperprolactinaemic disorders, 500 micrograms weekly (as a single dose *or* as 2 divided doses on separate days) increased at monthly intervals in steps of 500 micrograms until optimal therapeutic response (usually 1 mg weekly, range 0.25–2 mg weekly) with monthly monitoring of serum prolactin levels; reduce initial dose and increase more gradually if patient intolerant; over 1 mg weekly give as divided doses; up to 4.5 mg weekly has been used in hyperprolactinaemic patients; CHILD under 16 years, not recommended
- Parkinson's disease, section 4.9.1

Cabergoline (Non-proprietary) PoM

Tablet, scored, cabergoline 500 micrograms, net price 8-tab pack = £34.03. Label: 10, 21, counselling, driving, see notes above

Note Dispense in original container (contains desiccant)

Dostinex® (Pharmacia) PoM

Tablets, scored, cabergoline 500 micrograms. Net price 8-tab pack = £30.04. Label: 10, 21, counselling, driving, see notes above

Note Dispense in original container (contains desiccant)

QUINAGOLIDE

Indications see notes above and under Dose

Cautions see notes above; history of psychotic illness; advise non-hormonal contraception if pregnancy not desired; **interactions:** Appendix 1 (quinagolide)

Contra-indications hypersensitivity to quinagolide (but not ergot alkaloids)

Hepatic impairment avoid—no information available

Renal impairment avoid—no information available

Pregnancy discontinue when pregnancy confirmed unless medical reason for continuing (specialist advice needed)

Breast-feeding suppresses lactation

Side-effects nausea, vomiting, anorexia, abdominal pain, constipation or diarrhoea; syncope, hypotension (see also notes above), oedema, flushing; nasal congestion; headache, dizziness, fatigue, insomnia; *rarely* sudden onset of sleep (see notes above); *very rarely* psychosis

Dose

- Hyperprolactinaemia, 25 micrograms at bedtime for 3 days; increased at intervals of 3 days in steps of 25 micrograms to usual maintenance dose of 75–150 micrograms daily; for doses higher than 300 micrograms daily increase in steps of 75–150 micrograms at intervals of not less than 4 weeks; CHILD not recommended

Norprolac® (Ferring) PoM

Tablets, quinagolide (as hydrochloride) 75 micrograms (white), net price 30-tab pack = £27.00; starter pack of 3 × 25-microgram tabs (pink) with 3 × 50-microgram tabs (blue) = £4.50. Label: 10, 21, counselling, driving, see notes above

6.7.2 Drugs affecting gonadotrophins

Danazol inhibits pituitary gonadotrophins; it combines androgenic activity with antioestrogenic and antiprogestogenic activity. It is licensed for the treatment of *endometriosis* and for the relief of severe pain and tenderness in *benign fibrocystic breast disease* where other measures have proved unsatisfactory. It may also be effective in the long-term management of *hereditary angioedema* [unlicensed indication].

Cetrorelix and **ganirelix** are luteinising hormone releasing hormone antagonists, which inhibit the release of gonadotrophins (luteinising hormone and follicle-stimulating hormone). They are used in the treatment of infertility by assisted reproductive techniques.

CETRORELIX

Indications adjunct in the treatment of female infertility (under specialist supervision)

Hepatic impairment avoid in moderate or severe liver impairment

Renal impairment avoid in moderate or severe renal impairment

Pregnancy avoid in confirmed pregnancy

Breast-feeding avoid

Side-effects nausea, headache, injection site reactions; rarely hypersensitivity reactions

Dose

- By subcutaneous injection into the lower abdominal wall,

  either 250 micrograms in the morning, starting on day 5 or 6 of ovarian stimulation with gonadotrophins (*or* each evening starting on day 5 of ovarian stimulation); continue throughout administration of gonadotrophin including day of ovulation induction (*or* evening before ovulation induction)

  or 3 mg on day 7 of ovarian stimulation with gonadotrophins; if ovulation induction not possible on day 5 after 3-mg dose, additional 250 micrograms once daily until day of ovulation induction

Cetrotide® (Merck Serono) PoM

Injection, powder for reconstitution, cetrorelix (as acetate), net price 250-micrograms vial = £22.61; 3-mg vial = £158.26 (both with solvent)

DANAZOL

Indications see notes above and under Dose

Cautions cardiac impairment (avoid if severe), elderly, polycythaemia, epilepsy, diabetes mellitus, hypertension, migraine, lipoprotein disorder, history of thrombosis or thromboembolic disease; withdraw if virilisation (may be irreversible on continued use); non-hormonal contraceptive methods should be used, if appropriate; **interactions:** Appendix 1 (danazol)

Contra-indications ensure that patients with amenorrhoea are not pregnant; thromboembolic disease; undiagnosed genital bleeding; androgen-dependent tumours; acute porphyria (section 9.8.2)

Hepatic impairment caution in hepatic impairment (avoid if severe)

Renal impairment caution in renal impairment (avoid if severe)

Pregnancy avoid; has weak androgenic effects and virilisation of female fetus reported

Breast-feeding no data available but avoid because of possible androgenic effects in infant

Side-effects nausea, dizziness, skin reactions including rashes, photosensitivity and exfoliative dermatitis, fever, backache, nervousness, mood changes, anxiety, changes in libido, vertigo, fatigue, epigastric and pleuritic pain, headache, weight gain; menstrual disturbances, vaginal dryness and irritation, flushing and reduction in breast size; musculo-skeletal spasm, joint pain and swelling, hair loss; androgenic effects including acne, oily skin, oedema, hirsutism, voice changes and rarely clitoral hypertrophy (see also Cautions); temporary alteration in lipoproteins and other metabolic changes, insulin resistance; thrombotic events; leucopenia, thrombocytopenia, eosinophilia, reversible erythrocytosis or polycythaemia reported; headache and visual disturbances may indicate benign intracranial hypertension; rarely cholestatic jaundice, pancreatitis, peliosis hepatis and benign hepatic adenomata

Dose

Note In women of child-bearing potential, treatment should start during menstruation, preferably on day 1

- Endometriosis, 200–800 mg daily in up to 4 divided doses, adjusted to achieve amenorrhoea, usually for 3–6 months
- Severe pain and tenderness in benign fibrocystic breast disease not responding to other treatment, 300 mg daily in divided doses usually for 3–6 months
- Hereditary angioedema [unlicensed indication], initially 200 mg 2–3 times daily, then reduced according to response

Danazol (Non-proprietary) PoM

Capsules, danazol 100 mg, net price 28-cap pack = £18.40, 60-cap pack = £17.04; 200 mg, 56-cap pack = £66.20

Danol® (Sanofi-Aventis) PoM

Capsules, danazol 100 mg (grey/white), net price 60-cap pack = £16.38; 200 mg (pink/white), 60-cap pack = £32.43

GANIRELIX

Indications adjunct in the treatment of female infertility (under specialist supervision)

Hepatic impairment avoid in moderate or severe hepatic impairment

Renal impairment avoid in moderate to severe renal impairment

Pregnancy avoid in confirmed pregnancy—toxicity in *animal* studies

Breast-feeding avoid—no information available

Side-effects nausea, headache, malaise, injection-site reactions; *very rarely* hypersensitivity reactions including rash, facial oedema, and dyspnoea also reported

Dose

- By subcutaneous injection preferably into the upper leg (rotate injection sites to prevent lipoatrophy), 250 micrograms in the morning (or each afternoon) starting on day 5 or day 6 of ovarian stimulation with gonadotrophins; continue throughout administration of gonadotrophins including day of ovulation induction (if administering in afternoon, give last dose in afternoon *before* ovulation induction)

Orgalutran® (Organon) PoM

Injection, ganirelix, 500 micrograms/mL, net price 0.5-mL prefilled syringe = £21.48

Gonadorelin analogues

Administration of **gonadorelin analogues** produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility, anaemia due to uterine fibroids (together with iron supplementation), breast cancer (section 8.3.4.1), prostate cancer (section 8.3.4.2) and before intra-uterine surgery. Use of leuprorelin and triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding. For women undergoing hysterectomy or myomectomy, a vaginal procedure is made more feasible following the use of a gonadorelin analogue.

Cautions Non-hormonal, barrier methods of contraception should be used during entire treatment period with gonadorelin analogues; also use with caution in patients with metabolic bone disease because decrease in bone mineral density can occur.

Contra-indications Gonadorelin analogues are contra-indicated for use longer than 6 months in the treatment of endometriosis (do not repeat) and when there is unexplained vaginal bleeding.

Pregnancy The use of gonadorelin analogues in pregnancy is contra-indicated. Pregnancy should be excluded before treatment; the first injection should be given during menstruation or shortly afterwards *or* use barrier contraception for 1 month beforehand.

Breast-feeding Gonadorelin analogues are contra-indicated in breast-feeding.

Side-effects Side-effects of the gonadorelin analogues related to the inhibition of oestrogen production include menopausal-like symptoms (e.g. hot flushes, increased sweating, vaginal dryness, dyspareunia and loss of libido) and a decrease in trabecular bone density; these effects can be reduced by hormone replacement (e.g. with an oestrogen and a progestogen or with tibolone). Side-effects of gonadorelin analogues also include headache (rarely migraine) and hypersensitivity reactions including urticaria, pruritus, rash, asthma and anaphylaxis; when treating uterine fibroids, bleeding associated with fibroid degeneration can occur; spray formulations can cause irritation of the nasal mucosa including nose bleeds; local reactions at injection site can occur; other side-effects also reported with some gonadorelin analogues include palpitation, hypertension, ovarian cysts (may require withdrawal), changes in breast size, musculoskeletal pain or weakness, visual disturbances, paraesthesia, changes in scalp and body hair, oedema of the face and extremities, weight changes, and mood changes including depression.

BUSERELIN

Indications see under Dose; prostate cancer (section 8.3.4.2)

Cautions see notes above; polycystic ovarian disease, depression, hypertension, diabetes

Contra-indications see notes above; hormone-dependent tumours

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; initially withdrawal bleeding and subsequently breakthrough bleeding, leucorrhoea; nausea, vomiting, constipation, diarrhoea; anxiety, memory and concentration disturbances, sleep disturbances, nervousness, dizziness, drowsiness; breast tenderness, lactation; abdominal pain; fatigue; increased thirst, changes in appetite; acne, dry skin, splitting nails, dry eyes; altered blood lipids, leucopenia, thrombocytopenia; hearing disturbances; reduced glucose tolerance

Dose

- Endometriosis, intranasally, 300 micrograms (one 150-microgram spray in each nostril) 3 times daily (starting on days 1 or 2 of menstruation); max. duration of treatment 6 months (do not repeat)
- Pituitary desensitisation before induction of ovulation by gonadotrophins for *in vitro* fertilisation (under specialist supervision), by subcutaneous injection, 200–500 micrograms daily given as a single injection (occasionally up to 500 micrograms twice daily may be needed) starting in early follicular phase (day 1) *or*, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

  Intranasally, 150 micrograms (one spray in one nostril) 4 times daily during waking hours (occasionally up to 300 micrograms 4 times daily may be needed) starting in early follicular phase (day 1) *or*, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 2–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

  Counselling Avoid use of nasal decongestants before and for at least 30 minutes after treatment

Suprecur® (Sanofi-Aventis) PoM

Nasal spray, buserelin (as acetate) 150 micrograms/metered spray. Net price 2 × 100-dose pack (with metered dose pumps) = £87.63. Counselling, nasal decongestants

Injection, buserelin (as acetate) 1 mg/mL. Net price 5.5-mL vial = £13.76

GOSERELIN

Indications see under Dose; prostate cancer (section 8.3.4.2); early and advanced breast cancer (section 8.3.4.1)

Cautions see notes above; polycystic ovarian disease; diabetes

Contra-indications see notes above

Pregnancy use non-hormonal contraceptives during treatment; see also notes above

Breast-feeding see notes above

Side-effects see notes above; withdrawal bleeding

Dose

- By subcutaneous injection into anterior abdominal wall (as *Zoladex®*)

  Endometriosis, 3.6 mg every 28 days; max. duration of treatment 6 months (do not repeat)

  Endometrial thinning before intra-uterine surgery, 3.6 mg (may be repeated after 28 days if uterus is large or to allow flexible surgical timing)

  Before surgery in women who have anaemia due to uterine fibroids, 3.6 mg every 28 days (with supplementary iron); max. duration of treatment 3 months

  Pituitary desensitisation before induction of ovulation by gonadotrophins for *in vitro* fertilisation (under specialist supervision), after exclusion of pregnancy, 3.6 mg to achieve pituitary down-regulation (usually 1–3 weeks) then gonadotrophin is administered (stopping gonadotrophin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

Preparation

Section 8.3.4.2

LEUPRORELIN ACETATE

Indications see under Dose; prostate cancer (section 8.3.4.2)

Cautions see notes above; monitor liver function; family history of osteoporosis; chronic use of other drugs which reduce bone density including alcohol and tobacco; diabetes

Contra-indications see notes above

Pregnancy teratogenic in *animal* studies; see also notes above

Breast-feeding see notes above

Side-effects see notes above; breast tenderness; nausea, vomiting, diarrhoea, anorexia; fever, chills; sleep disturbances, dizziness, fatigue, leucopenia, thrombocytopenia, altered blood lipids, pulmonary embolism; spinal fracture, paralysis, hypotension and worsening of depression also reported

Dose

- By subcutaneous *or* intramuscular injection (as *Prostap® SR*)

  Endometriosis, 3.75 mg as a single dose in first 5 days of menstrual cycle then every month for max. 6 months (course not to be repeated)

  Endometrial thinning before intra-uterine surgery, 3.75 mg as a single dose (given between days 3 and 5 of menstrual cycle) 5–6 weeks before surgery

  Reduction of size of uterine fibroids and of associated bleeding before surgery, 3.75 mg as a single dose every month usually for 3–4 months (max. 6 months)
- By intramuscular injection (as *Prostap® 3*)

  Endometriosis, 11.25 mg as a single dose in first 5 days of menstrual cycle then every 3 months for max. 6 months (course not to be repeated)

Preparations

Section 8.3.4.2

NAFARELIN

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; acne

Dose

- Endometriosis, women over 18 years, 200 micrograms twice daily as one spray in one nostril in the morning and one spray in the other nostril in the evening (starting on days 2–4 of menstruation), max. duration of treatment 6 months (do not repeat)
- Pituitary desensitisation before induction of ovulation by gonadotrophins for *in vitro* fertilisation (under specialist supervision), 400 micrograms (one spray in each nostril) twice daily starting in early follicular phase (day 2) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually within 4 weeks) then maintained (usually for 8–12 days) during gonadotrophin administration (stopping gonadotrophin and nafarelin on administration of chorionic gonadotrophin at follicular maturity); discontinue if down-regulation not achieved within 12 weeks

  Counselling Avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration

Synarel® (Pharmacia) PoM

Nasal spray, nafarelin (as acetate) 200 micrograms/metered spray. Net price 30-dose unit = £30.41; 60-dose unit = £52.43. Label: 10, patient information leaflet, counselling, see above

TRIPTORELIN

Indications endometriosis, precocious puberty, reduction in size of uterine fibroids; advanced prostate cancer (section 8.3.4.2)

Cautions see notes above

Contra-indications see notes above

Pregnancy see notes above

Breast-feeding see notes above

Side-effects see notes above; also gastro-intestinal disturbances; in precocious puberty, withdrawal bleeding may occur in the first month of treatment; asthenia

Dose

- See under preparations below

Decapeptyl® SR (Ipsen) PoM

Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 3-mg vial (with diluent) = £69.00

Dose by intramuscular injection, endometriosis and reduction in size of uterine fibroids, 3 mg every 4 weeks starting during first 5 days of menstrual cycle; for uterine fibroids continue treatment for at least 3 months; max. duration of treatment 6 months (not to be repeated)

Note Each vial includes an overage to allow accurate administration of 3-mg dose

Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 11.25-mg vial (with diluent) = £207.00

Dose by intramuscular injection, endometriosis, 11.25 mg every 3 months starting during first 5 days of menstrual cycle; max. duration of treatment 6 months (not to be repeated)

Precocious puberty, 11.25 mg every 3 months; discontinue when bone maturation consistent with age of 12 years in girls or 13–14 years in boys

Note Each vial includes an overage to allow accurate administration of 11.25-mg dose

Gonapeptyl Depot® (Ferring) PoM

Injection, (powder for suspension), triptorelin (as acetate), net price 3.75-mg prefilled syringe (with prefilled syringe of vehicle) = £81.69

Dose by subcutaneous *or* deep intramuscular injection, endometriosis and reduction in size of uterine fibroids, 3.75 mg every 4 weeks starting during first 5 days of menstrual cycle; max. duration of treatment 6 months (not to be repeated)

Precocious puberty, body-weight over 30 kg, initially 3.75 mg every 2 weeks for 3 doses, then every 3–4 weeks; body-weight 20–30 kg, initially 2.5 mg every 2 weeks for 3 doses, then every 3–4 weeks; body-weight under 20 kg, initially 1.875 mg every 2 weeks for 3 doses, then every 3–4 weeks; discontinue when bone maturation consistent with age over 12 years in girls or over 13 years in boys

Breast pain (mastalgia)

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and reduction in dietary fat; withdrawal of an oral contraceptive or of hormone replacement therapy may help to resolve the pain.

Mild, non-cyclical breast pain is treated with simple analgesics (section 4.7.1); moderate to severe pain, cyclical pain or symptoms that persist for longer than 6 months may require specific drug treatment.

Danazol (section 6.7.2) is licensed for the relief of severe pain and tenderness in benign fibrocystic breast disease which has not responded to other treatment.

Tamoxifen (section 8.3.4.1) may be a useful adjunct in the treatment of mastalgia [unlicensed indication] especially when symptoms can definitely be related to cyclic oestrogen production; it may be given on the days of the cycle when symptoms are predicted.

Treatment for breast pain should be reviewed after 6 months and continued if necessary. Symptoms recur in about 50% of women within 2 years of withdrawal of therapy but may be less severe.

6.7.3 Metyrapone and trilostane

Metyrapone is a competitive inhibitor of 11β-hydroxylation in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. It may be used as a test of anterior pituitary function.

Although most types of *Cushing's syndrome* are treated surgically, that which occasionally accompanies carcinoma of the bronchus is not usually amenable to surgery. Metyrapone has been found helpful in controlling the symptoms of the disease; it is also used in other forms of Cushing's syndrome to prepare the patient for surgery. The dosages used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

Trilostane reversibly inhibits the enzyme system essential for the production of mineralocorticoids and gluco-

corticoids in the adrenal cortex, and may be useful in *Cushing's syndrome* and *primary hyperaldosteronism*. Trilostane appears to be less effective than metyrapone for Cushing's syndrome (where it is tailored to corticosteroid production). It also has a minor role in postmenopausal breast cancer that has relapsed following initial oestrogen antagonist therapy (corticosteroid replacement therapy is also required). **Ketoconazole** (section 5.2.2) is also used by specialists for the management of *Cushing's syndrome* [unlicensed indication].

METYRAPONE

Indications see notes above and under Dose (specialist supervision in hospital)

Cautions gross hypopituitarism (risk of precipitating acute adrenal failure); hypertension on long-term administration; hypothyroidism (delayed response); many drugs interfere with diagnostic estimation of steroids; avoid in acute porphyria (section 9.8.2)
Driving Drowsiness may affect the performance of skilled tasks (e.g. driving)

Contra-indications adrenocortical insufficiency (see Cautions)

Hepatic impairment use with caution in hepatic impairment (delayed response)

Pregnancy avoid (may impair biosynthesis of fetal-placental steroids)

Breast-feeding avoid—no information available

Side-effects occasional nausea, vomiting, dizziness, headache, hypotension, sedation; rarely abdominal pain, allergic skin reactions, hypoadrenalism, hirsutism

Dose

- Differential diagnosis of ACTH-dependent Cushing's syndrome, 750 mg every 4 hours for 6 doses; CHILD 15 mg/kg (minimum 250 mg) every 4 hours for 6 doses
- Management of Cushing's syndrome, range 0.25–6 g daily, tailored to cortisol production; see notes above
- Resistant oedema due to increased aldosterone secretion in cirrhosis, nephrotic syndrome, and congestive heart failure (with glucocorticoid replacement therapy) 3 g daily in divided doses

Metopirone® (Alliance) PoM
Capsules, ivory, metyrapone 250 mg, net price 100-tab pack = £38.88. Label: 21, counselling, driving

TRILOSTANE

Indications see notes above and under Dose (specialist supervision)

Cautions breast cancer (concurrent corticosteroid replacement therapy needed, see under Dose), adrenal cortical hyperfunction (tailored to cortisol and electrolytes, concurrent corticosteroid therapy may be needed, see under Dose); **interactions:** Appendix 1 (trilostane)

Contra-indications children

Hepatic impairment use with caution

Renal impairment use with caution

Pregnancy avoid; interferes with placental sex hormone production; use non-hormonal method of contraception

Breast-feeding avoid

Side-effects flushing, tingling and swelling of mouth, rhinorrhoea, nausea, vomiting, diarrhoea, and rashes reported; rarely granulocytopenia

Dose

- Adrenal cortical hyperfunction, 240 mg daily in divided doses for at least 3 days then tailored according to response with regular monitoring of plasma electrolytes and circulating corticosteroids (both mineralocorticoid and glucocorticoid replacement therapy may be needed); usual dose: 120–480 mg daily (may be increased to 960 mg)
- Postmenopausal breast cancer (with glucocorticoid replacement therapy) following relapse to initial oestrogen receptor antagonist therapy, initially 240 mg daily increased every 3 days in steps of 240 mg to a maintenance dose of 960 mg daily (720 mg daily if not tolerated)

Modrenal® (Bioenvision) PoM
Capsules, trilostane 60 mg (pink/black), net price 100-cap pack = £49.50; 120 mg (pink/yellow), 100-cap pack = £98.50. Label: 21

6.7.4 Somatomedins

Somatomedins are a group of polypeptide hormones structurally related to insulin and commonly known as insulin-like growth factors (IGFs). **Mecasermin**, a human insulin-like growth factor-I (rhIGF-I), is the principal mediator of the somatotropic effects of human growth hormone and is used to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.

MECASERMIN

(Recombinant human insulin-like growth factor-I; rhIGF-I)

Indications see notes above

Cautions correct hypothyroidism before initiating treatment; diabetes mellitus (adjustment of antidiabetic therapy may be necessary), monitor ECG before and on termination of treatment (and during treatment if ECG abnormal), papilloedema (see under Side-effects), monitor for disorders of the epiphysis of the hip (monitor for limping), monitor for signs of tonsillar hypertrophy (snoring, sleep apnoea, and chronic middle ear effusions)

Contra-indications evidence of tumour activity (discontinue treatment)

Pregnancy avoid unless essential; contraception advised in women of child-bearing potential

Breast-feeding avoid

Side-effects headache, funduscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); cardiomegaly, ventricular hypertrophy, tachycardia; convulsions, sleep apnoea, night terrors, dizziness, nervousness; tonsillar hypertrophy (see Cautions above); hypoglycaemia (especially in first month, and in younger children), hyperglycaemia, gynaecomastia; arthralgia, myalgia; visual disturbance, impaired hearing; antibody formation; injection-site reactions (rotate site)

Dose

- By subcutaneous injection, ADOLESCENT and CHILD over 2 years, initially 40 micrograms/kg twice daily for 1 week, if tolerated increase dose in steps of 40 micrograms/kg to max. 120 micrograms/kg twice daily; discontinue if no response within 1 year
  Counselling Dose should be administered just before or after food; do not increase dose if a dose is missed
  Note Reduce dose if hypoglycaemia occurs despite adequate food intake; withhold injection if patient unable to eat

Increlex® (Ipsen) ▼ PoM

Injection, mecasermin 10 mg/mL, net price 4-mL vial = £605.00. Counselling, administration

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

7 Obstetrics, gynaecology, and urinary-tract disorders

7.1 Drugs used in obstetrics 485
7.1.1 Prostaglandins and oxytocics 485
7.1.1.1 Drugs affecting the ductus arteriosus 488
7.1.2 Mifepristone 488
7.1.3 Myometrial relaxants 489
7.2 Treatment of vaginal and vulval conditions 491
7.2.1 Preparations for vaginal and vulval changes 491
7.2.2 Vaginal and vulval infections 492
7.3 Contraceptives 493
7.3.1 Combined hormonal contraceptives 494
7.3.2 Progestogen-only contraceptives 500
7.3.2.1 Oral progestogen-only contraceptives 500
7.3.2.2 Parenteral progestogen-only contraceptives 501
7.3.2.3 Intra-uterine progestogen-only device 502
7.3.3 Spermicidal contraceptives 503
7.3.4 Contraceptive devices 503
7.3.5 Emergency contraception 505
7.4 Drugs for genito-urinary disorders 506
7.4.1 Drugs for urinary retention 506
7.4.2 Drugs for urinary frequency, enuresis, and incontinence 508
7.4.3 Drugs used in urological pain 512
7.4.4 Bladder instillations and urological surgery 513
7.4.5 Drugs for erectile dysfunction 514

This chapter also includes advice on the drug management of the following:

- emergency contraception, p. 505
- induction of abortion, below
- induction and augmentation of labour, below
- nocturnal enuresis, p. 512
- premature labour, p. 489
- prevention and treatment of post-partum haemorrhage, p. 486
- priapism, p. 514

For hormonal therapy of gynaecological disorders see section 6.4.1 (including HRT), section 6.5.1 and section 6.7.2.

7.1 Drugs used in obstetrics

7.1.1 Prostaglandins and oxytocics
7.1.2 Mifepristone
7.1.3 Myometrial relaxants

Because of the complexity of dosage regimens in obstetrics, in all cases **detailed specialist literature** should be consulted.

7.1.1 Prostaglandins and oxytocics

Prostaglandins and oxytocics are used to induce abortion or induce or augment labour and to minimise blood loss from the placental site. They include oxytocin, carbetocin, ergometrine, and the prostaglandins. All induce uterine contractions with varying degrees of pain according to the strength of contractions induced.

Induction of abortion **Gemeprost**, a prostaglandin administered vaginally as pessaries, is suitable for the medical induction of late therapeutic abortion; gemeprost is also used to ripen the cervix before surgical abortion, particularly in primigravidas. The prostaglandin **misoprostol** (section 7.1.2) is given by mouth or by vaginal administration to induce medical abortion [unlicensed indication]; intravaginal use ripens the cervix before surgical abortion [unlicensed indication]. Extra-amniotic **dinoprostone** is rarely used nowadays.

Pre-treatment with **mifepristone** (section 7.1.2) can facilitate the process of medical abortion. It sensitises the uterus to subsequent administration of a prostaglandin and, therefore, abortion occurs in a shorter time and with a lower dose of prostaglandin.

Induction and augmentation of labour **Dinoprostone** is available as vaginal tablets, pessaries and

vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.

Oxytocin (*Syntocinon®*) is administered by slow intravenous infusion, using an infusion pump, to induce or augment labour, usually in conjunction with amniotomy. Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.

Misoprostol is given orally or vaginally for the induction of labour [unlicensed indication].

NICE guidance
Induction of labour (updated July 2008)
Available at www.nice.org.uk

Prevention and treatment of haemorrhage Bleeding due to incomplete abortion can be controlled with **ergometrine** and **oxytocin** (*Syntometrine®*) given intramuscularly, the dose is adjusted according to the patient's condition and blood loss. This is commonly used before surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine combined are more effective in early pregnancy than either drug alone.

Active management of the third stage of labour reduces the risk of postpartum haemorrhage; oxytocin is given by intramuscular injection [unlicensed] on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered. Alternatively, ergometrine 500 micrograms with oxytocin 5 units (*Syntometrine®* 1 mL) can be given by intramuscular injection in the absence of hypertension; oxytocin alone causes less nausea, vomiting, and hypertension than when given with ergometrine.

In excessive uterine bleeding, any placental products remaining in the uterus should be removed. Oxytocic drugs are used to treat postpartum haemorrhage caused by uterine atony; treatment options are as follows:

- oxytocin 5 units by slow intravenous injection (dose may be repeated), followed in severe cases by intravenous infusion of oxytocin 40 units in 500 mL infusion fluid (prolonged administration—see Appendix 6) at a rate that controls uterine atony *or*
- ergometrine 250–500 micrograms by intramuscular injection *or*
- ergometrine 250–500 micrograms by slow intravenous injection (use with caution—risk of hypertension) *or*
- ergometrine 500 micrograms with oxytocin 5 units (*Syntometrine®* 1 mL) by intramuscular injection

Carboprost has an important role in severe postpartum haemorrhage unresponsive to ergometrine and oxytocin.

Misoprostol [unlicensed] can be used in postpartum haemorrhage when oxytocin, ergometrine, and carboprost are not available or are inappropriate.

CARBETOCIN

Indications prevention of uterine atony after caesarean section

Cautions hyponatraemia; cardiovascular disease (avoid if severe); migraine; asthma

Contra-indications pre-eclampsia and eclampsia; epilepsy

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises avoid

Side-effects nausea, vomiting, abdominal pain, metallic taste; flushing, hypotension, chest pain; dyspnoea; headache, tremor, dizziness; anaemia; back pain; pruritus; feeling of warmth, chills; tachycardia and sweating also reported

Dose

- By slow intravenous injection over 1 minute, a single dose of 100 micrograms, as soon as possible after delivery, preferably before removal of placenta

Pabal® (Ferring) ▼ PoM
Injection, carbetocin 100 micrograms/mL, net price 1-mL amp = £17.64

CARBOPROST

Indications postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin

Cautions history of glaucoma or raised intra-ocular pressure, asthma, hypertension, hypotension, anaemia, jaundice, diabetes, epilepsy; uterine scars; excessive dosage may cause uterine rupture; **interactions:** Appendix 1 (prostaglandins)

Contra-indications untreated pelvic infection; cardiac or pulmonary disease

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises avoid

Side-effects nausea, vomiting and diarrhoea, hyperthermia and flushing, bronchospasm; less frequent effects include raised blood pressure, dyspnoea, and pulmonary oedema; chills, headache, diaphoresis, dizziness; cardiovascular collapse also reported; erythema and pain at injection site reported

Dose

- By deep intramuscular injection, 250 micrograms repeated if necessary at intervals of not less than 15 minutes; total dose should not exceed 2 mg (8 doses)

Hemabate® (Pharmacia) PoM
Injection, carboprost as trometamol salt (trometamine salt) 250 micrograms/mL, net price 1-mL amp = £18.20 (hosp. only)

DINOPROSTONE

Indications see notes above and under preparations below

Cautions history of asthma, glaucoma and raised intra-ocular pressure; hypertension; history of epilepsy; uterine scarring; monitor uterine activity and fetal status (particular care if history of uterine hypertony); uterine rupture; see also notes above; monitor for disseminated intravascular coagulation after parturition; risk factors for disseminated intravascular coagulation; effect of oxytocin enhanced (care needed in monitoring uterine activity when used in sequence); **interactions:** Appendix 1 (prostaglandins)

Contra-indications active cardiac, or pulmonary disease; placenta praevia or unexplained vaginal bleeding during pregnancy, ruptured membranes, major cephalopelvic disproportion or fetal malpresentation, history of caesarean section or major uterine surgery,

untreated pelvic infection, fetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery; avoid extra-amniotic route in cervicitis or vaginitis

Hepatic impairment manufacturers advise avoid

Renal impairment manufacturers advise avoid

Side-effects nausea, vomiting, diarrhoea; other side-effects include uterine hypertonus, severe uterine contractions, pulmonary or amniotic fluid embolism, abruptio placenta, fetal distress, maternal hypertension, bronchospasm, rapid cervical dilation, fever, backache; uterine hypercontractility with or without fetal bradycardia, low Apgar scores; cardiac arrest, uterine rupture, stillbirth or neonatal death also reported; vaginal symptoms (warmth, irritation, pain); after intravenous administration—flushing, shivering, headache, dizziness, temporary pyrexia and raised white blood cell count; disseminated intravascular coagulation reported; also local tissue reaction and erythema after intravenous administration and possibility of infection after extra-amniotic administration

Dose

- See under preparations, below

Important Do not confuse dose of *Prostin E2®* vaginal **gel** with that of *Prostin E2®* vaginal **tablets**—not bioequivalent.

Propess® (Ferring) PoM

Pessaries (within retrieval device), releasing dinoprostone approx. 10 mg over 24 hours; net price 1-pessary pack = £30.00

Dose by vagina, cervical ripening and induction of labour at term, 1 pessary (in retrieval device) inserted high into posterior fornix and removed when cervical ripening adequate; if oxytocin necessary, remove 30 minutes before oxytocin infusion; remove if cervical ripening inadequate after 24 hours (dose not to be repeated)

Prostin E2® (Pharmacia) PoM

Intravenous solution ◢ for dilution and use as an infusion, dinoprostone 1 mg/mL, net price 0.75-mL amp = £8.52; 10 mg/mL, 0.5-mL amp = £18.40 (both hosp. only; rarely used, consult product literature for dose and indications)

Extra-amniotic solution ◢ dinoprostone 10 mg/mL, net price 0.5-mL amp (with diluent) = £18.40 (hosp. only; less commonly used nowadays, consult product literature for dose and indications)

Vaginal gel, dinoprostone 400 micrograms/mL, net price 2.5 mL (1 mg) = £13.28; 800 micrograms/mL, 2.5 mL (2 mg) = £13.28

Dose by vagina, induction of labour, inserted high into posterior fornix (avoid administration into cervical canal), 1 mg (unfavourable primigravida 2 mg), followed after 6 hours by 1–2 mg if required; max. [gel] 3 mg (unfavourable primigravida 4 mg)

Vaginal tablets, dinoprostone 3 mg, net price 8-vaginal tab pack = £106.23

Dose by vagina, induction of labour, inserted high into posterior fornix, 3 mg, followed after 6–8 hours by 3 mg if labour is not established; max. 6 mg [vaginal tablets]

Note *Prostin E2 Vaginal Gel* and *Vaginal Tablets* are **not** bioequivalent

ERGOMETRINE MALEATE

Indications see notes above

Cautions cardiac disease; hypertension; multiple pregnancy; acute porphyria (section 9.8.2); **interactions:** Appendix 1 (ergot alkaloids)

Contra-indications induction of labour, first and second stages of labour, vascular disease, severe cardiac disease, sepsis, severe hypertension, eclampsia

Hepatic impairment manufacturer advises caution in mild or moderate impairment and avoid in severe impairment

Renal impairment manufacturer advises caution in mild or moderate impairment and avoid in severe impairment

Side-effects nausea, vomiting, abdominal pain; chest pain, arrhythmias (including bradycardia), palpitation, hypertension, vasoconstriction; dyspnoea, pulmonary oedema; headache, dizziness; tinnitus; rash; *very rarely* myocardial infarction

Dose

- See notes above

Ergometrine (Non-proprietary) PoM

Injection, ergometrine maleate 500 micrograms/mL, net price 1-mL amp = 60p

◢ With oxytocin

Syntometrine® (Alliance) PoM

Injection, ergometrine maleate 500 micrograms, oxytocin 5 units/mL, net price 1-mL amp = £1.35

Dose by intramuscular injection, 1 mL; by intravenous injection, no longer recommended

GEMEPROST

Indications see under Dose

Cautions obstructive airways disease, cardiovascular insufficiency, raised intra-ocular pressure, cervicitis or vaginitis; **interactions:** Appendix 1 (prostaglandins)

Important For warnings relating to use of gemeprost in a patient undergoing induction of abortion with mifepristone, see under Mifepristone and Note below

Contra-indications unexplained vaginal bleeding, uterine scarring, placenta praevia

Renal impairment manufacturer advises avoid

Side-effects vaginal bleeding and uterine pain; nausea, vomiting, or diarrhoea; headache, muscle weakness, dizziness, flushing, chills, backache, dyspnoea, chest pain, palpitation and mild pyrexia; uterine rupture reported (most commonly in multiparas or if history of uterine surgery or if given with intravenous oxytocics); also reported severe hypotension, coronary artery spasm and myocardial infarction

Dose

- By vagina, cervical ripening prior to first trimester surgical abortion, 1 mg inserted into posterior fornix 3 hours before surgery
- Second trimester abortion, 1 mg inserted into posterior fornix every 3 hours for max. of 5 administrations; second course may begin 24 hours after start of treatment (if treatment fails pregnancy should be terminated by another method)
- Second trimester intra-uterine death, 1 mg inserted into posterior fornix every 3 hours for max. of 5 administrations only; monitor for coagulopathy

Note If used in combination with mifepristone, carefully monitor blood pressure and pulse for 3 hours

Gemeprost (Sanofi-Aventis) PoM

Pessaries, gemeprost 1 mg, net price 5-pessary pack = £215.00

OXYTOCIN

Indications see under Dose and notes above

Cautions induction or enhancement of labour—presence of borderline cephalopelvic disproportion (avoid if significant), secondary uterine inertia, mild or moderate pregnancy-induced hypertension or cardiac disease, women over 35 years or with history of lower-uterine segment caesarean section (see also under Contra-indications below); risk factors for disseminated intravascular coagulation; monitor for disseminated intravascular coagulation after parturition; avoid large infusion volumes and restrict fluid intake by mouth (risk of hyponatraemia and water-intoxication—see also Appendix 6); effects enhanced by concomitant prostaglandins (very careful monitoring of uterine activity); caudal block anaesthesia (may enhance hypertensive effects of sympathomimetic vasopressors); see also **interactions:** Appendix 1 (oxytocin)

Contra-indications hypertonic uterine contractions, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia, or severe cardiovascular disease

Side-effects nausea, vomiting; arrhythmia; headache; *rarely* disseminated intravascular coagulation, rash, and anaphylactoid reactions (with dyspnoea, hypotension, or shock); uterine spasm (may occur at low doses), uterine hyperstimulation (usually with excessive doses—may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture); water intoxication and hyponatraemia associated with high doses with large infusion volumes of electrolyte-free fluid (see also under Dose below); placental abruption and amniotic fluid embolism also reported on overdose

Dose

- Induction of labour for medical reasons or stimulation of labour in hypotonic uterine inertia, by intravenous infusion (not to be started for at least 6 hours after administration of vaginal prostaglandin), initially 0.001–0.004 units/minute, increased at intervals of at least 30 minutes until a maximum of 3–4 contractions occur every 10 minutes (0.01 units/minute is often adequate) up to max. 0.02 units/minute; if regular contractions not established after total of 5 units stop induction attempt (may be repeated next day starting again at 0.001–0.004 units/minute)
  Important Careful monitoring of fetal heart rate and uterine motility essential for dose titration (**avoid** intravenous injection during labour); discontinue immediately in uterine hyperactivity or fetal distress
- Caesarean section, by slow intravenous injection immediately after delivery, 5 units
- Prevention of postpartum haemorrhage, after delivery of placenta, by slow intravenous injection, 5 units (if infusion used for induction or enhancement of labour, increase rate during third stage and for next few hours).
  Important Avoid rapid intravenous injection (may transiently reduce blood pressure)
  Note Can be given in a dose of 10 units by intramuscular injection [unlicensed route] instead of oxytocin with ergometrine (*Syntometrine®*), see notes above
- Treatment of postpartum haemorrhage, by slow intravenous injection, 5 units (dose may be repeated), followed in severe cases by intravenous infusion of 40 units in 500 mL infusion fluid at a rate sufficient to control uterine atony
  Important Avoid rapid intravenous injection (may transiently reduce blood pressure); prolonged administration, see warning below
- Incomplete, inevitable, or missed abortion, by slow intravenous injection, 5 units followed if necessary by intravenous infusion, 0.02–0.04 units/minute or faster

Important Prolonged intravenous administration at high doses with large volume of fluid (which is possible in inevitable or missed abortion or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (i.e. not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth; monitor fluid and electrolytes.

Note Oxytocin doses in the BNF may differ from those in the product literature

Syntocinon® (Alliance) PoM

Injection, oxytocin, net price 5 units/mL, 1-mL amp = 76p; 10 units/mL, 1-mL amp = 86p

With ergometrine

See *Syntometrine®*, p. 487

7.1.1.1 Drugs affecting the ductus arteriosus

This section is not included in the BNF. For the management of ductus arteriosus, see *BNF for Children* section 2.14.

7.1.2 Mifepristone

Mifepristone, an antiprogestogenic steroid, sensitises the myometrium to prostaglandin-induced contractions and ripens the cervix. For termination of pregnancy, a single dose of mifepristone is followed by administration of a prostaglandin (gemeprost or misoprostol [unlicensed]). Guidelines of the Royal College of Obstetricians and Gynaecologists (September 2004) include the following [unlicensed] regimens for inducing medical abortion:

- For gestation up to 9 weeks, mifepristone 200 mg by mouth followed 1–3 days later by misoprostol 800 micrograms vaginally; in women at more than 7 weeks gestation (49–63 days), if the abortion has not occurred 4 hours after misoprostol, a further dose of misoprostol 400 micrograms may be given vaginally or by mouth
- For gestation between 9 and 13 weeks, mifepristone 200 mg by mouth followed 36–48 hours later by misoprostol 800 micrograms vaginally followed if necessary by a maximum of 4 further doses at 3-hourly intervals of misoprostol 400 micrograms vaginally or by mouth
- For gestation between 13 and 24 weeks, mifepristone 200 mg by mouth followed 36–48 hours later by misoprostol 800 micrograms vaginally then a maximum of 4 further doses at 3-hourly intervals of misoprostol 400 micrograms by mouth

MIFEPRISTONE

Indications see under dose

Cautions asthma (avoid if severe and uncontrolled); haemorrhagic disorders and anticoagulant therapy; prosthetic heart valve or history of endocarditis (see

section 5.1 table 2); risk factors for or existing cardiovascular disease; adrenal suppression (may require corticosteroid); **interactions**: Appendix 1 (mifepristone)

Important For warnings relating to use of gemeprost in a patient undergoing induction of abortion with mifepristone, see under Gemeprost

Contra-indications uncontrolled severe asthma; suspected ectopic pregnancy (use other specific means of termination); chronic adrenal failure; acute porphyria (section 9.8.2)

Hepatic impairment manufacturer advises avoid

Renal impairment manufacturer advises avoid

Side-effects gastro-intestinal cramps; uterine contractions, vaginal bleeding (sometimes severe) may occur between administration of mifepristone and surgery (and rarely abortion may occur before surgery); *less commonly* hypersensitivity reactions including rash and urticaria; *rarely* hypotension, malaise, headache, fever, hot flushes, dizziness, and chills; infections (including toxic shock syndrome) also reported

Dose

- Medical termination of intra-uterine pregnancy of up to 49 days gestation, by mouth, mifepristone 600 mg as a single dose under medical supervision followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina *or* misoprostol 400 micrograms by mouth [unlicensed]; alternative regimen, mifepristone 200 mg by mouth as a single dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding
- Medical termination of intra-uterine pregnancy of 50–63 days gestation, by mouth, mifepristone 600 mg (200 mg also effective) as a single dose under medical supervision, followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg by vagina; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion and to assess vaginal bleeding
- Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 84 days gestation, by mouth, mifepristone 200 mg as a single dose under medical supervision 36–48 hours before procedure
- Termination of pregnancy of 13–24 weeks gestation (in combination with a prostaglandin), by mouth, mifepristone 600 mg (200 mg may be effective) as a single dose under medical supervision followed 36–48 hours later by gemeprost 1 mg by vagina every 3 hours up to max. 5 mg *or* misoprostol (see above [unlicensed]); if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg by vagina up to max. 5 mg; follow-up visit after appropriate interval to assess vaginal bleeding recommended

  Note Careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension)
- Labour induction in fetal death *in utero* where prostaglandin or oxytocin inappropriate, by mouth, mifepristone 600 mg daily as a single dose for 2 days under medical supervision; if labour not started within 72 hours of first dose, another method should be used

Mifegyne® (Nordic) PoM

Tablets, yellow, mifepristone 200 mg, net price 3-tab pack = £52.66 (supplied to NHS hospitals and premises approved under Abortion Act 1967). Label: 10, patient information leaflet

7.1.3 Myometrial relaxants

Tocolytic drugs postpone *premature labour* and they are used with the aim of reducing harm to the child. However, there is no satisfactory evidence that the use of these drugs reduces mortality. The greatest benefit is gained by using the delay to administer corticosteroid therapy or to implement other measures which improve perinatal health (including transfer to a unit with neonatal intensive care facility).

The oxytocin receptor antagonist, **atosiban**, is licensed for the inhibition of uncomplicated premature labour *between 24 and 33 weeks* of gestation. Atosiban may be preferable to a beta$_2$ agonist because it has fewer side-effects.

The dihydropyridine calcium-channel blocker **nifedipine** (section 2.6.2) also has fewer side-effects than a beta$_2$ agonist. Nifedipine [unlicensed indication] can be given initially in a dose of 20 mg followed by 10–20 mg 3–4 times daily adjusted according to uterine activity.

A beta$_2$ agonist (**ritodrine**, **salbutamol**, or **terbutaline**) is used for inhibiting uncomplicated premature labour between 24 and 33 weeks of gestation and it may permit a delay in delivery of at least 48 hours. Prolonged therapy should be avoided since risk to the mother increases after 48 hours and there is a lack of evidence of benefit from further treatment; maintenance treatment is therefore **not recommended**.

Indometacin (section 10.1.1), a cyclo-oxygenase inhibitor, also inhibits labour [unlicensed indication] and it can be useful in situations where a beta$_2$ agonist is not appropriate; however, there are concerns about neonatal complications such as transient impairment of renal function and premature closure of ductus arteriosus.

Atosiban

ATOSIBAN

Indications uncomplicated premature labour (see notes above)

Cautions monitor blood loss after delivery; intra-uterine growth restriction; abnormal placental site

Contra-indications eclampsia and severe pre-eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (requiring immediate delivery), placenta praevia, abruptio placenta, intra-uterine growth restriction with abnormal fetal heart rate, premature rupture of membranes after 30 weeks' gestation

Hepatic impairment no information available

Renal impairment no information available

Side-effects nausea, vomiting, tachycardia, hypotension, headache, dizziness, hot flushes, hyperglycaemia, injection-site reaction; *less commonly* pruritus, rash, fever, insomnia

Dose

- By intravenous injection, initially 6.75 mg over 1 minute, then by intravenous infusion 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours; max. duration of treatment 48 hours

Tractocile® (Ferring) PoM

Injection, atosiban (as acetate) 7.5 mg/mL, net price 0.9-mL (6.75-mg) vial = £18.41

Concentrate for intravenous infusion, atosiban (as acetate) 7.5 mg/mL, net price 5-mL vial = £52.82

Beta$_2$ agonists

Cautions Beta$_2$ agonists should be used with caution in patients with suspected cardiovascular disease (such patients should be assessed by a cardiologist before initiating therapy—see also Contra-indications, below), hypertension, mild to moderate pre-eclampsia, hyperthyroidism, and hypokalaemia (particular risk with potassium-depleting diuretics—see also Hypokalaemia, p. 176). It is important to monitor pulse rate (should not exceed 140 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), and the patient's fluid and electrolyte status (avoid over-hydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs). Beta$_2$ agonists should also be used with caution in diabetes—monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially with intravenous beta$_2$ agonists).

Contra-indications Beta$_2$ agonists are contra-indicated in cardiac disease and in patients with significant risk factors for myocardial ischaemia; they should also be avoided in antepartum haemorrhage, intra-uterine infection, intra-uterine fetal death, placenta praevia, abruptio placenta, threatened miscarriage, cord compression, and eclampsia or severe pre-eclampsia.

Side-effects Side-effects of the beta$_2$ agonists include nausea, vomiting, pulmonary oedema (see Cautions above and under Ritodrine dose), palpitation, tachycardia, arrhythmias, myocardial ischaemia, peripheral vasodilation, headache, tremor, hyperglycaemia, hypokalaemia (see Cautions), muscle cramps and tension, and hypersensitivity reactions (including angioedema, urticaria, rash, bronchospasm, hypotension, and collapse).

RITODRINE HYDROCHLORIDE

Indications uncomplicated premature labour (see notes above)

Cautions see notes above; **interactions:** Appendix 1 (sympathomimetics *and* sympathomimetics, beta$_2$)

Contra-indications see notes above

Side-effects see notes above; also reported flushing, sweating; salivary gland enlargement; leucopenia and agranulocytosis on prolonged administration (several weeks); liver function abnormalities (including increased transaminases and hepatitis)

Dose

- By intravenous infusion (**important:** minimum fluid volume, see below), initially 50 micrograms/minute, increased gradually according to response by 50 micrograms/minute every 10 minutes until contractions stop or maternal heart rate reaches 140 beats per minute; continue for 12–48 hours after contractions cease (usual rate 150–350 micrograms/minute); max. rate 350 micrograms/minute; or by intramuscular injection, 10 mg every 3–8 hours continued for 12–48 hours after contractions have ceased; then by mouth (but see notes above), 10 mg 30 minutes before termination of intravenous infusion, repeated every 2 hours for 24 hours, followed by 10–20 mg every 4–6 hours, max. oral dose 120 mg daily

Important Manufacturer states that although *fatal pulmonary oedema* associated with ritodrine infusion is almost certainly multifactorial in origin, evidence suggests that **fluid overload** may be the most important single factor. The volume of infusion should therefore be kept to a minimum; for further guidance see Appendix 6. For specific guidance on infusion rates, consult product literature

Yutopar® (Durbin) PoM

Tablets, yellow, scored, ritodrine hydrochloride 10 mg, net price 90-tab pack = £30.40

Injection, ritodrine hydrochloride 10 mg/mL, net price 5-mL amp = £3.55

SALBUTAMOL
(Albuterol)

Indications uncomplicated premature labour (see notes above); asthma (section 3.1.1)

Cautions see notes above; **interactions:** Appendix 1 (sympathomimetics, beta$_2$)

Contra-indications see notes above

Side-effects see notes above

Dose

- By intravenous infusion, initially 10 micrograms/minute, rate increased gradually according to response at 10-minute intervals until contractions diminish then increase rate slowly until contractions cease (max. rate 45 micrograms/minute); maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours; then by mouth (but see notes above), 4 mg every 6–8 hours

Preparations

Section 3.1.1.1

TERBUTALINE SULPHATE

Indications uncomplicated premature labour (see notes above); asthma (section 3.1.1)

Cautions see notes above; **interactions:** Appendix 1 (sympathomimetics, beta$_2$)

Contra-indications see notes above

Side-effects see notes above; also reported sleep disturbances and behavioural disturbances

Dose

- By intravenous infusion, 5 micrograms/minute for 20 minutes, increased every 20 minutes in steps of 2.5 micrograms/minute until contractions have ceased (more than 10 micrograms/minute should **seldom** be given—20 micrograms/minute should **not** be exceeded), continue for 1 hour then decrease every 20 minutes in steps of 2.5 micrograms/minute to lowest dose that maintains suppression, continue at this level for 12 hours then by mouth (but see notes above), 5 mg every 8 hours for as long as is desirable to prolong pregnancy (or alternatively follow the intravenous infusion by subcutaneous injection 250 micrograms every 6 hours for a few days then by mouth as above)

Preparations

Section 3.1.1.1

7.2 Treatment of vaginal and vulval conditions

7.2.1 Preparations for vaginal and vulval changes
7.2.2 Vaginal and vulval infections

Symptoms are often restricted to the vulva, but infections almost invariably involve the vagina which should also be treated. Applications to the vulva alone are likely to give only symptomatic relief without cure.

Aqueous medicated douches may disturb normal vaginal acidity and bacterial flora.

Topical anaesthetic agents give only symptomatic relief and may cause sensitivity reactions. They are indicated only in cases of pruritus where specific local causes have been excluded.

Systemic drugs are required in the treatment of infections such as gonorrhoea and syphilis (section 5.1).

7.2.1 Preparations for vaginal and vulval changes

Topical HRT for vaginal atrophy

A cream containing an oestrogen may be applied on a short-term basis to improve the vaginal epithelium in *menopausal atrophic vaginitis*. It is **important** to bear in mind that topical oestrogens should be used in the **smallest effective** amount to minimise systemic effects. Modified-release vaginal tablets and an impregnated vaginal ring are now also available.

The risk of endometrial hyperplasia and carcinoma is increased when *systemic* oestrogens are administered alone for prolonged periods (section 6.4.1.1). The endometrial safety of long-term or repeated use of *topical* vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Topical oestrogens are also used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy.

For a general comment on hormone replacement therapy, including the role of topical oestrogens, see section 6.4.1.1.

OESTROGENS, TOPICAL

Indications see notes above

Cautions see notes above; see also Oestrogens for HRT (section 6.4.1.1); interrupt treatment periodically to assess need for continued treatment

Contra-indications see notes above; see also Oestrogens for HRT (section 6.4.1.1)

Hepatic impairment see Combined Hormonal Contraceptives, section 7.3.1

Pregnancy see Combined Hormonal Contraceptives, section 7.3.1

Breast-feeding avoid; adverse effects on lactation; see also Combined Hormonal Contraceptives, section 7.3.1

Side-effects see notes above; see also Oestrogens for HRT (section 6.4.1.1); local irritation

Gynest® (Marlborough) PoM
Intravaginal cream, estriol 0.01%, net price 80 g with applicator = £4.67
Excipients include arachis (peanut) oil
Condoms may damage latex condoms and diaphragms
Dose insert 1 applicatorful daily, preferably in the evening until improvement occurs, reduced to 1 applicatorful twice a week; attempts to discontinue should be made at 3–6 month intervals with re-examination

Ortho-Gynest® (Janssen-Cilag) PoM
Pessaries, estriol 500 micrograms, net price 15 pessaries = £4.73
Excipients include butylated hydroxytoluene
Condoms damages latex condoms and diaphragms
Dose insert 1 pessary daily, preferably in the evening, until improvement occurs; maintenance 1 pessary twice a week; attempts to reduce or discontinue should be made at 3–6 month intervals with re-examination

Ovestin® (Organon) PoM
Intravaginal cream, estriol 0.1%, net price 15 g with applicator = £4.45
Excipients include cetyl alcohol, polysorbates, stearyl alcohol
Condoms effect on latex condoms and diaphragms not yet known
Dose insert 1 applicator-dose daily for 2–3 weeks, then reduce to twice a week (discontinue every 2–3 months for 4 weeks to assess need for further treatment); vaginal surgery, 1 applicator-dose daily for 2 weeks before surgery, resuming 2 weeks after surgery

Vagifem® (Novo Nordisk) PoM
Vaginal tablets, f/c, estradiol 10 micrograms in disposable applicators, net price 24-applicator pack = £16.72; estradiol 25 micrograms in disposable applicators, 15-applicator pack = £9.50
Excipients none as listed in section 13.1.3
Condoms no evidence of damage to latex condoms and diaphragms
Dose insert 1 vaginal tablet daily for 2 weeks then reduce to 1 tablet twice weekly; initiate therapy with 10 microgram vaginal tablets, increased after 3 months to 25 microgram vaginal tablet if response inadequate

Vaginal ring

Estring® (Pharmacia) PoM
Vaginal ring, releasing estradiol approx. 7.5 micrograms/24 hours, net price 1-ring pack = £31.42. Label: 10, patient information leaflet
Dose for postmenopausal urogenital conditions (not suitable for vasomotor symptoms or osteoporosis prophylaxis), to be inserted into upper third of vagina and worn continuously; replace after 3 months; max. duration of continuous treatment 2 years

Non-hormonal preparations for vaginal atrophy

Replens MD® and *Sylk®* are acidic, non-hormonal vaginal moisturisers; *Replens MD®* provides a high moisture content for up to 3 days.

7.2.2 Vaginal and vulval infections

Effective specific treatments are available for the common vaginal infections.

Fungal infections

Candidal vulvitis can be treated locally with cream, but is almost invariably associated with vaginal infection which should also be treated. *Vaginal candidiasis* is treated primarily with antifungal pessaries or cream inserted high into the vagina (including during menstruation). Single-dose preparations offer an advantage when compliance is a problem. Local irritation may occur on application of vaginal antifungal products.

Imidazole drugs (clotrimazole, econazole, fenticonazole, and miconazole) are effective against candida in short courses of 1 to 14 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur. Vaginal applications may be supplemented with antifungal cream for vulvitis and to treat other superficial sites of infection.

Oral treatment of vaginal infection with **fluconazole** or **itraconazole** (section 5.2.1) is also effective; oral ketoconazole has been associated with fatal hepatotoxicity (see section 5.2.2).

Vulvovaginal candidiasis in pregnancy Vulvovaginal candidiasis is common during pregnancy and can be treated with vaginal application of an imidazole (such as clotrimazole), and a topical imidazole cream for vulvitis. Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

Recurrent vulvovaginal candidiasis Recurrence of vulvovaginal candidiasis is particularly likely if there are predisposing factors such as antibacterial therapy, pregnancy, diabetes mellitus and possibly oral contraceptive use. Reservoirs of infection may also lead to recontamination and should be treated; these include other skin sites such as the digits, nail beds, and umbilicus as well as the gastro-intestinal tract and the bladder. The partner may also be the source of reinfection and, if symptomatic, should be treated with cream at the same time.

Treatment against candida may need to be extended for 6 months in recurrent vulvovaginal candidiasis. Some recommended regimens [all unlicensed] include:

- initially, fluconazole (section 5.2.1) by mouth 150 mg every 72 hours for 3 doses, then 150 mg once every week for 6 months;
- initially, vaginal application of a topical imidazole for 10–14 days, then clotrimazole vaginally 500-mg pessary once every week for 6 months;
- initially, vaginal application of a topical imidazole for 10–14 days, then itraconazole (section 5.2.1) by mouth 50–100 mg daily for 6 months.

PREPARATIONS FOR VAGINAL AND VULVAL CANDIDIASIS

Indications see notes above

Pregnancy see notes above

Side-effects occasional local irritation

Dose

- See under preparations below

Clotrimazole (Non-proprietary)

Cream (topical), clotrimazole 1%, net price 20 g = £1.52 50 g = £4.12

Condoms check with manufacturer of cream for effect on latex condoms and diaphragms

Dose apply to anogenital area 2–3 times daily

Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £3.13

Dose insert 1 pessary at night as a single dose; can be repeated once if necessary

Canesten® (Bayer Consumer Care)

Cream (topical), clotrimazole 1%, net price 20 g = £2.14; 50 g = £3.50

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose apply to anogenital area 2–3 times daily

Thrush Cream (topical), clotrimazole 2%, net price 20 g = £3.99

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose apply to anogenital area 2–3 times daily

Intravaginal cream (*10% VC®*) PoM, clotrimazole 10%, net price 5-g applicator pack = £4.50

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose insert 5 g at night as a single dose; can be repeated once if necessary

Note Brands for sale to the public include *Canesten® Internal Cream*

Cream Combi, clotrimazole 10% vaginal cream and 2% topical cream, net price 5-g vaginal cream (with applicator) and 10-g topical cream = £6.81

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates

Condoms damages latex condoms and diaphragms

Dose see under individual components

Pessaries, clotrimazole 100 mg, net price 6 pessaries with applicator = £3.63; 200 mg, 3 pessaries with applicator = £3.63

Condoms damages latex condoms and diaphragms

Dose insert 200 mg for 3 nights *or* 100 mg for 6 nights; course can be repeated once if necessary

Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £2.00

Excipients none as listed in section 13.1.3

Condoms damages latex condoms and diaphragms

Dose insert 1 pessary at night as a single dose; can be repeated once if necessary

Combi, clotrimazole 500-mg pessary and cream (topical) 2%, net price 1 pessary and 10-g cream = £5.21

Condoms damages latex condoms and diaphragms

Dose see under individual components

Gyno-Daktarin® (Janssen-Cilag) PoM

Intravaginal cream, miconazole nitrate 2%, net price 78 g with applicators = £4.33

Excipients include butylated hydroxyanisole

Condoms damages latex condoms and diaphragms

Dose insert 5-g applicatorful once daily for 10–14 days *or* twice daily for 7 days; course can be repeated once if necessary; *topical*, apply to anogenital area twice daily

Ovule (= vaginal capsule) (*Gyno-Daktarin 1®*), miconazole nitrate 1.2 g in a fatty basis, net price 1 ovule = £2.94
Excipients include hydroxybenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose insert 1 ovule at night as a single dose; can be repeated once if necessary

Gyno-Pevaryl® (Janssen-Cilag) PoM
Cream, econazole nitrate 1%, net price 15 g = £1.32; 30 g = £3.02
Excipients none as listed in section 13.1.3
Condoms damages latex condoms and diaphragms
Dose insert 5-g applicatorful intravaginally and apply to vulva at night for at least 14 nights; course can be repeated once if necessary
Note Applicator available separately from Marlborough
Pessaries, econazole nitrate 150 mg, net price 3 pessaries = £2.78
Excipients none as listed in section 13.1.3
Condoms damages latex condoms and diaphragms
Dose ADULT and CHILD over 16 years, insert 1 pessary for 3 nights; course can be repeated once if necessary
Pessary (*Gyno-Pevaryl 1®*), econazole nitrate 150 mg, formulated for single-dose therapy, net price 1 pessary with applicator = £2.95
Excipients none as listed in section 13.1.3
Condoms damages latex condoms and diaphragms
Dose ADULT and CHILD over 16 years, insert 1 pessary at night as a single dose; can be repeated once if necessary

Gynoxin® (Recordati) PoM
Intravaginal cream, fenticonazole nitrate 2%, net price 30 g with applicator = £3.74
Excipients include cetyl alcohol, hydrogenated wool fat, propylene glycol
Condoms damages latex condoms and diaphragms
Dose insert 5-g applicatorful intravaginally twice daily for 3 days
Vaginal capsule, fenticonazole nitrate 200 mg, net price 3 vaginal capsules = £2.42
Excipients include hydrobenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose insert 1 vaginal capsule at night for 3 nights
Vaginal capsule, fenticonazole nitrate 600 mg, net price 1 vaginal capsule = £2.62
Excipients include hydrobenzoates (parabens)
Condoms damages latex condoms and diaphragms
Dose insert 1 vaginal capsule at night as a single dose

Nizoral® (Janssen-Cilag) PoM
Cream (topical), ketoconazole 2%, net price 30 g = £3.40
Excipients include polysorbates, propylene glycol, stearyl alcohol
Condoms effect on latex condoms and diaphragms not yet known
Dose apply to anogenital area once or twice daily

Other infections

Trichomonal infections commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole or tinidazole (section 5.1.11).

Bacterial infections with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effective against certain Gram-negative organisms, especially *Bacteroides* spp. and can be used prophylactically in gynaecological surgery.

Clindamycin cream and metronidazole gel are indicated for bacterial vaginosis.

Vaginal preparations intended to restore normal acidity may prevent recurrence of vaginal infections and permit the re-establishment of the normal vaginal flora.

The antiviral drugs aciclovir, famciclovir, and valaciclovir can be used in the treatment of genital infection due to *herpes simplex virus*, the HSV type 2 being a major cause of genital ulceration; they have a beneficial effect on virus shedding and healing, generally giving relief from pain and other symptoms. See section 5.3.2.1 for systemic preparations, and section 13.10.3 for topical preparations.

PREPARATIONS FOR OTHER VAGINAL INFECTIONS

Dalacin® (Pharmacia) PoM
Cream, clindamycin 2% (as phosphate), net price 40-g pack with 7 applicators = £10.86
Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol
Condoms damages latex condoms and diaphragms
Side-effects irritation, cervicitis, and vaginitis; poorly absorbed into the blood—low risk of systemic effects, see section 5.1.6
Dose bacterial vaginosis, insert 5-g applicatorful at night for 3–7 nights

Zidoval® (Meda) PoM
Vaginal gel, metronidazole 0.75%, net price 40-g pack with 5 applicators = £4.31
Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol
Cautions not recommended during menstruation; some absorption may occur, see section 5.1.11 for systemic effects
Side-effects local effects including irritation, candidiasis, abnormal discharge, pelvic discomfort
Dose bacterial vaginosis, insert 5-g applicatorful at night for 5 nights

Relactagel® (KoRa)
Vaginal gel, lactic acid 4.5%, glycogen 0.1%, net price 7 × 5 mL-tube = £5.25
Excipients include propylene glycol
Cautions not recommended if trying to conceive
Side-effects mild irritation
Dose prevention of bacterial vaginosis, ADULT over 18 years insert contents of 1 tube at night for 2–3 nights after menstruation

7.3 Contraceptives

7.3.1 Combined hormonal contraceptives
7.3.2 Progestogen-only contraceptives
7.3.3 Spermicidal contraceptives
7.3.4 Contraceptive devices
7.3.5 Emergency contraception

The Fraser Guidelines[1] should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use (available at www.fsrh.org) is published by the Faculty of Sexual and Reproductive Healthcare; it categorises the risks of using contraceptive methods with pre-existing medical conditions.

Hormonal contraception is the most effective method of fertility control, but can have major and minor side-effects, especially for certain groups of women.

Intra-uterine devices are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irre-

1. See Department of Health Guidance (July 2004): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health. Available at www.dh.gov.uk

spective of parity, but are less appropriate for those with an increased risk of pelvic inflammatory disease.

Barrier methods alone (condoms, diaphragms, and caps) are less effective but can be reliable for well-motivated couples if used in conjunction with a **spermicide**. Occasionally sensitivity reactions occur. A female condom (*Femidom®*) is also available; it is prelubricated but does not contain a spermicide.

7.3.1 Combined hormonal contraceptives

Oral contraceptives containing an oestrogen and a progestogen ('combined oral contraceptives') are effective preparations for general use. Advantages of combined oral contraceptives include:

- reliable and reversible;
- reduced dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual tension;
- less symptomatic fibroids and functional ovarian cysts;
- less benign breast disease;
- reduced risk of ovarian and endometrial cancer;
- reduced risk of pelvic inflammatory disease.

Combined oral contraceptives containing a fixed amount of an oestrogen and a progestogen in each active tablet are termed 'monophasic'; those with varying amounts of the two hormones are termed 'phasic'. A transdermal patch and a vaginal ring, both containing an oestrogen with a progestogen, are also available.

Choice The majority of combined oral contraceptives contain ethinylestradiol as the oestrogen component; mestranol and estradiol valerate are also used. The ethinylestradiol content of combined oral contraceptives ranges from 20 to 40 micrograms. Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen.

- *Low strength preparations* (containing ethinylestradiol 20 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable. It is recommended that the combined oral contraceptive is not continued beyond 50 years of age since more suitable alternatives exist.
- *Standard strength preparations* (containing ethinylestradiol 30 or 35 micrograms or in 30–40 microgram *phased* preparations) are appropriate for standard use—but see Risk of Venous Thromboembolism below. Phased preparations are generally reserved for women who *either* do not have withdrawal bleeding *or* who have breakthrough bleeding with monophasic products.

The progestogens desogestrel, drospirenone, and gestodene (in combination with ethinylestradiol) may be considered for women who have side-effects (such as acne, headache, depression, weight gain, breast symptoms, and breakthrough bleeding) with other progestogens. However, women should be advised that desogestrel and gestodene have also been associated with an increased risk of *venous thromboembolism*. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous.

The progestogen norelgestromin is combined with ethinylestradiol in a transdermal patch (*Evra®*).

The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol (*NuvaRing®*).

Risk of venous thromboembolism There is an increased risk of venous thromboembolic disease (particularly during the first year) in users of oral contraceptives, but this risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100 000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors for venous thromboembolism, such as obesity.

The incidence of venous thromboembolism in healthy, non-pregnant women who are not taking an oral contraceptive is about 5–10 cases per 100 000 women per year. For those using combined oral contraceptives containing second-generation progestogens, such as levonorgestrel, this incidence is about 15 per 100 000 women per year of use. The risk of venous thromboembolism with transdermal patches may be slightly increased compared with combined oral contraceptives that contain levonorgestrel. Some studies have reported a greater risk of venous thromboembolism in women using combined oral contraceptives containing the third-generation progestogens desogestrel and gestodene; the incidence in these women is about 25 per 100 000 women per year of use. The absolute risk of venous thromboembolism in women using combined oral contraceptives containing these third-generation progestogens is very small and well below the risk associated with pregnancy. The risk of venous thromboembolism in women using a combined oral contraceptive containing drospirenone may be between that associated with combined oral contraceptives containing second-generation progestogens and those containing third-generation progestogens. The risk of venous thromboembolism associated with vaginal ring use compared to the risk with other combined hormonal contraceptives is unknown.

Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Travel Women taking oral contraceptives or using the patch or vaginal ring are at an increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

Missed pill The critical time for loss of contraceptive protection is when a pill is omitted at the *beginning* or *end* of a cycle (which lengthens the pill-free interval).

If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late; for women taking *Qlaira®*, see below. If a woman misses only one pill, she should take an active pill as soon as

she remembers and then resume normal pill-taking. No additional precautions are necessary.

If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of *everyday* (ED) pills, omitting the 7 inactive tablets).

A missed pill for a woman taking *Qlaira®* is one that is 12 hours or more late; for information on how to manage missed pills in women taking *Qlaira®*, refer to product literature.

Emergency contraception (section 7.3.5) is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet.

Note The Faculty of Sexual and Reproductive Healthcare offers 2 different types of missed pill advice depending on the ethinylestradiol content of the contraceptive pill. The missed pill information above offers the same advice regardless of the ethinylestradiol content of the contraceptive pill; it is a simplified, more cautious version of advice issued by the Faculty of Sexual and Reproductive Healthcare.

Delayed application or detached patch If a patch is partly detached for less than 24 hours, reapply to the same site or replace with a new patch immediately; no additional contraception is needed and the next patch should be applied on the usual 'change day'. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached, then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new 'Day 1'; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch should be applied as soon as remembered giving a new 'Day 1'; additional non-hormonal methods of contraception should be used for the first 7 days of the new cycle. If intercourse has occurred during this extended patch-free interval, a possibility of fertilisation should be considered. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch 'change day' remains the same and no additional contraception is required;
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new 'Day 1'; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual 'change day', the day after day 28; no additional contraception is required.

Expulsion, delayed insertion or removal, or broken vaginal ring If the vaginal ring is expelled for *less than 3 hours*, rinse the ring with cool water and reinsert immediately; no additional contraception is needed.

If the ring remains outside the vagina for *more than 3 hours* or if the user does not know when the ring was expelled, contraceptive protection may be reduced:

- If ring expelled during week 1 or 2 of cycle, rinse ring with cool water and reinsert; use additional precautions (barrier methods) for next 7 days;
- If ring expelled during week 3 of cycle, either insert a new ring to start a new cycle *or* allow a withdrawal bleed and insert a new ring no later than 7 days after ring was expelled; latter option only available if ring was used continuously for at least 7 days before expulsion.

If insertion of a new ring at the start of a new cycle is delayed, contraceptive protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered.

No additional contraception is required if removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring.

If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of combined oral contraceptives. If vomiting occurs within 2 hours of taking a combined oral contraceptive another pill should be taken as soon as possible. In cases of persistent vomiting or severe diarrhoea lasting more than 24 hours, additional precautions should be used during and for 7 days (9 days for *Qlaira®*) after recovery (see also under Missed pill, above). If the vomiting and diarrhoea occurs during the last 7 tablets, the next pill-free interval should be omitted (in the case of ED tablets the inactive ones should be omitted).

Interactions The effectiveness of *combined* oral contraceptives, *progestogen-only* oral contraceptives (section 7.3.2.1), contraceptive patches, and vaginal rings can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. **carbamazepine**, **eslicarbazepine**, **modafinil**, **nelfinavir**, **nevirapine**, **oxcarbazepine**, **phenytoin**, **phenobarbital**, **primidone**, **ritonavir**, **St John's Wort**, **topiramate**, and, above all, **rifabutin** and **rifampicin**). A condom together with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with antiretroviral drugs should be sought from HIV specialists.

For a *short course of an enzyme-inducing drug*, the dose of combined oral contraceptives should be adjusted to provide ethinylestradiol 50 micrograms or more daily [unlicensed use]; furthermore, additional contraceptive precautions should be taken whilst taking the enzyme-inducing drug and for 4 weeks after stopping it. Additional contraceptive precautions are also required for women using contraceptive patches and vaginal rings whilst taking the enzyme-inducing drug and for 4 weeks after stopping. If concomitant administration runs

beyond the 3 weeks of patch or vaginal ring use, a new treatment cycle should be started immediately without a patch-free or ring-free break.

Women requiring a *long-term course of an enzyme-inducing drug* should be encouraged to consider a contraceptive method that is unaffected by the interacting drug. In women unable to use an alternative method of contraception (for rifampicin and rifabutin see also below), a regimen of combined oral contraceptives should be taken which provides a daily intake of ethinylestradiol 50 micrograms or more [unlicensed use]; 'tricycling' (i.e. taking 3 or 4 packets of monophasic tablets without a break followed by a short tablet-free interval of 4 days) may be recommended. **Rifampicin** and **rifabutin** are such potent enzyme-inducing drugs that an alternative method of contraception (such as an IUD) is **always** recommended. Since enzyme activity does not return to normal for several weeks after stopping an enzyme-inducing drug, appropriate contraceptive measures are required for 4 to 8 weeks after stopping. Contraceptive patches and vaginal rings are not recommended for women taking enzyme-inducing drugs over a long period.

In the past there have been concerns that some antibacterials that do not induce liver enzymes (e.g ampicillin, doxycycline) reduce the efficacy of *combined* oral contraceptives by impairing the bacterial flora responsible for recycling ethinylestradiol from the large bowel. However, there is a lack of evidence to support this interaction. Current recommendations are that no additional contraceptive precautions are required when *combined* oral contraceptives are used with antibacterials that do not induce liver enzymes, unless diarrhoea or vomiting occur (see above).

It is also currently recommended that no additional contraceptive precautions are required when contraceptive patches or vaginal rings are used with antibacterials that do not induce liver enzymes.

Surgery Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A progestogen-only contraceptive may be offered as an alternative and the oestrogen-containing contraceptive restarted after mobilisation, as above. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with unfractionated or low molecular weight heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives.

Reason to stop immediately Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped (pending investigation and treatment), if any of the following occur:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse *or* sudden partial or complete loss of vision *or* sudden disturbance of hearing or other perceptual disorders *or* dysphasia *or* bad fainting attack or collapse *or* first unexplained epileptic seizure *or* weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment (see Cautions and Contra-indications under Combined Hormonal Contraceptives below or under Oestrogens for HRT (section 6.4.1.1)).

COMBINED HORMONAL CONTRACEPTIVES

Indications contraception; menstrual symptoms (section 6.4.1.2)

Cautions see notes above; risk factors for venous thromboembolism (see below and also notes above), arterial disease and migraine, see below; personal or family history of hypertriglyceridaemia (increased risk of pancreatitis); hyperprolactinaemia (seek specialist advice); history of severe depression especially if induced by hormonal contraceptive; undiagnosed breast mass; gene mutations associated with breast cancer (e.g. BRCA 1); sickle-cell disease; inflammatory bowel disease including Crohn's disease; reduced efficacy of contraceptive patch in women with body-weight $\geq$ 90 kg; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; **interactions:** see above and Appendix 1 (oestrogens, progestogens)

Risk factors for venous thromboembolism See also notes above. Use with **caution** if any of following factors present but **avoid** if two or more factors present:

- *family history of venous thromboembolism* in first-degree relative aged under 45 years (avoid contraceptive containing desogestrel or gestodene, *or* avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
- *obesity*—body mass index $\geq$ 30 kg/m^2 (avoid if body mass index $\geq$ 35 kg/m^2 unless no suitable alternative);
- *long-term immobilisation* e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
- *history of superficial thrombophlebitis*;
- *age* over 35 years (avoid if over 50 years);
- *smoking*.

Risk factors for arterial disease Use with **caution** if any one of following factors present but **avoid** if two or more factors present:

- *family history of arterial disease* in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
- *diabetes mellitus* (avoid if diabetes complications present);
- *hypertension*—blood pressure above *systolic 140 mmHg* or *diastolic 90 mmHg* (avoid if blood pressure above *systolic 160 mmHg* or *diastolic 95 mmHg*);
- *smoking* (avoid if smoking 40 or more cigarettes daily);
- *age* over 35 years (avoid if over 50 years);
- *obesity* (avoid if body mass index $\geq$ 35 kg/m^2 unless no suitable alternative);

- *migraine without aura* (avoid if *migraine with aura* (focal symptoms), *or* severe migraine frequently lasting over 72 hours despite treatment, *or* migraine treated with ergot derivatives).

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour—see also Reason To Stop Immediately in notes above)

Contra-indications see notes above; personal history of venous or arterial thrombosis, severe or multiple risk factors for arterial disease or for venous thromboembolism (see above), heart disease associated with pulmonary hypertension or risk of embolus; sclerosing treatment for varicose veins; migraine with aura (see also above); transient cerebral ischaemic attacks without headaches; systemic lupus erythematosus with (or unknown) antiphospholipid antibodies; acute porphyria (section 9.8.2); gallstones; history of haemolytic uraemic syndrome or history during pregnancy of pruritus, cholestatic jaundice, chorea, pemphigoid gestationis; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable; undiagnosed vaginal bleeding

Hepatic impairment avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and liver tumours

Pregnancy not known to be harmful

Breast-feeding avoid until weaning or for 6 months after birth (adverse effects on lactation)

Side-effects see notes above; also nausea, vomiting, abdominal cramps, changes in body-weight, liver impairment, hepatic tumours; fluid retention, thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB; see also notes above), hypertension, changes in lipid metabolism; headache, depression, chorea, nervousness, irritability; changes in libido, breast tenderness, enlargement, and secretion; reduced menstrual loss, 'spotting' in early cycles, absence of withdrawal bleeding, amenorrhoea after discontinuation, changes in vaginal discharge, cervical erosion; contact lenses may irritate, visual disturbances; leg cramps; skin reactions, chloasma, photosensitivity; rarely gallstones and systemic lupus erythematosus

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill; this relative risk may be due to an earlier diagnosis. In users of combined oral contraceptive pills the cancers are more likely to be localised to the breast. The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use; any increase in the rate of diagnosis diminishes gradually during the 10 years after stopping and disappears by 10 years

Cervical cancer Use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years. The risk of cervical cancer with transdermal patches and vaginal rings is not yet known

Note The possible small increase in the risk of breast cancer and cervical cancer should be weighed against the protective effect against cancers of the ovary and endometrium

Dose

- By mouth, each tablet should be taken at approximately same time each day; if delayed, contraceptive protection may be lost (see missed pill)

  21-day combined (monophasic) preparations, 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs); first course usually started on day 1 of cycle—if starting on day 4 of cycle or later, additional precautions (barrier methods) necessary during first 7 days

  Every day (ED) combined (monophasic) preparations, 1 *active* tablet starting on day 1 of cycle (see also under preparations below)—if starting on day 4 of cycle or later, additional precautions (barrier methods) necessary during first 7 days; withdrawal bleeding occurs when *inactive* tablets being taken; subsequent courses repeated without interval

  Phasic preparations, see under individual preparations below

  Changing to combined preparation containing different progestogen *21-day combined preparations:* continue current pack until last tablet and start first tablet of new brand the next day. If a 7-day break is taken before starting new brand, additional precautions (barrier methods) should be used during first 7 days (9 days for *Qlaira®*) of taking the new brand

  Every Day (ED) combined preparations: start the new brand (first tablet of a *21-day preparation* or the first *active* tablet of an *ED preparation*) the day after taking the last *active* tablet of previous brand (omitting the *inactive* tablets)

  Changing from progestogen-only tablet Start on day 1 of menstruation or any day if amenorrhoea present and pregnancy has been excluded

  Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days (9 days for *Qlaira®*)

  After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days (9 days for *Qlaira®*)

  After abortion or miscarriage Start same day

- By transdermal application, apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle

  Note If first patch applied later than day 1, additional precautions (abstinence or barrier methods) should be used for the next 7 days

  Changing from combined oral contraception Apply patch on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last *active* tablet, rule out pregnancy before applying first patch. Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days

  Changing from progestogen-only method From an implant, apply first patch on the day implant removed; from an injection, apply first patch when next injection due; from oral progestogen, first patch may be started on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days

  After childbirth (not breast-feeding) Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days

  After abortion or miscarriage Before 20 weeks' gestation start immediately; no additional contraception required if started immediately. After 20 weeks' gestation start on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days after applying the patch

- By vagina, insert ring into vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs)

  Note If first ring inserted later than day 1, additional precautions (barrier methods) should be used for the next 7 days

  Changing from combined hormonal contraception Insert ring at the latest on the day after the usual tablet-free, patch-free, or placebo-tablet interval. If previous con-

traceptive used correctly and pregnancy unlikely, can switch to ring on any day of cycle

Changing from progestogen-only method From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when next injection due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days

After first trimester abortion Start immediately

After childbirth (not breast-feeding) or second trimester abortion Start 4 weeks after birth or abortion; if started later than 4 weeks after birth or abortion, additional precautions (barrier methods) should be used for first 7 days

Oral (low and standard strength)

For information on these preparations, see Combined Oral Contraceptives table, below

Transdermal (standard strength)

Ethinylestradiol with Norelgestromin

See Risk of Venous Thromboembolism in notes above before prescribing

Evra® (Janssen-Cilag) PoM

Patches, self-adhesive (releasing ethinylestradiol approx. 33.9 micrograms/24 hours and norelgestromin approx. 203 micrograms/24 hours); net price 9-patch pack = £16.70. Counselling, administration

Dose 1 patch to be applied once weekly for three weeks, followed by a 7-day patch-free interval; subsequent courses repeated after 7-day patch-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Note Adhesives or bandages should not be used to hold patch in place. If patch no longer sticky do not reapply but use a new patch.

The *Scottish Medicines Consortium* has advised (September 2003) that *Evra®* patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives

Combined Oral Contraceptives
See Risk of Venous Thromboembolism in notes above before prescribing

Type of preparation	Oestrogen content	Progestogen content	Tablets per cycle	Brand	Price, 3-cycle pack (unless stated)	Manufacturer
[1]Monophasic low strength (21-day preparations)	Ethinylestradiol 20 micrograms	Desogestrel 150 micrograms	21	**Gedarel® 20/150**	£5.98	Consilient
				Mercilon®	£7.97	Organon
		Gestodene 75 micrograms	21	**Femodette®**	£8.85	Bayer Schering
				Millinette® 20/75	£6.37	Consilient
				Sunya 20/75®	£6.62	Stragen
		Norethisterone acetate 1 mg	21	**Loestrin 20®**	£2.75	Galen
[1]Monophasic standard strength (21-day preparations)	Ethinylestradiol 30 micrograms	Desogestrel 150 micrograms	21	**Gedarel® 30/150**	£4.93	Consilient
				Marvelon®	£6.45	Organon
		Drospirenone 3 mg	21	[2]**Yasmin®**	£14.70	Bayer Schering
		Gestodene 75 micrograms	21	**Femodene®**	£6.73	Bayer Schering
				Katya 30/75®	£5.03	Stragen
				Millinette® 30/75	£4.85	Consilient
		Levonorgestrel 150 micrograms	21	**Levest®**	£2.55	Morningside
				Microgynon 30®	£2.82	Bayer Schering
				Ovranette®	£2.20	Wyeth
				Rigevidon®	£1.89	Consilient
		Norethisterone acetate 1.5 mg	21	**Loestrin 30®**	£3.95	Galen
	Ethinylestradiol 35 micrograms	Norgestimate 250 micrograms	21	**Cilest®**	3-cycle pack = £2.87; 6-cycle pack = £5.74	Janssen-Cilag
		Norethisterone 500 micrograms	21	**Brevinor®**	£1.99	Pharmacia
				Ovysmen®	£1.49	Janssen-Cilag
		Norethisterone 1 mg	21	**Norimin®**	£2.28	Pharmacia
	Mestranol 50 micrograms	Norethisterone 1 mg	21	**Norinyl-1®**	£2.19	Pharmacia

1. *Dose* 1 tablet daily for 21 days starting on day 1 of cycle; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above
2. *Caution* use with care if increased plasma-potassium concentration might be hazardous; *renal impairment* avoid if eGFR less than 30 mL/minute/1.73 m^2

Combined Oral Contraceptives (*continued*)
See Risk of Venous Thromboembolism in notes above before prescribing

Type of preparation	Oestrogen content	Progestogen content	Tablets per cycle	Brand	Price, 3-cycle pack (unless stated)	Manufacturer
[1]Monophasic standard strength (28-day '*Every day*' preparations)	Ethinylestradiol 30 micrograms	Gestodene 75 micrograms	21 active 7 inactive	**Femodene® ED**	£6.73	Bayer Schering
	Ethinylestradiol 30 micrograms	Levonorgestrel 150 micrograms	21 active 7 inactive	**Microgynon 30 ED®**	£2.54	Bayer Schering
[2]Phasic standard strength (21-day preparations)	Ethinylestradiol 30 micrograms Ethinylestradiol 40 micrograms Ethinylestradiol 30 micrograms	Gestodene 50 micrograms Gestodene 70 micrograms Gestodene 100 micrograms	6 5 10	**Triadene®**	£8.99	Bayer Schering
	Ethinylestradiol 30 micrograms Ethinylestradiol 40 micrograms Ethinylestradiol 30 micrograms	Levonorgestrel 50 micrograms Levonorgestrel 75 micrograms Levonorgestrel 125 micrograms	6 5 10	**Logynon®**	£3.96	Bayer Schering
				TriRegol®	£2.87	Consilient
	Ethinylestradiol 35 micrograms Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms Norethisterone 1 mg	7 14	**BiNovum®**	£1.96	Janssen-Cilag
	Ethinylestradiol 35 micrograms Ethinylestradiol 35 micrograms Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms Norethisterone 1 mg Norethisterone 500 micrograms	7 9 5	**Synphase®**	1-cycle pack = £1.20	Pharmacia
	Ethinylestradiol 35 micrograms Ethinylestradiol 35 micrograms Ethinylestradiol 35 micrograms	Norethisterone 500 micrograms Norethisterone 750 micrograms Norethisterone 1 mg	7 7 7	**TriNovum®**	£2.72	Janssen-Cilag
[1]Phasic standard strength (28-day '*Every day*' preparation)	Ethinylestradiol 30 micrograms Ethinylestradiol 40 micrograms Ethinylestradiol 30 micrograms	Levonorgestrel 50 micrograms Levonorgestrel 75 micrograms Levonorgestrel 125 micrograms	6 active 5 active 10 active 7 inactive	**Logynon ED®**	£3.82	Bayer Schering
[1]Phasic (28-day '*Every day*' preparation)	Estradiol valerate 3 mg Estradiol valerate 2 mg Estradiol valerate 2 mg Estradiol valerate 1 mg	Dienogest 2 mg Dienogest 3 mg	2 active 5 active 17 active 2 active 2 inactive	**Qlaira®** ▼	£25.18	Bayer Schering

1. *Dose* 1 tablet daily for 28 days, starting on day 1 of cycle with first active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval; for starting routines see under Dose above
2. *Dose* 1 tablet daily for 21 days starting on day 1 of cycle; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Vaginal (low strength)

Ethinylestradiol with Etonogestrel

See Risk of Venous Thromboembolism in notes above before prescribing

NuvaRing® (Organon) ▼ PoM

Vaginal ring, releasing ethinylestradiol approx. 15 micrograms/24 hours and etonogestrel approx. 120 micrograms/24 hours, net price 3-ring pack = £27.00. Counselling, administration

Dose 1 ring to be inserted into the vagina, removed on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Counselling The presence of the ring should be checked regularly. In case of expulsion see Expulsion, Delayed Insertion or Removal, or Broken Vaginal Ring, p. 495

7.3.2 Progestogen-only contraceptives

7.3.2.1 Oral progestogen-only contraceptives
7.3.2.2 Parenteral progestogen-only contraceptives
7.3.2.3 Intra-uterine progestogen-only device

7.3.2.1 Oral progestogen-only contraceptives

Oral progestogen-only preparations may offer a suitable alternative when oestrogens are contra-indicated (including those patients with venous thrombosis or a past history or predisposition to venous thrombosis), but may have a higher failure rate than combined preparations. They are suitable for older women, for heavy smokers, and for those with hypertension, valvular heart disease, diabetes mellitus, and migraine. Menstrual irregularities (oligomenorrhoea, menorrhagia) are more common but tend to resolve on long-term treatment.

Interactions Effectiveness of oral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs and an additional or alternative contraceptive method is recommended during treatment with an enzyme-inducing drug and for at least 4 weeks afterwards—see p. 495 and Appendix 1 (progestogens).

Surgery All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined oral contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

Starting routine One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours (12 hours for *Cerazette®*) contraceptive protection may be lost). Additional contraceptive precautions are not necessary when initiating treatment.

Changing from a combined oral contraceptive Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

After childbirth Start any time after 3 weeks postpartum (increased risk of breakthrough bleeding if started earlier).

Missed pill The following advice is now recommended by family planning organisations:

'If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours (12 hours for *Cerazette®*) overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days.'

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception (see p. 505) if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours (12 hours for *Cerazette®*) late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

Diarrhoea and vomiting Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours (12 hours for *Cerazette®*) of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery (see also under Missed pill above).

ORAL PROGESTOGEN-ONLY CONTRACEPTIVES

(Progestogen-only pill, 'POP')

Indications contraception

Cautions arterial disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies; functional ovarian cysts; history of jaundice in pregnancy; **interactions:** see notes above and Appendix 1 (progestogens)

Other conditions The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory

Contra-indications undiagnosed vaginal bleeding; severe arterial disease; acute porphyria (section 9.8.2); history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

Hepatic impairment caution in severe liver disease and recurrent cholestatic jaundice; avoid in liver tumour

Pregnancy not known to be harmful

Breast-feeding progestogen-only contraceptives do not affect lactation; see also After Childbirth above

Side-effects menstrual irregularities (see also notes above); nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbance of appetite, weight changes, changes in libido

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women using, or who have

recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. A possible small increase in the risk of breast cancer should be weighed against the benefits

Dose

- 1 tablet daily at same time each day, starting on day 1 of cycle then continuously; if administration delayed for 3 hours (12 hours for *Cerazette®*) or more it should be regarded as a 'missed pill', see notes above

Cerazette® (Organon) PoM
Tablets, f/c, desogestrel 75 micrograms, net price 3 × 28-tab pack = £8.68
The *Scottish Medicines Consortium* has advised (September 2003) that *Cerazette®* should be restricted for use in women who cannot tolerate oestrogen-containing contraceptives or in whom such preparations are contra-indicated

Femulen® (Pharmacia) PoM
Tablets, etynodiol diacetate 500 micrograms, net price 3 × 28-tab pack = £3.31

Micronor® (Janssen-Cilag) PoM
Tablets, norethisterone 350 micrograms, net price 3 × 28-tab pack = £1.66

Norgeston® (Bayer Schering) PoM
Tablets, s/c, levonorgestrel 30 micrograms, net price 35-tab pack = 92p

Noriday® (Pharmacia) PoM
Tablets, norethisterone 350 micrograms, net price 3 × 28-tab pack = £2.10

7.3.2.2 Parenteral progestogen-only contraceptives

Medroxyprogesterone acetate (*Depo-Provera®*) is a long-acting progestogen given by intramuscular injection; it is as effective as the combined oral preparations but because of its prolonged action it should never be given without *full counselling backed by the patient information leaflet*. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Heavy bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium; delaying the first injection until 6 weeks after birth may minimise bleeding problems. If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of heavy or prolonged bleeding may be increased). The manufacturer advises that in women who are breast-feeding, the first dose should be delayed until 6 weeks after birth; however, evidence suggests no harmful effect to infant if given earlier. The benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks.

Reduction in bone mineral density and, rarely, osteoporosis and osteoporotic fractures have also been reported with medroxyprogesterone acetate. The reduction in bone mineral density occurs in the first 2–3 years of use and then stabilises. See also below.

- In adolescents, medroxyprogesterone acetate (*Depo-Provera®*) should be used only when other methods of contraception are inappropriate;
- in all women, the benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against the risks;
- in women with risk factors for osteoporosis, a method of contraception other than medroxyprogesterone acetate should be considered.

Norethisterone enantate (*Noristerat®*) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

Nexplanon® is a highly effective long-acting contraceptive, consisting of an **etonogestrel-releasing implant** that is inserted subdermally into the lower surface of the upper arm and provides contraception for up to 3 years. The manufacturer advises that in heavier women, blood etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third year; they advise that earlier replacement may be considered in such patients—however, evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of etonogestrel is rapidly reversed on removal of the implant. *The doctor or nurse administering (or removing) the system should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.*

Implanon®, also an etonogestrel-releasing implant, has been discontinued (October 2010), but some women may have the implant in place until 2013.

The cautions, contra-indications, and side-effects of oral progestogen-only contraceptives apply to parenteral progestogen-only contraceptives, except that parenteral preparations reliably inhibit ovulation and therefore protect against ectopic pregnancy and functional ovarian cysts.

Interactions Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. However, effectiveness of norethisterone and etonogestrel (but not depot medroxyprogesterone acetate) may be reduced by enzyme-inducing drugs; additional contraceptive precautions should be taken whilst taking the enzyme-inducing drug and for 4 weeks after stopping it *or* an alternative contraceptive method should be considered if *long-term* use of the enzyme-inducing drug is contemplated.

PARENTERAL PROGESTOGEN-ONLY CONTRACEPTIVES

Indications contraception, see also notes above and under preparations (roles vary according to preparation)

Cautions see notes above and under preparations; possible risk of breast cancer, see oral progestogen-only contraceptives (section 7.3.2.1); history during pregnancy of pruritus or of deterioration of oto-

sclerosis, disturbances of lipid metabolism; **interactions:** see notes above and Appendix 1 (progestogens)
Counselling Full counselling backed by *patient information leaflet* required before administration

Contra-indications see notes above; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

Hepatic impairment see Oral Progestogen-only Contraceptives, section 7.3.2.1

Pregnancy not known to be harmful; for *Implanon®* or *Nexplanon®* if pregnancy occurs remove implant

Breast-feeding progestogen-only contraceptives do not affect lactation; see also notes above and under preparations

Side-effects see notes above; injection-site reactions
Cervical cancer Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives, see p. 496. The risk of cervical cancer with other progestogen-only contraceptives is not yet known.

Dose

- See under preparations

Injectable preparations

Depo-Provera® (Pfizer) PoM
Injection (aqueous suspension), medroxyprogesterone acetate 150 mg/mL, net price 1-mL prefilled syringe = £6.01, 1-mL vial = £6.01. Counselling, see patient information leaflet
Dose by deep intramuscular injection, 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding); for long-term contraception, repeated every 12 weeks (if interval greater than 12 weeks and 5 days, rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection)

Noristerat® (Bayer Schering) PoM
Injection (oily), norethisterone enantate 200 mg/mL, net price 1-mL amp = £3.38. Counselling, see patient information leaflet
Dose by deep intramuscular injection given very slowly *into gluteal muscle*, short-term contraception, 200 mg within first 5 days of cycle or immediately after parturition (duration 8 weeks); may be repeated once after 8 weeks (withhold breast-feeding for neonates with severe or persistent jaundice requiring medical treatment)

Implants

Nexplanon® (Organon) ▼ PoM
Implant, containing etonorgestrel 68 mg in radiopaque flexible rod, net price = £79.46. Counselling, see patient information leaflet
Dose by subdermal implantation, no hormonal contraceptive use in previous month, 1 implant inserted during first 5 days of cycle; postpartum, 1 implant inserted 21–28 days after delivery; in breast-feeding mothers, 1 implant inserted after 28 days postpartum; abortion or miscarriage in the second trimester, 1 implant inserted 21–28 days after abortion or miscarriage; abortion or miscarriage in first trimester, 1 implant inserted within 5 days; changing from other hormonal contraceptive, consult product literature; remove implant within 3 years of insertion

7.3.2.3 Intra-uterine progestogen-only device

The progestogen-only intra-uterine system, *Mirena®*, releases **levonorgestrel** directly into the uterine cavity. It is licensed for use as a contraceptive, for the treatment of primary menorrhagia and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. This may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogenic activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete.

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhoea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time (section 6.4.1.2).

Cautions and contra-indications Generally the cautions and contra-indications for the progestogen-only intra-uterine system are as for standard intra-uterine devices (section 7.3.4), but the risk of ectopic pregnancy is considerably smaller. Although the progestogen-only intra-uterine system produces little systemic progestogenic activity, it is usually avoided for 5 years after any evidence of breast cancer. However, the system can be considered for a woman in long-term remission from breast cancer who has menorrhagia and requires effective contraception. Since levonorgestrel is released close to the site of the main contraceptive action (on cervical mucus and endometrium) progestogenic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen-only intra-uterine system and additional contraceptive precautions are not required.

Side-effects Initially, changes in the pattern and duration of menstrual bleeding (spotting or prolonged bleeding) are common; endometrial disorders should be ruled out before insertion and the patient should be fully counselled (and provided with a patient information leaflet). Improvement in progestogenic side-effects, such as mastalgia and in the bleeding pattern usually occurs a few months after insertion and bleeding may often become very light or absent. Functional ovarian cysts (usually asymptomatic) can occur and usually resolve spontaneously (ultrasound monitoring recommended).

INTRA-UTERINE PROGESTOGEN-ONLY SYSTEM

Indications see under preparation

Cautions see notes above; history of depression; advanced uterine atrophy; systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies; not suitable for emergency contraception; **interactions:** see notes above and Appendix 1 (progestogens)

Contra-indications see notes above

Hepatic impairment see Oral Progestogen-only Contraceptives, section 7.3.2.1

Pregnancy avoid; if pregnancy occurs remove system

Breast-feeding progestogen-only contraceptives do not affect lactation

Side-effects see notes above; also abdominal pain; peripheral oedema; depression (sometimes severe), nervousness; salpingitis and pelvic inflammatory disease; pelvic pain, back pain; *rarely* hirsutism, hair loss, pruritus, migraine, rash

Dose

- See under preparation

Mirena® (Bayer Schering) PoM

Intra-uterine system, T-shaped plastic frame (impregnated with barium sulphate and with threads attached to base) with polydimethylsiloxane reservoir releasing levonorgestrel 20 micrograms/24 hours, net price = £85.66. Counselling, see patient information leaflet

Dose contraception and menorrhagia, insert into uterine cavity within 7 days of onset of menstruation or any time if replacement, or any time if reasonably certain woman is not pregnant and there is no risk of conception (additional precautions (e.g. barrier methods) necessary for next 7 days), or immediately after first-trimester termination by curettage; postpartum insertions should be delayed until at least 4 weeks after delivery; effective for 5 years.

Prevention of endometrial hyperplasia during oestrogen replacement therapy, insert during last days of menstruation or withdrawal bleeding or any time if amenorrhoeic; effective for 4 years

Note When system is removed (and not immediately replaced), if pregnancy is not desired, remove during the first few days of the onset of menstruation, otherwise additional contraceptive measures should be used for at least 7 days before removal

7.3.3 Spermicidal contraceptives

Spermicidal contraceptives are useful additional safeguards but do **not** give adequate protection if used alone unless fertility is already significantly diminished (section 6.4.1.1). They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however, spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted infections (including HIV); high frequency use of the spermicide nonoxinol '9' has been associated with genital lesions, which may increase the risk of acquiring these infections.

Products such as petroleum jelly (*Vaseline®*), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted infections (including HIV).

Gygel® (Marlborough)

Gel, nonoxinol '9' 2%, net price 30 g = £4.25

Excipients include hydroxybenzoates (parabens), propylene glycol, sorbic acid

Condoms no evidence of harm to latex condoms and diaphragms

Breast-feeding present in milk in *animal* studies

7.3.4 Contraceptive devices

Intra-uterine devices

The intra-uterine device (IUD) is a suitable contraceptive for women of all ages irrespective of parity; however, it is less appropriate for those with an increased risk of pelvic inflammatory disease (see below). The most effective intra-uterine devices have at least 380 mm^2 of copper and have banded copper on the arms.

Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper. Fertility declines with age and therefore a copper intra-uterine device which is fitted in a woman over the age of 40, may remain in the uterus until menopause.

A frameless, copper-bearing intra-uterine device (*GyneFix®*) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus. The intra-uterine devices *Multiload® Cu250* and *Multiload® Cu250 Short* (Organon) have been discontinued, but some women may have the devices in place until 2011.

The timing and technique of fitting an intra-uterine device are critical for its subsequent performance. *The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling backed, where available, by the patient information leaflet.* Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation. The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted infection. Women are considered to be at a higher risk of sexually transmitted infections if:

- they are under 25 years old *or*
- they are over 25 years old *and*
  - have a new partner *or*
  - have had more than one partner in the past year *or*
  - their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history and local prevalence of disease, *Neisseria gonorrhoeae*) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend *as an emergency* if she experiences sustained pain during the next 20 days.

An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for

the previous 7 days. If removal is essential post-coital contraception should be considered.

If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible.

INTRA-UTERINE CONTRACEPTIVE DEVICES

Indications see notes above

Cautions see notes above; also anaemia, menorrhagia (progestogen intra-uterine system might be preferable, section 7.3.2.3), endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, diabetes, fertility problems, nulliparity and young age, severely scarred uterus (including after endometrial resection) or severe cervical stenosis; drug- or disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression); epilepsy (risk of seizure at time of insertion); increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion, 6–8 weeks after then annually but counsel women to see doctor promptly in case of significant symptoms, especially pain; anticoagulant therapy (avoid if possible)

Contra-indications severe anaemia, recent sexually transmitted infection (if not fully investigated and treated), unexplained uterine bleeding, distorted or small uterine cavity, genital malignancy, active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration), pelvic inflammatory disease, established or marked immunosuppression; *copper devices:* copper allergy, Wilson's disease, medical diathermy

Pregnancy remove device; if pregnancy occurs, increased likelihood that it may be ectopic

Breast-feeding not known to be harmful

Side-effects uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated, menorrhagia, dysmenorrhoea, allergy; *on insertion*: pain (alleviated by NSAID such as ibuprofen 30 minutes before insertion) and bleeding, occasionally epileptic seizure and vasovagal attack

Cu-Safe® T300 (Williams) NHS

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 300 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.11

For uterine length over 5 cm; replacement every 5 years (see also notes above)

Flexi-T® 300 (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 300 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.47

For uterine length over 5 cm; replacement every 5 years (see also notes above)

Flexi-T® + 380 (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeve on each arm, total surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £10.06

For uterine length over 6 cm; replacement every 5 years (see also notes above)

GyneFix® (Williams)

Intra-uterine device, 6 copper sleeves with surface area of 330 mm^2 on polypropylene thread, net price = £26.64

Suitable for all uterine sizes; replacement every 5 years

Load® 375 (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.52

For uterine length over 7 cm; replacement every 5 years (see also notes above)

Mini TT 380® Slimline (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; easy-loading system, no capsule, net price = £12.46

For minimum uterine length 5 cm; replacement every 5 years (see also notes above)

Multiload® Cu375 (Organon)

Intra-uterine device, as *Load® 375*, with copper surface area approx. 375 mm^2 and vertical stem length 3.5 cm, net price = £9.24

For uterine length 6–9 cm; replacement every 5 years (see also notes above)

Multi-Safe® 375 (Williams)

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.80

For uterine length over 6–9 cm; replacement every 5 years (see also notes above)

Multi-Safe® 375 Short Stem (Williams) NHS

Intra-uterine device, copper wire, wound on vertical stem of U-shaped plastic carrier, surface area approx. 375 mm^2, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.80

For uterine length 5–7 cm; replacement every 5 years (see also notes above)

Neo-Safe® T380 (Williams)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, threads attached to base of vertical stem, net price = £13.80

For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Nova-T® 380 (Bayer Schering)

Intra-uterine device, copper wire with silver core, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, threads attached to base of vertical stem, net price = £12.97

For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

T-Safe® 380A QuickLoad (Williams)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper collar on the distal portion of each arm, total surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, threads attached to base of vertical stem, quick-loading system, net price = £10.29; also available with a capsule loading device (*T-Safe® 380A Capped* NHS), net price = £10.29

For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)

TT 380® Slimline (Durbin)

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area approx. 380 mm^2, impregnated with barium sulphate for

radio-opacity, thread attached to base of vertical stem; easy-loading system, no capsule, net price = £12.46
For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)

UT 380 Short® (Durbin)
Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; net price = £11.22
For uterine length 5–7 cm; replacement every 5 years (see also notes above)

UT 380 Standard® (Durbin)
Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier, surface area approx. 380 mm^2, impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; net price = £11.22
For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Other contraceptive devices

Rubber contraceptive caps

Type A Contraceptive Pessary
Opaque rubber, sizes 1 (50 mm), 2 (55 mm), 3 (60 mm), 4 (65 mm), 5 (75 mm), net price = £6.85

Type B Contraceptive Pessary
Opaque rubber, sizes 22 to 31 mm (rising in steps of 3 mm), net price = £8.46

Type C Contraceptive Pessary
Opaque rubber, sizes 1 to 3 (42, 48, and 54 mm), net price = £7.26

Silicone contraceptive caps

Silicone Contraceptive Pessary
Silicone, sizes 22, 26, and 30 mm, net price = £15.00
Brands include *FemCap®*

Rubber contraceptive diaphragms

Type A Diaphragm with Flat Metal Spring
Transparent rubber with flat metal spring, sizes 55–95 mm (rising in steps of 5 mm), net price = £5.78
Brands include *Reflexions®*

Type B Diaphragm with Coiled Metal Spring
Opaque rubber with coiled metal spring, sizes 60–100 mm (rising in steps of 5 mm), net price = £6.79

Type C Arcing Spring Diaphragm
Opaque rubber with arcing spring, sizes 60–95 mm (rising in steps of 5 mm), net price = £7.72

Silicone contraceptive diaphragms

Type B Diaphragm with Coiled Metal Spring
Silicone with coiled metal spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35
Brands include *Milex Omniflex®*

Type C Arcing Spring Diaphragm
Silicone with arcing spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35
Brands include *Milex Arcing Style®*, *Ortho All-flex®*

7.3.5 Emergency contraception

Hormonal methods

Hormonal emergency contraceptives include **levonorgestrel** and **ulipristal**; either drug should be taken as soon as possible after unprotected intercourse to increase efficacy.

Levonorgestrel is effective if taken within 72 hours (3 days) of unprotected intercourse and may also be used between 72 and 120 hours after unprotected intercourse [unlicensed use], but efficacy decreases with time. Ulipristal, a progesterone receptor modulator, is effective if taken within 120 hours (5 days) of unprotected intercourse.

Levonorgestrel is less effective than insertion of an intra-uterine device (see below). Ulipristal is as effective as levonorgestrel, but its efficacy compared to an intra-uterine device is not yet known.

If vomiting occurs within 2 hours of taking levonorgestrel or within 3 hours of taking ulipristal, a replacement dose should be given. If an antiemetic is required domperidone is preferred.

When prescribing hormonal emergency contraception the doctor should explain:

- that the next period may be early or late;
- that a barrier method of contraception needs to be used until the next period;
- the need to return promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy (and also in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned).

Interactions The effectiveness of levonorgestrel, and possibly ulipristal, is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping); a copper intra-uterine device can be offered instead or the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.

LEVONORGESTREL

Indications emergency contraception
Cautions see notes above; past ectopic pregnancy; severe malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration)—seek specialist advice; **interactions:** see notes above and Appendix 1 (progestogens)
Contra-indications acute porphyria (section 9.8.2)
Pregnancy not known to be harmful
Breast-feeding progestogen-only contraceptives do not affect lactation
Side-effects menstrual irregularities (see also notes above), nausea, low abdominal pain, fatigue, headache, dizziness, breast tenderness, vomiting
Dose
- 1.5 mg as a single dose as soon as possible after coitus (preferably within 12 hours but no later than after 72 hours)

[1]**Levonelle® One Step** (Bayer Schering)
Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £13.83

1. Can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society of Great Britain

Levonelle® 1500 (Bayer Schering) PoM
Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £5.20

ULIPRISTAL ACETATE

Indications emergency contraception

Cautions see notes above; uncontrolled severe asthma; effectiveness of combined hormonal and progestogen-only contraceptives may be reduced—additional precautions (barrier methods) required; repeated use within a menstrual cycle; **interactions:** see notes above and Appendix 1 (ulipristal)

Hepatic impairment manufacturer advises avoid in severe impairment—no information available

Pregnancy limited information available

Breast-feeding manufacturer advises avoid for at least 36 hours—no information available

Side-effects gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, and abdominal pain); dizziness, fatigue, headache; menstrual irregularities (see notes above); back pain, muscle spasms; *less commonly* tremor, hot flushes, uterine spasm, breast tenderness, dry mouth, blurred vision, pruritus, and rash

Dose

- 30 mg as a single dose as soon as possible after coitus, but no later than after 120 hours

ellaOne® (HRA Pharma) ▼ PoM

Tablets, ulipristal acetate 30 mg, net price 1-tab pack = £16.95

Intra-uterine device

Insertion of an intra-uterine device is more effective than oral levonorgestrel for emergency contraception. A copper intra-uterine contraceptive device (section 7.3.4) can be inserted up to 120 hours (5 days) after unprotected intercourse; sexually transmitted infections should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis (e.g. azithromycin 1 g as a single dose). If intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation), regardless of the number of episodes of unprotected intercourse earlier in the cycle.

7.4 Drugs for genito-urinary disorders

7.4.1 Drugs for urinary retention
7.4.2 Drugs for urinary frequency, enuresis, and incontinence
7.4.3 Drugs used in urological pain
7.4.4 Bladder instillations and urological surgery
7.4.5 Drugs for erectile dysfunction

For drugs used in the treatment of urinary-tract infections see section 5.1.13.

7.4.1 Drugs for urinary retention

Acute retention is painful and is treated by catheterisation.

Chronic retention is painless and often long-standing. Catheterisation is unnecessary unless there is deterioration of renal function. After the cause has initially been established and treated, drugs may be required to increase detrusor muscle tone.

Benign prostatic hyperplasia is treated either surgically or medically with alpha-blockers (see below). Dutasteride and finasteride (section 6.4.2) are alternatives to alpha-blockers, particularly in men with a significantly enlarged prostate.

Alpha-blockers

The alpha$_1$-selective alpha blockers, **alfuzosin**, **doxazosin**, **indoramin**, **prazosin**, **tamsulosin** and **terazosin** relax smooth muscle in benign prostatic hyperplasia producing an increase in urinary flow-rate and an improvement in obstructive symptoms.

Cautions Since alpha$_1$-selective alpha blockers reduce blood pressure, patients receiving antihypertensive treatment may require reduced dosage and specialist supervision. Caution is required in the elderly and in patients undergoing cataract surgery (risk of intra-operative floppy iris syndrome). For **interactions**, see Appendix 1 (alpha-blockers).

Contra-indications Alpha-blockers should be avoided in patients with a history of postural hypotension and micturition syncope.

Side-effects Side-effects of alpha$_1$-selective alpha blockers include drowsiness, hypotension (notably postural hypotension), syncope, asthenia, dizziness, depression, headache, dry mouth, gastro-intestinal disturbances, oedema, blurred vision, intra-operative floppy iris syndrome (most strongly associated with tamsulosin), rhinitis, erectile disorders (including priapism), tachycardia, and palpitations. Hypersensitivity reactions including rash, pruritus and angioedema have also been reported.

ALFUZOSIN HYDROCHLORIDE

Indications benign prostatic hyperplasia

Cautions see notes above; discontinue if angina worsens

Driving May affect performance of skilled tasks e.g. driving

Contra-indications see notes above

Hepatic impairment initial dose 2.5 mg once daily, adjusted according to response to 2.5 mg twice daily in mild to moderate impairment—avoid if severe; avoid modified-release preparations

Renal impairment initial dose 2.5 mg twice daily and adjust according to response; manufacturers advise use modified-release preparations with caution in severe impairment as limited experience

Side-effects see notes above; also *less commonly* flushes and chest pain; *also reported* liver damage and cholestasis

Dose

- 2.5 mg 3 times daily, max. 10 mg daily; ELDERLY initially 2.5 mg twice daily

  First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely

Alfuzosin hydrochloride (Non-proprietary) PoM

Tablets, f/c, alfuzosin hydrochloride 2.5 mg, net price 60-tab pack = £20.37. Counselling, initial dose, driving, see above

Xatral® (Sanofi-Aventis) PoM

Tablets, f/c, alfuzosin hydrochloride 2.5 mg, net price 60-tab pack = £20.37. Counselling, initial dose, driving, see above

Modified release

Besavar® XL (Winthrop) PoM

Tablets, m/r, yellow/white, alfuzosin hydrochloride 10 mg, net price 30-tab pack = £12.51. Label: 21, 25, counselling, initial dose, driving, see above

Dose benign prostatic hyperplasia 10 mg once daily

Acute urinary retention associated with benign prostatic hyperplasia in men over 65 years, 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days

Vasran® XL (Ranbaxy) PoM

Tablets, m/r, alfuzosin hydrochloride 10 mg, net price 30-tab pack = £11.48. Label: 21, 25, counselling, initial dose, driving, see above

Dose benign prostatic hyperplasia 10 mg once daily

Xatral® XL (Sanofi-Aventis) PoM

Tablets, m/r, yellow/white, alfuzosin hydrochloride 10 mg, net price 10-tab pack = £4.17, 30-tab pack = £12.51. Label: 21, 25, counselling, initial dose, driving, see above

Dose benign prostatic hyperplasia 10 mg once daily

Acute urinary retention associated with benign prostatic hyperplasia in men over 65 years, 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days

DOXAZOSIN

Indications benign prostatic hyperplasia; hypertension (section 2.5.4)

Cautions see notes above and section 2.5.4

Contra-indications see notes above

Hepatic impairment section 2.5.4

Side-effects see notes above and section 2.5.4

Dose

- Initially 1 mg daily; dose may be doubled at intervals of 1–2 weeks according to response, up to max. 8 mg daily; usual maintenance 2–4 mg daily

Preparations

Section 2.5.4

INDORAMIN

Indications benign prostatic hyperplasia; hypertension (section 2.5.4)

Cautions see notes above and section 2.5.4

Contra-indications see notes above and section 2.5.4

Hepatic impairment section 2.5.4

Renal impairment section 2.5.4

Side-effects see notes above and section 2.5.4

Dose

- 20 mg twice daily; increased if necessary by 20 mg every 2 weeks to max. 100 mg daily in divided doses; ELDERLY, 20 mg at night may be adequate

Doralese® (Chemidex) PoM

Tablets, yellow, f/c, indoramin 20 mg, net price 60-tab pack = £25.85. Label: 2

PRAZOSIN

Indications benign prostatic hyperplasia; hypertension, congestive heart failure and Raynaud's syndrome (section 2.5.4)

Cautions see notes above and section 2.5.4

Contra-indications see notes above and section 2.5.4

Hepatic impairment section 2.5.4

Renal impairment section 2.5.4

Side-effects see notes above and section 2.5.4

Dose

- Initially 500 micrograms twice daily for 3–7 days, subsequently adjusted according to response; usual maintenance (and max.) 2 mg twice daily; ELDERLY initiate with lowest possible dose

  First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely

Preparations

Section 2.5.4

TAMSULOSIN HYDROCHLORIDE

Indications benign prostatic hyperplasia

Cautions see notes above

Driving May affect performance of skilled tasks e.g. driving

Contra-indications see notes above

Hepatic impairment avoid in severe impairment

Renal impairment use with caution if eGFR less than 10 mL/minute/1.73 m^2

Side-effects see notes above

Dose

- 400 micrograms daily

[1]**Tamsulosin hydrochloride** (Non-proprietary) PoM

Capsules, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-cap pack = £4.62. Label: 25, counselling, driving

Brands include *Bazetham® MR, Contiflo® XL, Diffundox® XL, Pinexel® PR, Stronazon® MR, Tabphyn® MR*

1. Tamsulosin hydrochloride 400 microgram capsules can be sold to the public for the treatment of functional symptoms of benign prostatic hyperplasia in men aged 45–75 years to be taken for up to 6 weeks before clinical assessment by a doctor; a proprietary brand *Flomax Relief® MR* is on sale to the public

Flomaxtra® XL (Astellas) PoM

Tablets, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-tab pack = £10.47. Label: 25, counselling, driving

With dutasteride

For prescribing information on dutasteride, see section 6.4.2

Combodart® (GSK) ▼ PoM

Capsules, m/r, brown/orange, tamsulosin hydrochloride 400 micrograms, dutasteride 500 micrograms, net price 30-cap pack = £19.80. Label: 25, counselling, driving

Dose benign prostatic hyperplasia, 1 capsule daily

TERAZOSIN

Indications benign prostatic hyperplasia; hypertension (section 2.5.4)

Cautions see notes above and section 2.5.4

Driving May affect performance of skilled tasks e.g. driving

Contra-indications see notes above

Side-effects see notes above and section 2.5.4

Dose

- Initially 1 mg at bedtime; if necessary dose may be doubled at intervals of 1–2 weeks according to response, up to max. 10 mg once daily; usual maintenance 5–10 mg daily

  First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely

Terazosin (Non-proprietary) PoM

Tablets, terazosin (as hydrochloride) 2 mg, net price 28-tab pack = £2.16; 5 mg, 28-tab pack = £2.58; 10 mg, 28-tab pack = £7.88. Counselling, initial dose, driving

Hytrin® (Amdipharm) PoM

Tablets, terazosin (as hydrochloride) 2 mg (yellow) net price, 28-tab pack = £2.29; 5 mg (tan), 28-tab pack = £4.29; 10 mg (blue), 28-tab pack = £8.57; starter pack (for benign prostatic hyperplasia) of 7 × 1-mg tab with 14 × 2-mg tab and 7 × 5-mg tab = £10.97. Label: 3, counselling, see dose above

Parasympathomimetics

The parasympathomimetic **bethanechol** increases detrusor muscle contraction. However, it has only a limited role in the relief of urinary retention; its use has been superseded by catheterisation.

Distigmine inhibits the breakdown of acetylcholine. It may help patients with an upper motor neurone neurogenic bladder.

BETHANECHOL CHLORIDE

Indications urinary retention, but see notes above

Cautions autonomic neuropathy (use lower initial dose); **interactions:** Appendix 1 (parasympathomimetics)

Contra-indications peptic ulcer; intestinal or urinary obstruction; conditions where increased motility of the urinary or gastro-intestinal tract could be harmful; cardiovascular disorders (including recent myocardial infarction, bradycardia, and heart block); hypotension; obstructive airways disease; epilepsy; parkinsonism; hyperthyroidism

Pregnancy manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid; gastrointestinal disturbances in infant reported

Side-effects nausea, vomiting, diarrhoea, abdominal pain, increased salivation, eructation; flushing, hypotension, bradycardia; bronchoconstriction, rhinorrhoea; headache; increased lacrimation; increased sweating

Dose

- 10–25 mg 3–4 times daily half an hour before food

Myotonine® (Glenwood) PoM

Tablets, scored, bethanechol chloride 10 mg, net price 100-tab pack = £5.07; 25 mg, 100-tab pack = £6.48. Label: 22

DISTIGMINE BROMIDE

Indications postoperative urinary retention (see notes above), neurogenic bladder; myasthenia gravis (section 10.2.1)

Cautions peptic ulcer; conditions where increased motility of the urinary or gastro-intestinal tract could be harmful; oesophagitis; cardiovascular disease; bronchospasm; epilepsy; parkinsonism; **interactions:** Appendix 1 (parasympathomimetics)

Contra-indications intestinal or urinary obstruction; severe circulatory insufficiency; asthma

Pregnancy manufacturer advises avoid (may stimulate uterine contractions)

Breast-feeding manufacturer advises avoid—no information available

Side-effects abdominal pain, diarrhoea, increased salivation; bradycardia, AV block, hypotension; dyspnoea; muscle twitching; increased lacrimation, miosis; increased sweating

Dose

- Urinary retention, 5 mg daily, half an hour before breakfast
- Neurogenic bladder, 5 mg daily or on alternate days, half an hour before breakfast

Ubretid® (Sanofi-Aventis) PoM

Tablets, scored, distigmine bromide 5 mg, net price 30-tab pack = £41.22. Label: 22

7.4.2 Drugs for urinary frequency, enuresis, and incontinence

Urinary incontinence

Incontinence in adults which arises from detrusor instability is managed by combining drug therapy with conservative methods for managing urge incontinence such as pelvic floor exercises and bladder training; stress incontinence is generally managed by non-drug methods. **Duloxetine**, an inhibitor of serotonin and noradrenaline re-uptake can be added and is licensed for the treatment of moderate to severe stress incontinence in women; it may be more effective when used as an adjunct to pelvic floor exercises.

Antimuscarinic drugs reduce symptoms of urgency and urge incontinence and increase bladder capacity. **Oxybutynin** also has a direct relaxant effect on urinary smooth muscle. Side-effects limit the use of oxybutynin, but they may be reduced by starting at a lower dose. A modified-release preparation of oxybutynin is effective and has fewer side-effects; a transdermal patch is also available. The efficacy and side-effects of **tolterodine** are comparable to those of modified-release oxybutynin. **Flavoxate** has less marked side-effects but it is also less effective. **Darifenacin**, **fesoterodine**, **propiverine**,

solifenacin, and **trospium** are newer antimuscarinic drugs licensed for urinary frequency, urgency, and incontinence. The need for continuing antimuscarinic drug therapy should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months.

The *Scottish Medicines Consortium* (p. 4) has advised (June 2008) that fesoterodine (*Toviaz®*) is accepted for restricted use within NHS Scotland as a second-line treatment for overactive bladder syndrome.

Propantheline and tricyclic antidepressants were used for urge incontinence but they are little used now because of their side-effects. The use of imipramine is limited by its potential to cause cardiac side-effects.

Purified bovine collagen implant (*Contigen®*, Bard) is indicated for *urinary incontinence* caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism). The implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.

Cautions Antimuscarinic drugs should be used with caution in the elderly (especially if frail), in those with autonomic neuropathy, and in those susceptible to angle-closure glaucoma. They should also be used with caution in hiatus hernia with reflux oesophagitis. Antimuscarinics can worsen hyperthyroidism, coronary artery disease, congestive heart failure, hypertension, prostatic hyperplasia, arrhythmias, and tachycardia. For **interactions**, see Appendix 1 (antimuscarinics).

Contra-indications Antimuscarinic drugs should be avoided in patients with myasthenia gravis, significant bladder outflow obstruction or urinary retention, severe ulcerative colitis, toxic megacolon, and in gastro-intestinal obstruction or intestinal atony.

Side-effects Side-effects of antimuscarinic drugs include dry mouth, gastro-intestinal disturbances including constipation, flatulence, taste disturbances, blurred vision, dry eyes, drowsiness, dizziness, fatigue, difficulty in micturition (less commonly urinary retention), palpitation, and skin reactions (including dry skin, rash, and photosensitivity); also headache, diarrhoea, angioedema, arrhythmias, and tachycardia. Central nervous system stimulation, such as restlessness, disorientation, hallucination, and convulsion may occur; children are at higher risk of these effects. Antimuscarinic drugs can reduce sweating, leading to heat sensations and fainting in hot environments or in patients with fever, and *very rarely* may precipitate angle-closure glaucoma.

DARIFENACIN

Indications urinary frequency, urgency, and incontinence

Cautions see notes above

Contra-indications see notes above

Hepatic impairment max. 7.5 mg daily in moderate impairment; avoid in severe impairment

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding present in milk in *animal* studies—manufacturer advises caution

Side-effects see notes above; also *less commonly* ulcerative stomatitis, oedema, hypertension, dyspnoea, cough, rhinitis, weakness, insomnia, impotence, and vaginitis

Dose

- ADULT over 18 years, 7.5 mg once daily, increased if necessary after 2 weeks to 15 mg once daily

Emselex® (Novartis) PoM

Tablets, m/r, darifenacin (as hydrobromide) 7.5 mg (white), net price 28-tab pack = £20.90; 15 mg (peach), 28-tab pack = £20.90. Label: 3, 25

DULOXETINE

Indications moderate to severe stress urinary incontinence in women; major depressive disorder (section 4.3.4); diabetic neuropathy (section 4.3.4); generalised anxiety disorder (section 4.3.4)

Cautions elderly; cardiac disease; hypertension (avoid if uncontrolled); history of mania; history of seizures; raised intra-ocular pressure, susceptibility to angle-closure glaucoma; bleeding disorders or concomitant use of drugs that increase risk of bleeding; **interactions**: Appendix 1 (duloxetine)

Withdrawal Nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances, and tremor are the most common features of abrupt withdrawal or marked reduction of the dose; dose should be reduced over at least 1–2 weeks

Hepatic impairment manufacturer advises avoid

Renal impairment avoid if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy toxicity in *animal* studies—avoid in patients with stress urinary incontinence; risk of neonatal withdrawal symptoms if used near term

Breast-feeding present in milk—manufacturer advises avoid

Side-effects nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain, weight changes, decreased appetite, flatulence, dry mouth; palpitation, hot flush; insomnia, abnormal dreams, paraesthesia, drowsiness, anxiety, headache, dizziness, fatigue, weakness, tremor, nervousness, anorexia; sexual dysfunction; visual disturbances; sweating, pruritus; *less commonly* gastritis, halitosis, hepatitis, bruxism, tachycardia, hypertension, postural hypotension, syncope, raised cholesterol, vertigo, taste disturbance, cold extremities, impaired temperature regulation, impaired attention, movement disorders, muscle twitching, musculoskeletal pain, thirst, stomatitis, hypothyroidism, urinary disorders, and photosensitivity; *rarely* mania; *very rarely* angle-closure glaucoma; *also reported* supraventricular arrhythmia, chest pain, hallucinations, suicidal behaviour (see Suicidal Behaviour and Antidepressant Therapy, p. 233), seizures, hypersensitivity reactions including urticaria, angioedema, rash (including Stevens-Johnson syndrome) and anaphylaxis, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 233)

Dose

- ADULT over 18 years, 40 mg twice daily, assess for benefit and tolerability after 2–4 weeks

  Note Initial dose of 20 mg twice daily for 2 weeks can minimise side-effects

Yentreve® (Lilly) ▼ PoM

Capsules, duloxetine (as hydrochloride) 20 mg (blue), net price 28-cap pack = £18.48, 56-cap pack = £30.80; 40 mg (orange/blue), 56-cap pack = £36.96. Label: 2

Cymbalta® (Lilly) ▼ PoM

Section 4.3.4 (major depressive episode, generalised anxiety disorder, and diabetic neuropathy)

FESOTERODINE FUMARATE

Indications urinary frequency, urgency, and urge incontinence

Cautions see notes above; gastro-oesophageal reflux

Contra-indications see notes above

Hepatic impairment manufacturer advises increase dose cautiously; max. 4 mg daily in moderate impairment; avoid in severe impairment; consult product literature before concomitant use of cytochrome P450 enzyme inhibitors

Renal impairment increase dose cautiously if eGFR 30–80 mL/minute/1.73 m^2; max. 4 mg daily if eGFR less than 30 mL/minute/1.73 m^2; consult product literature before concomitant use of cytochrome P450 enzyme inhibitors

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also insomnia; *less commonly* nasal dryness, pharyngolaryngeal pain, cough, and vertigo

Dose

- ADULT over 18 years, 4 mg once daily, increased if necessary to max. 8 mg once daily

Note Max. 4 mg daily with concomitant atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, or telithromycin; in patients with hepatic or renal impairment, consult product literature before concomitant use with amprenavir, aprepitant, atazanavir, clarithromycin, diltiazem, erythromycin, fluconazole, fosamprenavir, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin, verapamil, or grapefruit juice

Toviaz® (Pfizer) ▼ PoM

Tablets, m/r, f/c, fesoterodine fumarate 4 mg (light blue), net price 28-tab pack = £25.78; 8 mg (blue), 28-tab pack = £25.78. Label: 3, 25

FLAVOXATE HYDROCHLORIDE

Indications urinary frequency and incontinence, dysuria, urgency; bladder spasms due to catheterisation, cytoscopy, or surgery

Cautions see notes above

Contra-indications see notes above; gastro-intestinal haemorrhage

Pregnancy manufacturer advises avoid unless no safer alternative

Breast-feeding manufacturer advises caution—no information available

Side-effects see notes above; also vertigo, eosinophilia, leucopenia, urticaria, erythema, and pruritus

Dose

- ADULT and CHILD over 12 years, 200 mg 3 times daily

Urispas 200® (Recordati) PoM

Tablets, f/c, flavoxate hydrochloride 200 mg, net price 90-tab pack = £11.67

OXYBUTYNIN HYDROCHLORIDE

Indications urinary frequency, urgency and incontinence, neurogenic bladder instability, and nocturnal enuresis associated with overactive bladder

Cautions see notes above; acute porphyria (section 9.8.2)

Contra-indications see notes above

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturers advise avoid unless essential—toxicity in *animal* studies

Breast-feeding manufacturers advise avoid—present in milk

Side-effects see notes above; also *less commonly* anorexia, facial flushing; *rarely* night terrors; application site reactions with *patches*; also reported cognitive impairment

Dose

- ADULT and CHILD over 12 years, initially 5 mg 2–3 times daily, increased if necessary to max. 5 mg 4 times daily; ELDERLY initially 2.5–3 mg twice daily, increased to 5 mg twice daily according to response and tolerance; CHILD 5–12 years, neurogenic bladder instability, 2.5–3 mg twice daily, increased to 5 mg 2–3 times daily; CHILD under 5 years, see *BNF for Children*; CHILD 7–18 years, nocturnal enuresis associated with overactive bladder, 2.5–3 mg twice daily increased to 5 mg 2–3 times daily (last dose before bedtime)

Oxybutynin Hydrochloride (Non-proprietary) PoM

Tablets, oxybutynin hydrochloride 2.5 mg, net price 56-tab pack = £6.58; 3 mg, 56-tab pack = £9.15; 5 mg, 56-tab pack = £5.53, 84-tab pack = £12.50. Label: 3

Cystrin® (Sanofi-Aventis) PoM

Tablets, oxybutynin hydrochloride 3 mg, net price 56-tab pack = £9.15; 5 mg (scored), 84-tab pack = £21.99. Label: 3

Ditropan® (Sanofi-Aventis) PoM

Tablets, both blue, scored, oxybutynin hydrochloride 2.5 mg, net price 84-tab pack = £6.59; 5 mg, 84-tab pack = £12.82. Label: 3

Elixir, oxybutynin hydrochloride 2.5 mg/5 mL, net price 150-mL pack = £6.88. Label: 3

Modified release

Lyrinel® XL (Janssen-Cilag) PoM

Tablets, m/r, oxybutynin hydrochloride 5 mg (yellow), net price 30-tab pack = £10.81; 10 mg (pink), 30-tab pack = £21.62. Label: 3, 25

Dose initially 5 mg once daily, adjusted according to response in steps of 5 mg at weekly intervals; max. 20 mg once daily; CHILD over 6 years, neurogenic bladder instability, initially 5 mg once daily, adjusted according to response in steps of 5 mg at weekly intervals; max. 15 mg once daily

Note Patients taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of *Lyrinel® XL*

Transdermal preparations

Kentera® (Orion) PoM

Patches, self-adhesive, oxybutynin 36 mg (releasing oxybutynin approx. 3.9 mg/24 hours), net price 8-patch pack = £27.20. Label: 3, counselling, administration

Dose ADULT over 18 years, urinary frequency, urgency and incontinence, apply 1 patch twice weekly to clean, dry, unbroken skin on abdomen, hip or buttock, remove after every 3–4 days and

site replacement patch on a different area (avoid using same area for 7 days)

Note The *Scottish Medicines Consortium* has advised (July 2005) that *Kentera*® should be restricted for use in patients who benefit from oral oxybutynin but cannot tolerate its side-effects

PROPANTHELINE BROMIDE

Indications adult enuresis

Cautions see notes above; ulcerative colitis

Contra-indications see notes above

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid—no information available

Breast-feeding may suppress lactation

Side-effects see notes above; also facial flushing

Dose

- Initially 15 mg 3 times daily at least one hour before food and 30 mg at bedtime, subsequently adjusted according to response (max. 120 mg daily)

Preparations

Section 1.2

PROPIVERINE HYDROCHLORIDE

Indications urinary frequency, urgency and incontinence; neurogenic bladder instability

Cautions see notes above

Contra-indications see notes above

Hepatic impairment avoid in moderate to severe impairment

Renal impairment doses above 30 mg daily should be used with caution if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid (restriction of skeletal development in *animals*)

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects see notes above

Dose

- ADULT over 18 years, 15 mg 1–3 times daily, increased if necessary to max. 15 mg 4 times daily

Detrunorm® (Amdipharm) PoM

Tablets, pink, s/c, propiverine hydrochloride 15 mg, net price 56-tab pack = £18.00. Label: 3

Modified release

Detrunorm® XL (Amdipharm) PoM

Capsules, orange/white, m/r, propiverine hydrochloride 30 mg, net price 28-cap pack = £24.45. Label: 3, 25

Dose ADULT over 18 years, urinary frequency, urgency, and incontinence, 30 mg once daily

SOLIFENACIN SUCCINATE

Indications urinary frequency, urgency and urge incontinence

Cautions see notes above; neurogenic bladder disorder

Contra-indications see notes above

Hepatic impairment max. 5 mg daily in moderate impairment; avoid in moderate impairment in those already taking itraconazole, ketoconazole, nelfinavir, or ritonavir; avoid in severe impairment

Renal impairment max. 5 mg daily if eGFR less than 30 mL/minute/1.73 m^2; avoid if eGFR less than 30 mL/minute/1.73 m^2 in those already taking itraconazole, ketoconazole, nelfinavir, or ritonavir

Pregnancy manufacturer advises caution—no information available

Breast-feeding manufacturer advises avoid—present in milk in *animal* studies

Side-effects see notes above; also gastro-oesophageal reflux, oedema

Dose

- ADULT over 18 years, 5 mg daily, increased if necessary to 10 mg once daily

  Note Max. 5 mg daily with concomitant itraconazole, ketoconazole, nelfinavir, or ritonavir

Vesicare® (Astellas) PoM

Tablets, f/c, solifenacin succinate 5 mg (yellow), net price 30-tab pack = £27.62; 10 mg (pink), 30-tab pack = £35.91. Label: 3

TOLTERODINE TARTRATE

Indications see under Dose

Cautions see notes above; history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval

Contra-indications see notes above

Hepatic impairment reduce dose to 1 mg twice daily; avoid *Detrusitol® XL*

Renal impairment reduce dose to 1 mg twice daily if eGFR less than 30 mL/minute/1.73 m^2; avoid *Detrusitol® XL* if eGFR less than 30 mL/minute/1.73 m^2

Pregnancy manufacturer advises avoid—toxicity in *animal* studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also chest pain, peripheral oedema; sinusitis, bronchitis; paraesthesia, fatigue, vertigo, weight gain; flushing also reported

Dose

- Urinary frequency, urgency, and incontinence, ADULT over 18 years, 2 mg twice daily; reduce to 1 mg twice daily if necessary to minimise side-effects; CHILD 2–18 years, see *BNF for Children*
- Nocturnal enuresis associated with overactive bladder, CHILD 7–18 years, see *BNF for Children*

Detrusitol® (Pharmacia) PoM

Tablets, f/c, tolterodine tartrate 1 mg, net price 56-tab pack = £29.03; 2 mg, 56-tab pack = £30.56. Label: 3

Modified release

Detrusitol® XL (Pharmacia) PoM

Capsules, blue, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £25.78. Label: 3, 25

Dose urinary frequency, urgency and incontinence, ADULT over 18 years, 4 mg once daily

TROSPIUM CHLORIDE

Indications urinary frequency, urgency and incontinence

Cautions see notes above

Contra-indications see notes above

Hepatic impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Renal impairment use with caution; reduce dose to 20 mg once daily or 20 mg on alternate days if eGFR 10–30 mL/minute/1.73 m^2; avoid *Regurin® XL*

Pregnancy manufacturer advises caution

Breast-feeding manufacturer advises caution

Side-effects see notes above; *rarely* chest pain, dyspnoea, and asthenia; *very rarely* myalgia and arthralgia

Dose

- ADULT and CHILD over 12 years, 20 mg twice daily before food

Trospium chloride (Non-proprietary) PoM

Tablets, f/c, trospium chloride 20 mg, net price 60-tab pack = £18.20. Label: 23

Brands include *Flotros®*

Regurin® (Speciality European) PoM

Tablets, brown-yellow, f/c, trospium chloride 20 mg, net price 60-tab pack = £26.00. Label: 23

Modified release

Regurin® XL (Speciality European) PoM

Capsules, orange/white, m/r, trospium chloride 60 mg, net price 28-cap pack = £23.05. Label: 23, 25

Dose ADULT over 18 years, 60 mg once daily

Nocturnal enuresis

Nocturnal enuresis is common in young children, but persists in as many as 5% by 10 years of age. Treatment is not appropriate in children under 5 years and it is usually not needed in those aged under 7 years and in cases where the child and parents are not anxious about the bedwetting; however, children over 10 years usually require prompt treatment. An **enuresis alarm** should be first-line treatment for well-motivated, well-supported children aged over 7 years because alarms have a lower relapse rate than drug treatment when discontinued. Use of an alarm can be combined with drug therapy if either method alone is unsuccessful.

Drug therapy is not usually appropriate for children under 7 years of age; it can be used when alternative measures have failed, preferably on a short-term basis, for example to cover periods away from home, or if the child and family are anxious about the condition.

Desmopressin (section 6.5.2), an analogue of vasopressin, is used for nocturnal enuresis; it is given by oral or by sublingual administration. Particular care is needed to avoid fluid overload. Treatment should not be continued for longer than 3 months without interrupting treatment for 1 week for full re-assessment. Desmopressin should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects.

Tricyclic antidepressants (section 4.3.1) such as **imipramine**, and rarely **amitriptyline** and **nortriptyline**, are used but behavioural disturbances can occur and relapse is common after withdrawal. Treatment should not normally exceed 3 months unless a full physical examination is made and the child is fully re-assessed; toxicity following overdosage with tricyclics is of particular concern.

Nocturnal enuresis associated with daytime symptoms (overactive bladder) can be managed by antimuscarinic drugs (see Urinary incontinence, p. 508), with the addition of desmopressin if necessary.

7.4.3 Drugs used in urological pain

The acute pain of *ureteric colic* may be relieved with **pethidine** (section 4.7.2). **Diclofenac** by injection or as suppositories (section 10.1.1) is also effective and compares favourably with pethidine; other non-steroidal anti-inflammatory drugs are occasionally given by injection.

Lidocaine gel is a useful topical application in *urethral pain* or to relieve the discomfort of catheterisation (section 15.2).

Alkalinisation of urine

Alkalinisation of urine can be undertaken with **potassium citrate**. The alkalinising action may relieve the discomfort of *cystitis* caused by lower urinary tract infections. **Sodium bicarbonate** is used as a urinary alkalinising agent in some metabolic and renal disorders (section 9.2.1.3).

POTASSIUM CITRATE

Indications relief of discomfort in mild urinary-tract infections; alkalinisation of urine

Cautions cardiac disease; elderly; **interactions:** Appendix 1 (potassium salts)

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Side-effects hyperkalaemia on prolonged high dosage, mild diuresis

Dose

- See under preparation

Potassium Citrate Mixture BP (Potassium Citrate Oral Solution)

Oral solution, potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillaia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K^+/10 mL. Label: 27

Dose 10 mL 3 times daily well diluted with water

Proprietary brands of potassium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections

SODIUM BICARBONATE

Indications relief of discomfort in mild urinary-tract infections; alkalinisation of urine

Cautions cardiac disease; patients on sodium-restricted diet; elderly; avoid prolonged use; **interactions:** Appendix 1 (antacids)

Hepatic impairment section 1.1.1

Renal impairment avoid; specialised role in some forms of renal disease, see section 9.2.1.3

Pregnancy use with caution