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

British National Formulary

BNF

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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

March 2011

BMA

ROYAL PHARMACEUTICAL SOCIETY

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Tel: +44 (0) 207 572 2266
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Distribution of BNFs
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

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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
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Lumecare® Long Lasting Tear Gel [carbomers], p. 680
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Marol® [tramadol m/r], p. 272
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Monofer® [iron isomaltoside 1000], p. 579
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Neokay® [phytomenadione], p. 621
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NuTRIflex® Omega plus, p. 605
NuTRIflex® Omega special, p. 605
Onbrez Breezhaler® [indacaterol], p. 177
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Rebif® (*Rebidose®*) injection [interferon beta-1a], p. 562
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Simponi® [golimumab], p. 653
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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.

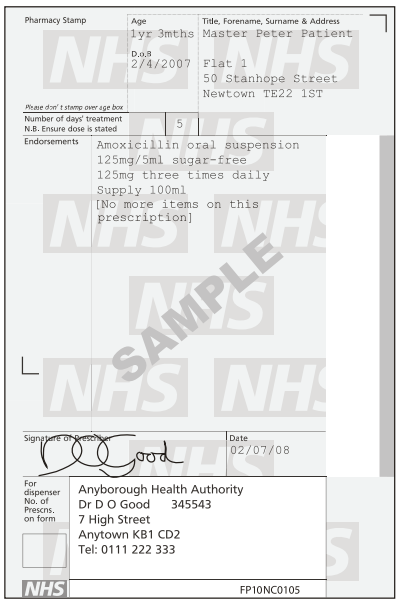
(f) The names of drugs and preparations should be written clearly and **not** abbreviated, using approved titles **only** (see also advice in box on p. 3 to **avoid** creating generic titles for modified-release preparations).

(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).

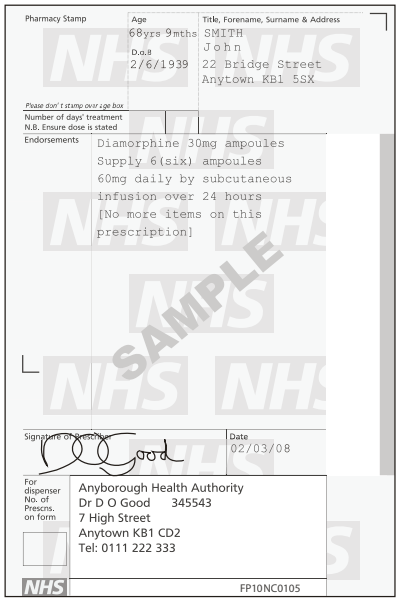
Prescription requirements

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.

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.

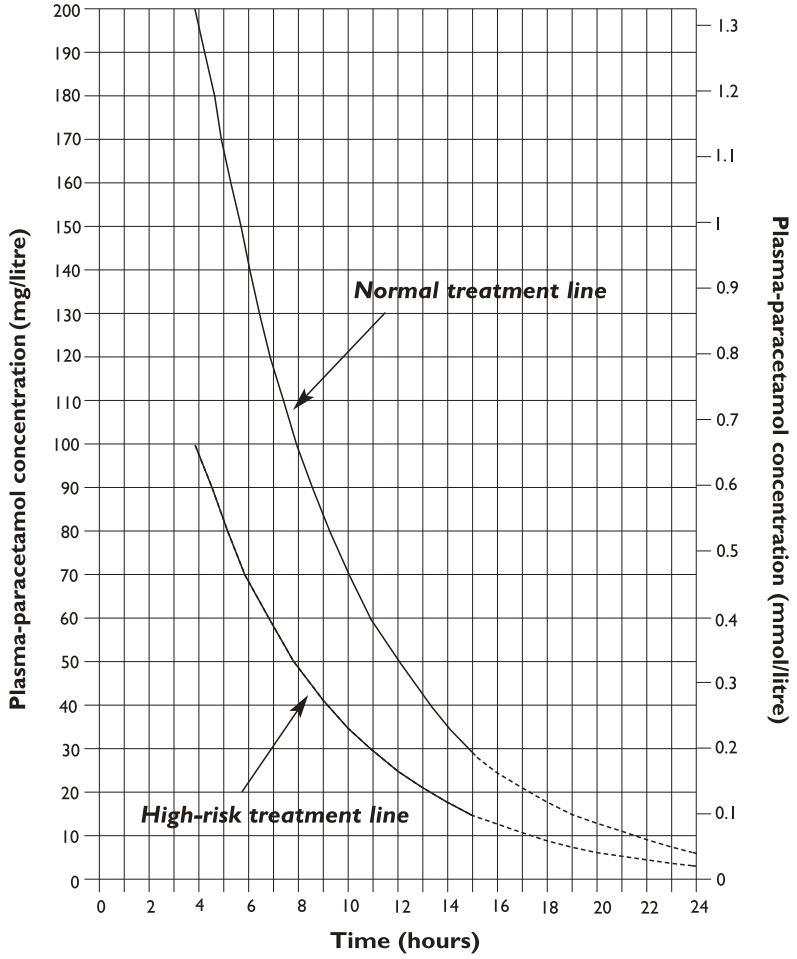
Single or repeated doses totalling as little as 10–15 g (20–30 tablets) or 150 mg/kg of paracetamol ingested within 24 hours may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Patients at *high-risk* of liver damage, including those taking enzyme-inducing drugs 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

This chapter also includes advice on the drug management of the following:

1.1 Dyspepsia and gastro-oesophageal reflux disease

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

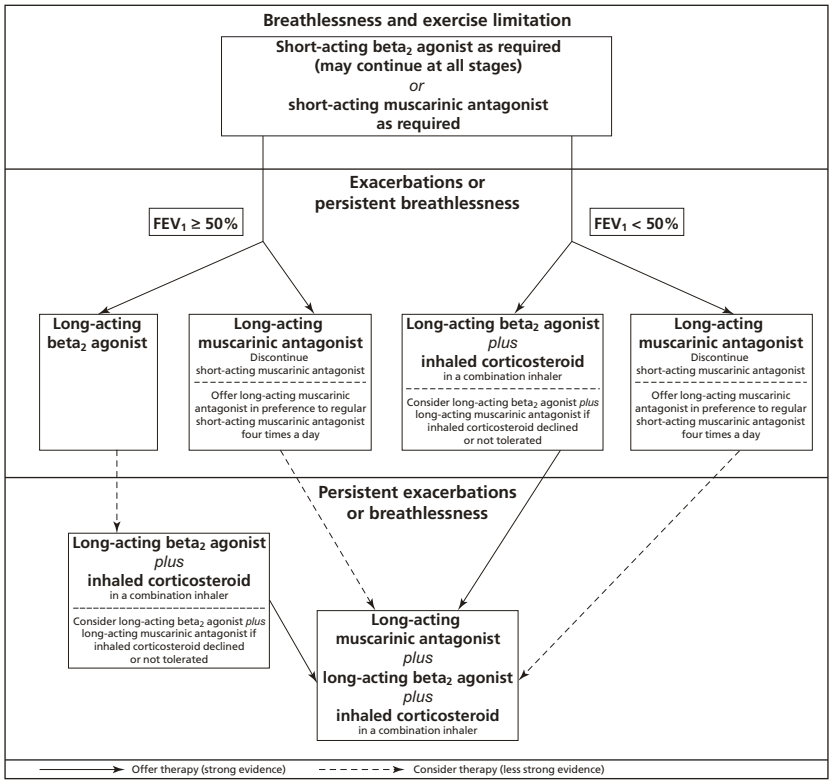
Follow up in all cases

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)

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

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

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

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