

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN I.V. (Imipenem and Cilastatin for Injection) were fever, hypotension, seizures (see PRECAUTIONS), dizziness, pruritus, urticaria, and somnolence.

Additional adverse systemic clinical reactions reported possibly, probably, or definitely drug related or reported since the drug was marketed are listed within each body system in order of decreasing severity: **Gastrointestinal:** pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment, see WARNINGS), hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillary hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, increased salivation; **Hematologic:** pancytopenia, bone marrow depression, thrombocytopenia, neutropenia, leukopenia, hemolytic anemia; **CNS:** encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances including hallucinations; **Special Senses:** hearing loss, tinnitus, taste perversion; **Respiratory:** chest discomfort, dyspnea, hyperventilation, thoracic spine pain; **Cardiovascular:** palpitations, tachycardia; **Renal:** acute renal failure, oliguria/anuria, polyuria, urine discoloration; **Skin:** toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; **Body as a whole:** polyarthralgia, asthenia/weakness, drug fever.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: increased LDH; **Hemic:** positive Coombs test, decreased neutrophils, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; **Electrolytes:** decreased serum sodium, increased potassium, increased chloride; **Urinalysis:** presence of urine protein, urine bilirubin, and urine urobilinogen.

Lidocaine HCl— Refer to the package circular for lidocaine HCl.

OVERDOSAGE

The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was studied in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxia was rapidly produced and clonic convulsions were noted in about 45 minutes. Deaths occurred within 4-56 minutes at all doses.

The acute intravenous toxicity of imipenem-cilastatin sodium was produced within 5-10 minutes in rats at doses of 771 to 1583 mg/kg. In all dosage groups, females had decreased activity, bradypnea and ptosis with clonic convulsions preceding death; in males, ptosis was seen at all dose levels while tremors and clonic convulsions were seen at all but the lowest dose (771 mg/kg). In another rat study, female rats showed ataxia, bradypnea and decreased activity in all but the lowest dose (550 mg/kg); deaths were preceded by clonic convulsions. Male rats showed tremors at all doses and clonic convulsions and ptosis were seen at the two highest doses (1130 and 1734 mg/kg). Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

In the case of overdosage, discontinue PRIMAXIN I.M., treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

DOSAGE AND ADMINISTRATION**PRIMAXIN I.M. is for intramuscular use only.**

The dosage recommendations for PRIMAXIN I.M. represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present.

Patients with lower respiratory tract infections, skin and skin structure infections, and gynecologic infections of mild to moderate severity may be treated with 500 mg or 750 mg administered every 12 hours depending on the severity of the infection.

Intra-abdominal infection may be treated with 750 mg every 12 hours. [See table below.]

DOSAGE GUIDELINES

Type ^{††} /Location of Infection	Severity	Dosage Regimen
Lower respiratory tract	Mild/Moderate	500 or 750 mg q 12 h
Skin and skin structure		depending on the severity of infection
Gynecologic		severity of infection
Intra-abdominal	Mild/Moderate	750 mg q 12 h

^{††}See INDICATIONS AND USAGE section.

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Total daily IM dosages greater than 1500 mg per day are not recommended.

The dosage for any particular patient should be based on the location of and severity of the infection, the susceptibility of the infecting pathogen(s), and renal function.

The duration of therapy depends upon the type and severity of the infection. Generally, PRIMAXIN I.M. should be continued for at least two days after the signs and symptoms of infection have resolved. Safety and efficacy of treatment beyond fourteen days have not been established.

PRIMAXIN I.M. should be administered by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh) with a 21 gauge 2" needle. Aspiration is necessary to avoid inadvertent injection into a blood vessel.

ADULTS WITH IMPAIRED RENAL FUNCTION

The safety and efficacy of PRIMAXIN I.M. have not been studied in patients with creatinine clearance of less than 20 mL/min/1.73 m². Serum creatinine alone may not be a sufficiently accurate measure of renal function. Creatinine clearance (C_{cr}) may be estimated from the following equation:

$$C_{cc} \text{ (Males)} = \frac{\text{(wt. in kg)}(140 - \text{age})}{(72)(\text{creatinine in mg/dL})}$$

$$C_{cc} \text{ (Females)} = 0.85 \times \text{above value}$$

PREPARATION FOR ADMINISTRATION

PRIMAXIN I.M. should be prepared for use with 1.0% lidocaine HCl solution^{†††} (without epinephrine). PRIMAXIN I.M. 500 should be prepared with 2 mL and PRIMAXIN I.M. 750 with 3 mL of lidocaine HCl. Agitate to form a suspension, then withdraw and inject the entire contents of vial intramuscularly. The suspension of PRIMAXIN I.M. in lidocaine HCl should be used within one hour after preparation. **Note: The IM formulation is not for IV use.**

COMPATIBILITY AND STABILITY**Before reconstitution:**

The dry powder should be stored at a temperature below 25°C (77°F).

Suspensions for IM Administration

Suspensions of PRIMAXIN I.M. are white to light tan in color. Variations of color within this range do not affect the potency of the product.

The suspension of PRIMAXIN I.M. in lidocaine HCl should be used within one hour after preparation.

PRIMAXIN I.M. should not be mixed with or physically added to other antibiotics. However, PRIMAXIN I.M. may be administered concomitantly but at separate sites with other antibiotics, such as aminoglycosides.

HOW SUPPLIED

PRIMAXIN I.M. is supplied as a sterile powder mixture in vials for IM administration as follows:

- No. 3582 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent NDC 0006-3582-75 in trays of 10 vials.
- No. 3583 — 750 mg imipenem equivalent and 750 mg cilastatin equivalent NDC 0006-3583-76 in trays of 10 vials.

REFERENCES

- National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically — Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2 NCCLS, Villanova, PA, 1997.
- National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests — Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1 NCCLS, Villanova, PA, 1997.
- National Committee for Clinical Laboratory Standards, Method for Antimicrobial Susceptibility Testing of Anaerobic Bacteria — Third Edition. Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26 NCCLS, Villanova, PA, 1993.

^{†††}Refer to the package circular for lidocaine HCl for detailed information concerning CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

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PRIMAXIN® I.M.

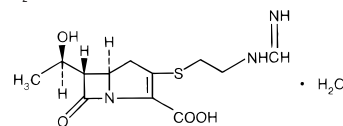
(IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PRIMAXIN I.M.[†] and other antibacterial drugs, PRIMAXIN I.M. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

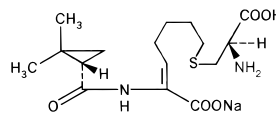
For Intramuscular Injection Only**DESCRIPTION**

PRIMAXIN I.M. (Imipenem and Cilastatin for Injectable Suspension) is a formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I). PRIMAXIN I.M. is a potent broad spectrum antibacterial agent for intramuscular administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces catleya*. Its chemical name is [5*R*-[5*α*, 6*α* (*R**)]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl) amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is C₁₂H₁₇N₃O₅S·H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is [1*R*-(*R**, *S**,*Z*)]-7-[[2-amino-2-carboxyethyl]thio]-2-[[[2,2-dimethyl-cyclopropyl]carbonyl]amino]-2-heptenoic acid, monosodium salt. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is C₁₆H₂₅N₂O₅Na, and its structural formula is:



PRIMAXIN I.M. 500 contains 32 mg of sodium (1.4 mEq) and PRIMAXIN I.M. 750 contains 48 mg of sodium (2.1 mEq). Prepared PRIMAXIN I.M. suspensions are white to light tan in color. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

Following intramuscular administrations of 500 or 750 mg doses of imipenem-cilastatin sodium in a 1:1 ratio with 1% lidocaine, peak plasma levels of imipenem antimicrobial activity occur within 2 hours and average 10 and 12 µg/mL, respectively. For cilastatin, peak plasma levels average 24 and 33 µg/mL, respectively, and occur within 1 hour. When compared to intravenous administration of imipenem-cilastatin sodium, imipenem is approximately 75% bioavailable following intramuscular administration while cilastatin is approximately 95% bioavailable. The absorption of imipenem from the IM injection site continues for 6 to 8 hours while that for cilastatin is essentially complete within 4 hours. This prolonged absorption of imipenem following the administration of the intramuscular formulation of imipenem-cilastatin sodium results in an effective plasma half-life of imipenem of approximately 2 to 3 hours and plasma levels of the antibiotic which remain above 2 µg/mL for at least 6 or 8 hours, following a 500 mg or 750 mg dose, respectively. This plasma profile for imipenem permits IM administration of the intramuscular formulation of imipenem-cilastatin sodium every 12 hours with no accumulation of cilastatin and only slight accumulation of imipenem.

A comparison of plasma levels of imipenem after a single dose of 500 mg or 750 mg of imipenem-cilastatin sodium (intravenous formulation) administered intravenously or of imipenem-cilastatin sodium (intramuscular formulation) diluted with 1% lidocaine and administered intramuscularly is as follows:

PLASMA CONCENTRATIONS OF IMIPENEM (µg/mL)

TIME	500 MG		750 MG	
	I.V.	I.M.	I.V.	I.M.
25 min	45.1	6.0	57.0	6.7
1 hr	21.6	9.4	28.1	10.0
2 hr	10.0	9.9	12.0	11.4
4 hr	2.6	5.6	3.4	7.3
6 hr	0.6	2.5	1.1	3.8
12 hr	ND**	0.5	ND**	0.8

**ND: Not Detectable (<0.3 µg/mL)

Imipenem urine levels remain above 10 µg/mL for the 12 hour dosing interval following the administration of 500 mg or 750 mg doses of the intramuscular formulation of imipenem-cilastatin sodium. Total urinary excretion of imipenem averages 50% while that for cilastatin averages 75% following either dose of the intramuscular formulation of imipenem-cilastatin sodium.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly, increased levels of imipenem are achieved in the urine. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%.

In a clinical study in which a 500 mg dose of the intramuscular formulation of imipenem-cilastatin sodium was administered to healthy subjects, the average peak level of imipenem in interstitial fluid (skin blister fluid) was approximately 5.0 µg/mL within 3.5 hours after administration.

Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable. (See **OVERDOSAGE**.)

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin-binding proteins (PBPs) 1A, 1B, 2, 4, 5 and 6 of *Escherichia coli*, and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B.

Imipenem has a high degree of stability in the presence of beta-lactamases, including penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria which are inherently resistant to many beta-lactam antibiotics, e.g., *Pseudomonas aeruginosa*, *Serratia* spp. and *Enterobacter* spp.

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections treated with the intramuscular formulation of imipenem-cilastatin sodium as described in the INDICATIONS AND USAGE section.

Gram-positive aerobes:

- Staphylococcus aureus* including penicillinase-producing strains (NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)
- Group D streptococcus including *Enterococcus faecalis* (formerly *S. faecalis*) (NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*].)
- Streptococcus pneumoniae*
- Streptococcus pyogenes* (Group A streptococci)
- Streptococcus viridans* group

Gram-negative aerobes:

- Acinetobacter* spp., including *A. calcoaceticus*
- Citrobacter* spp.
- Enterobacter cloacae*
- Escherichia coli*
- Haemophilus influenzae*
- Klebsiella pneumoniae*
- Pseudomonas aeruginosa* (NOTE: Imipenem is inactive *in vitro* against *Xanthomonas* (*Pseudomonas*) *maltophilia* and *P. cepacia*.)

Gram-positive anaerobes:

- Peptostreptococcus* spp.

Gram-negative anaerobes:

- Bacteroides* spp., including *Bacteroides distasonis*
- Bacteroides intermedium* (formerly *B. melaninogenicus intermedium*)
- Bacteroides fragilis*

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Bacteroides thetaioamicron
Fusobacterium spp.

Imipenem exhibits *in vitro* minimal inhibitory concentrations (MICs) of 4 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of imipenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes:

Bacillus spp.
Listeria monocytogenes
Nocardia spp.
Group C streptococci
Group G streptococci

Gram-negative aerobes:

Aeromonas hydrophila
Alcaligenes spp.
Campytophaga spp.
Enterobacter agglomerans
Haemophilus ducreyi
Klebsiella oxytoca
Neisseria gonorrhoeae including penicillinase-producing strains
Pasteurella spp.
Proteus mirabilis
Providencia stuartii

Gram-positive anaerobes:

Clostridium perfringens

Gram-negative anaerobes:

Prevotella bivia
Prevotella disiens
Prevotella melaninogenica
Veillonella spp.

In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

Susceptibility Tests:

Dilution techniques:

Use a standardized dilution method¹ (broth, agar, microdilution) or equivalent with imipenem powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 4	Susceptible
8	Moderately Susceptible
≥ 16	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control organisms. Standard imipenem powder should provide the following MIC values:

Organism	MIC (µg/mL)
<i>E. coli</i> ATCC 25922	0.06-0.25
<i>S. aureus</i> ATCC 29213	0.015-0.06
<i>E. faecalis</i> ATCC 29212	0.5-2.0
<i>P. aeruginosa</i> ATCC 27853	1.0-4.0

Diffusion techniques:

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such standard procedure², which has been recommended for use with disks to test susceptibility of organisms to imipenem, uses the 10-µg imipenem disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for imipenem.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10-µg imipenem disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible
14-15	Moderately Susceptible
≤ 13	Resistant

Standardized procedures require the use of laboratory control organisms. The 10-µg imipenem disk should give the following zone diameters:

Organism	Zone Diameter (mm)
<i>E. coli</i> ATCC 25922	26-32
<i>P. aeruginosa</i> ATCC 27853	20-28

For anaerobic bacteria, the MIC of imipenem can be determined by agar or broth dilution (including microdilution) techniques³.

The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 4	Susceptible
8	Moderately Susceptible
≥ 16	Resistant

INDICATIONS AND USAGE

PRIMAXIN I.M. is indicated for the treatment of serious infections (listed below) of mild to moderate severity for which intramuscular therapy is appropriate. **PRIMAXIN I.M. is not intended for the therapy of severe or life-threatening infections, including bacterial sepsis or endocarditis, or in instances of major physiological impairments such as shock.**

PRIMAXIN I.M. is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

(1) **Lower respiratory tract infections**, including pneumonia and bronchitis as an exacerbation of COPD, caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

(2) **Intra-abdominal infections**, including acute gangrenous or perforated appendicitis and appendicitis with peritonitis, caused by Group D streptococcus including *Enterococcus faecalis*^{*}; *Streptococcus viridans* group^{*}; *Escherichia coli*; *Klebsiella pneumoniae*^{*}; *Pseudomonas aeruginosa*^{*}; *Bacteroides* species including *B. fragilis*, *B. distasonis*^{*}, *B. intermedium*^{*} and *B. thetaioamicron*^{*}; *Fusobacterium* species and *Peptostreptococcus*^{*} species.

(3) **Skin and skin structure infections**, including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus* including penicillinase-producing strains; *Streptococcus pyogenes*^{*}; Group D streptococcus including *Enterococcus faecalis*; *Acinetobacter* species^{*} including *A. calcoaceticus*^{*}; *Citrobacter* species^{*}; *Escherichia coli*; *Enterobacter cloacae*; *Klebsiella pneumoniae*^{*}; *Pseudomonas aeruginosa*^{*} and *Bacteroides* species^{*} including *B. fragilis*^{*}.

(4) **Gynecologic infections**, including postpartum endomyometritis, caused by Group D streptococcus including *Enterococcus faecalis*^{*}; *Escherichia coli*; *Klebsiella pneumoniae*^{*}; *Bacteroides intermedium*^{*}; and *Peptostreptococcus* species^{*}.

As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with PRIMAXIN I.M. During therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done when clinically appropriate.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PRIMAXIN I.M. and other antibacterial drugs, PRIMAXIN I.M. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

PRIMAXIN I.M. is contraindicated in patients who have shown hypersensitivity to any component of this product. Due to the use of lidocaine hydrochloride diluent, this product is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block. (Refer to the package circular for lidocaine hydrochloride.)

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH PRIMAXIN® I.M., CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, PRIMAXIN® SHOULD BE DISCONTINUED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including PRIMAXIN, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Lidocaine HCl— Refer to the package circular for lidocaine HCl.

PRECAUTIONS

General

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN I.V. (Imipenem and Cilastatin for Injection). These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) who also have compromised renal function. However, there were reports in which there was no recognized or documented underlying CNS disorder. These adverse CNS effects have not been seen with PRIMAXIN I.M.; however, should they occur during treatment, PRIMAXIN I.M. should be discontinued. Anticonvulsant therapy should be continued in patients with a known seizure disorder.

As with other antibiotics, prolonged use of PRIMAXIN I.M. may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing PRIMAXIN I.M. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Caution should be taken to avoid inadvertent injection into a blood vessel. (See **DOSE AND ADMINISTRATION**.) For additional precautions, refer to the package circular for lidocaine HCl.

Information for Patients

Patients should be counseled that antibacterial drugs including PRIMAXIN I.M. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When PRIMAXIN I.M. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by PRIMAXIN I.M. or other antibacterial drugs in the future.

Drug Interactions

Since concomitant administration of PRIMAXIN (Imipenem-Cilastatin Sodium) and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN I.M.

PRIMAXIN I.M. should not be mixed with or physically added to other antibiotics. However, PRIMAXIN I.M. may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin. Genetic toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were: V79 mammalian cell mutagenesis assay (imipenem-cilastatin sodium alone and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem-cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any evidence of genetic alterations.

Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day, 2.1 times*** the maximum recommended daily human dose of the intramuscular formulation (on a mg/m² body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups.

Pregnancy: Teratogenic Effects

Pregnancy Category C: Teratology studies with cilastatin sodium at doses of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day administered subcutaneously to rats, up to approximately 3.9 and 6.5 times*** the maximum recommended daily human dose (on a mg/m² body surface area basis) of the intramuscular formulation of PRIMAXIN (25 mg/kg/day) in the two species, respectively, showed no evidence of adverse effects on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at intravenous doses of 15, 30, or 60 mg/kg/day and rats given imipenem at intravenous doses of 225, 450, or 900 mg/kg/day, up to approximately 0.8 and 5.8 times*** the maximum recommended daily human dose (on a mg/m² body surface area basis) in the two species, respectively.

Teratology studies with imipenem-cilastatin sodium at intravenous doses of 20 and 80 and a subcutaneous dose of 320 mg/kg/day, approximately equal to (mice) and up to 2.1 times*** (rats) the maximum recommended daily intramuscular human dose (on a mg/m² body surface area basis) in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem-cilastatin sodium, when administered to pregnant rabbits subcutaneously at dosages above the usual human dose of the intramuscular

*** Based on patient body surface area of 1.6 m² (weight of 60 kg).

formulation (1000-1500 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 1.3 times*** the maximum recommended daily human dose of the intramuscular formulation) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to the control groups.

No adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, 2.1 times the maximum recommended daily human dose (on a mg/m² body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN I.M. should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether imipenem-cilastatin sodium or lidocaine HCl (diluent) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.M. is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Clinical studies of PRIMAXIN I.M. did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects; however, clinical studies of PRIMAXIN I.V. in a sufficient number of subjects aged 65 and over have not revealed overall differences in safety or effectiveness between these subjects and younger subjects (refer to the package circular for PRIMAXIN I.V.). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of renal impairment is necessary (see DOSAGE AND ADMINISTRATION, ADULTS WITH IMPAIRED RENAL FUNCTION).

ADVERSE REACTIONS

PRIMAXIN I.M.

In 686 patients in multiple dose clinical trials of PRIMAXIN I.M., the following adverse reactions were reported:

Local Adverse Reactions

The most frequent adverse local clinical reaction that was reported as possibly, probably, or definitely related to therapy with PRIMAXIN I.M. was pain at the injection site (1.2%).

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN I.M. were nausea (0.6%), diarrhea (0.6%), vomiting (0.3%) and rash (0.4%).

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hemic: decreased hemoglobin and hematocrit, eosinophilia, increased and decreased WBC, increased and decreased platelets, decreased erythrocytes, and increased prothrombin time.

Hepatic: increased AST, ALT, alkaline phosphatase, and bilirubin.

Renal: increased BUN and creatinine.

Urinalysis: presence of red blood cells, white blood cells, casts, and bacteria in the urine.

Potential ADVERSE EFFECTS:

In addition, a variety of adverse effects, not observed in clinical trials with PRIMAXIN I.M., have been reported with intravenous administration of PRIMAXIN I.V. (Imipenem and Cilastatin for Injection). Those listed below are to serve as alerting information to physicians.