

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-587 / S-061

50-630 / S-023

**Trade Name: Primaxin IV for Injection
Primaxin IM Injectable Suspension**

Generic Name: Imipenem and Cilastatin

Sponsor: Merck & Co.

Approval Date: May 20, 2004

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-587/S-061

NDA 50-630/S-023

Merck & Co., Inc.
Attention: Virginia G. Snyder
Associate Director, Regulatory Affairs
BLA-20
P.O. Box 4
West Point, PA 19486

Dear Ms. Snyder:

Please refer to your supplemental new drug applications dated November 25, 2003, received November 26, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRIMAXIN™ IV for Injection (Imipenem and Cilastatin)[NDA 50-587] and PRIMAXIN™ IM Injectable (Imipenem and Cilastatin) [NDA 50-630]. We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

These "Changes Being Effected" supplemental new drug applications provide for revised labeling to comply with the FDA's Final Rule entitled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use (21 CFR Part 201)", published on February 6, 2003 (68 FR 6062).

We completed our review of these supplemental applications and they are approved, effective on the date of this letter.

The final printed labeling (FPLs) must be identical to the labeling submitted November 25, 2003 (package inserts #7882128 [IV] and #7632911 [IM]).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 50-587S-061 and NDA 50-630/S-023." Approval of these submissions by FDA is not required before the labeling is used.

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If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDA’s and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for approved NDA’s (21 CFR 314.80 and 314.81).

If you have any questions, call Maureen Dillon-Parker, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Janice Soreth
5/20/04 03:50:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-061

50-630 / S-023

LABELING

PRIMAXIN® I.V. **(IMIPENEM AND CILASTATIN FOR INJECTION)**

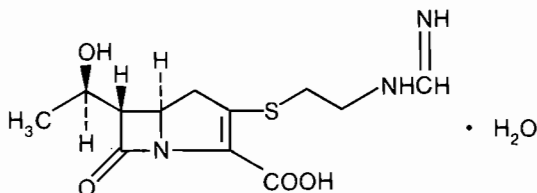
To reduce the development of drug-resistant bacteria and maintain the effectiveness of PRIMAXIN I.V.† and other antibacterial drugs, PRIMAXIN I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intravenous Injection Only

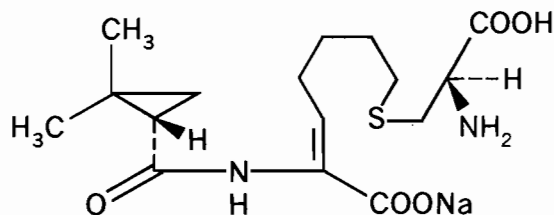
DESCRIPTION

PRIMAXIN I.V. (Imipenem and Cilastatin for Injection) is a sterile formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer. PRIMAXIN I.V. is a potent broad spectrum antibacterial agent for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl]thio]-6-[[*R*]-1-hydroxyethyl]-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 C₁₂H₁₇N₃O₄S•H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is sodium (Z)-7[[[*R*]-2-amino-2-carboxyethyl]thio]-2-[[*S*]-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. 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 C₁₆H₂₅N₂O₅SNa, and its structural formula is:



PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 8.5. There is no significant change in pH when solutions are prepared and used as directed. (See **COMPATIBILITY AND STABILITY**.) PRIMAXIN I.V. 250 contains 18.8 mg of sodium (0.8 mEq) and PRIMAXIN I.V. 500 contains 37.5 mg of sodium (1.6 mEq). Solutions of PRIMAXIN I.V. range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

Adults

Intravenous Administration

Intravenous infusion of PRIMAXIN I.V. over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 µg/mL for the 250 mg dose, from 21 to 58 µg/mL for the 500 mg dose, and from 41 to 83 µg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem

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antimicrobial activity decline to below 1 µg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN I.V. range from 15 to 25 µg/mL for the 250 mg dose, from 31 to 49 µg/mL for the 500 mg dose, and from 56 to 88 µg/mL for the 1000 mg dose.

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 µg/mL can be maintained for up to 8 hours with PRIMAXIN I.V. at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN I.V.

No accumulation of imipenem/cilastatin in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem 500 mg and cilastatin 500 mg administered intravenously over 20 minutes are consistent with those expected in subjects with slight renal impairment for which no dosage alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin are 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem/cilastatin is observed.

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, fully adequate antibacterial levels of imipenem are achieved in the urine.

After a 1 gram dose of PRIMAXIN I.V., the following average levels of imipenem were measured (usually at 1 hour post dose except where indicated) in the tissues and fluids listed:

Tissue or Fluid	N	Imipenem Level µg/mL or µg/g	Range
Vitreous Humor	3	3.4 (3.5 hours post dose)	2.88–3.6
Aqueous Humor	5	2.99 (2 hours post dose)	2.4–3.9
Lung Tissue	8	5.6 (median)	3.5–15.5
Sputum	1	2.1	—
Pleural	1	22.0	—
Peritoneal	12	23.9 S.D.±5.3 (2 hours post dose)	—
Bile	2	5.3 (2.25 hours post dose)	4.6–6.0
CSF (uninflamed)	5	1.0 (4 hours post dose)	0.26–2.0
CSF (inflamed)	7	2.6 (2 hours post dose)	0.5–5.5
Fallopian Tubes	1	13.6	—
Endometrium	1	11.1	—
Myometrium	1	5.0	—
Bone	10	2.6	0.4–5.4
Interstitial Fluid	12	16.4	10.0–22.6
Skin	12	4.4	NA
Fascia	12	4.4	NA

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, both 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 most 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 intravenous formulation of imipenem-cilastatin sodium as described in the **INDICATIONS AND USAGE** section.

Gram-positive aerobes:

Enterococcus faecalis (formerly *S. faecalis*)

(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*].)

Staphylococcus aureus including penicillinase-producing strains

Staphylococcus epidermidis including penicillinase-producing strains

(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)

Streptococcus agalactiae (Group B streptococci)

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative aerobes:

Acinetobacter spp.

Citrobacter spp.

Enterobacter spp.

Escherichia coli

Gardnerella vaginalis

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella spp.

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Pseudomonas aeruginosa

(NOTE: Imipenem is inactive *in vitro* against *Xanthomonas (Pseudomonas) maltophilia* and some strains of *P. cepacia*.)

Serratia spp., including *S. marcescens*

Gram-positive anaerobes:

Bifidobacterium spp.

Clostridium spp.

Eubacterium spp.

Peptococcus spp.

Peptostreptococcus spp.

Propionibacterium spp.

Gram-negative anaerobes:

Bacteroides spp., including *B. fragilis*

Fusobacterium spp.

The following *in vitro* data are available, **but their clinical significance is unknown.**

Imipenem exhibits *in vitro* minimum 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.

Staphylococcus saprophyticus

Group C streptococci

Group G streptococci

Viridans group streptococci

Gram-negative aerobes:

Aeromonas hydrophila

Alcaligenes spp.

Capnocytophaga spp.

Haemophilus ducreyi

Neisseria gonorrhoeae including penicillinase-producing strains

Pasteurella spp.

Providencia stuartii

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:

Measurement of MIC or minimum bactericidal concentration (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Dilution Techniques:

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such procedure uses a standardized dilution method¹ (broth, agar, or microdilution) or equivalent with imipenem powder.

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

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

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<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 provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² that has been recommended for use with disks to test the susceptibility of microorganisms to imipenem uses the 10-µg imipenem disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for imipenem.

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

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥16	Susceptible (S)
14–15	Intermediate (I)
≤13	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 10-µg imipenem disk should provide the following diameters in these laboratory test quality control strains:

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

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to imipenem can be determined by the reference agar dilution method or by alternate standardized test methods.³

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

As with other susceptibility techniques, the use of laboratory control microorganisms is required. Standard imipenem powder should provide the following MIC values:

Reference Agar Dilution Testing:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>B. fragilis</i> ATCC 25285	0.03–0.12
<i>B. thetaiotaomicron</i> ATCC 29741	0.06–0.25
<i>E. lentum</i> ATCC 43055	0.25–1.0

Broth Microdilution Testing:

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>B. thetaiotaomicron</i> ATCC 29741	0.06–0.25
<i>E. lentum</i> ATCC 43055	0.12–0.5

INDICATIONS AND USAGE

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

(1) **Lower respiratory tract infections.** *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter* species, *Enterobacter* species, *Escherichia coli*, *Haemophilus influenzae*, *Haemophilus parainfluenzae**, *Klebsiella* species, *Serratia marcescens*

(2) **Urinary tract infections** (complicated and uncomplicated). *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii**, *Proteus vulgaris**, *Providencia rettgeri**, *Pseudomonas aeruginosa*

(3) **Intra-abdominal infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*, *Staphylococcus epidermidis*, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii**, *Proteus* species, *Pseudomonas aeruginosa*, *Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species*, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species

(4) **Gynecologic infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*, *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species*, *Escherichia coli*, *Gardnerella vaginalis*, *Klebsiella* species*, *Proteus* species, *Bifidobacterium* species*, *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bacteroides* species including *B. fragilis**

(5) **Bacterial septicemia.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species*, *Bacteroides* species including *B. fragilis**

(6) **Bone and joint infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Enterobacter* species, *Pseudomonas aeruginosa*

(7) **Skin and skin structure infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Acinetobacter* species, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri**, *Pseudomonas aeruginosa*, *Serratia* species, *Peptococcus* species, *Peptostreptococcus* species, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species*

(8) **Endocarditis.** *Staphylococcus aureus* (penicillinase-producing strains)

(9) **Polymicrobial infections.** PRIMAXIN I.V. is indicated for polymicrobial infections including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

PRIMAXIN I.V. is not indicated in patients with meningitis because safety and efficacy have not been established.

For Pediatric Use information, see **PRECAUTIONS**, *Pediatric Use*, and **DOSAGE AND ADMINISTRATION** sections.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, PRIMAXIN I.V. is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by *Pseudomonas aeruginosa*, bacterial eradication may not necessarily be achieved.

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

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

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with PRIMAXIN I.V.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PRIMAXIN I.V. and other antibacterial drugs, PRIMAXIN I.V. 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.V. is contraindicated in patients who have shown hypersensitivity to any component of this product.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH PRIMAXIN I.V., 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.

Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with PRIMAXIN I.V. (See **PRECAUTIONS**.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including imipenem-cilastatin sodium, 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 supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN I.V., especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

When recommended doses were exceeded, adult patients with creatinine clearances of ≤ 20 mL/min/1.73 m², whether or not undergoing hemodialysis, had a higher risk of seizure activity than

those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended. (See **DOSAGE AND ADMINISTRATION**.)

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m² should not receive PRIMAXIN I.V. unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN I.V. is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN I.V. re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN I.V. 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.V. 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.

Information for Patients

Patients should be counseled that antibacterial drugs including PRIMAXIN I.V. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When PRIMAXIN I.V. 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.V. or other antibacterial drugs in the future.

Laboratory Tests

While PRIMAXIN I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions

Generalized seizures have been reported in patients who received ganciclovir and PRIMAXIN. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Since concomitant administration of PRIMAXIN 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.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN 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, approximately equal to the highest recommended human dose of the intravenous 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 1.9 and 3.2 times^{††} the maximum recommended daily human dose (on a mg/m² body surface area basis) of the intravenous formulation of imipenem-cilastatin sodium (50 mg/kg/day) in the two species, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem at intravenous doses of 15, 30 or 60

^{††} Based on patient body surface area of 1.6 m² (weight of 60 kg).

mg/kg/day and rats given imipenem at intravenous doses of 225, 450, or 900 mg/kg/day, up to approximately 0.4 and 2.9 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, up to 0.5 times^{††} (mice) to approximately equal to (rats) the highest recommended daily intravenous 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 subcutaneously to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher (1000-4000 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 0.6 times^{††} the maximum recommended daily human dose of the intravenous 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 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, approximately equal to the highest recommended human dose (on a mg/m² body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN I.V. 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 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.V. is administered to a nursing woman.

Pediatric Use

Use of PRIMAXIN I.V. in pediatric patients, neonates to 16 years of age, is supported by evidence from adequate and well-controlled studies of PRIMAXIN I.V. in adults and by the following clinical studies and published literature in pediatric patients: Based on published studies of 178^{**} pediatric patients ≥3 months of age (with non-CNS infections), the recommended dose of PRIMAXIN I.V. is 15-25 mg/kg/dose administered every six hours. Doses of 25 mg/kg/dose in patients 3 months to <3 years of age, and 15 mg/kg/dose in patients 3-12 years of age were associated with mean trough plasma concentrations of imipenem of 1.1±0.4 µg/mL and 0.6±0.2 µg/mL following multiple 60-minute infusions, respectively; trough urinary concentrations of imipenem were in excess of 10 µg/mL for both doses. These doses have provided adequate plasma and urine concentrations for the treatment of non-CNS infections. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4.0 g/day. (See Table 1, **DOSAGE AND ADMINISTRATION.**) Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis. (See **DOSAGE AND ADMINISTRATION.**)

Based on studies of 135^{***} pediatric patients ≤3 months of age (weighing ≥1,500 gms), the following dosage schedule is recommended for non-CNS infections:

- <1 wk of age: 25 mg/kg every 12 hrs
- 1-4 wks of age: 25 mg/kg every 8 hrs
- 4 wks-3 mos. of age: 25 mg/kg every 6 hrs.

In a published dose-ranging study of smaller premature infants (670-1,890 gms) in the first week of life, a dose of 20 mg/kg q12h by 15-30 minutes infusion was associated with mean peak and trough plasma imipenem concentrations of 43 µg/mL and 1.7 µg/mL after multiple doses, respectively. However,

^{**} Two patients were less than 3 months of age.

^{***} One patient was greater than 3 months of age.

moderate accumulation of cilastatin in neonates may occur following multiple doses of PRIMAXIN I.V. The safety of this accumulation is unknown.

PRIMAXIN I.V. is not recommended in pediatric patients with CNS infections because of the risk of seizures.

PRIMAXIN I.V. is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

Geriatric Use

Of the approximately 3600 subjects ≥18 years of age in clinical studies of PRIMAXIN I.V., including postmarketing studies, approximately 2800 received PRIMAXIN I.V. Of the subjects who received PRIMAXIN I.V., data are available on approximately 800 subjects who were 65 and over, including approximately 300 subjects who were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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.

No dosage adjustment is required based on age (see **CLINICAL PHARMACOLOGY, Adults**). Dosage adjustment in the case of renal impairment is necessary (see **DOSAGE AND ADMINISTRATION, Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg**).

ADVERSE REACTIONS

Adults

PRIMAXIN I.V. is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN I.V.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN I.V. were:

- Phlebitis/thrombophlebitis — 3.1%
- Pain at the injection site — 0.7%
- Erythema at the injection site — 0.4%
- Vein induration — 0.2%
- Infused vein infection — 0.1%

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN I.V. were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see **PRECAUTIONS**), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients 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 antibacterial treatment, see **WARNINGS**), hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar 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; *Skin* — Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole* — polyarthralgia, asthenia/weakness, drug fever; *Renal* — acute renal failure, oliguria/anuria, polyuria, urine discoloration. The role of PRIMAXIN I.V. in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

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 ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH

Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils

Electrolytes: Decreased serum sodium, increased potassium, increased chloride

Renal: Increased BUN, creatinine

Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

Pediatric Patients

In studies of 178 pediatric patients ≥3 months of age, the following adverse events were noted:

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence >1%)

Adverse Experience	No. of Patients (%)
<i>Digestive System</i>	
Diarrhea	7* (3.9)
Gastroenteritis	2 (1.1)
Vomiting	2* (1.1)
<i>Skin</i>	
Rash	4 (2.2)
Irritation, I.V. site	2 (1.1)
<i>Urogenital System</i>	
Urine discoloration	2 (1.1)
<i>Cardiovascular System</i>	
Phlebitis	4 (2.2)

*One patient had both vomiting and diarrhea and is counted in each category.

In studies of 135 patients (newborn to 3 months of age), the following adverse events were noted:

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence >1%)

Adverse Experience	No. of Patients (%)
<i>Digestive System</i>	
Diarrhea	4 (3.0%)
Oral Candidiasis	2 (1.5%)
<i>Skin</i>	
Rash	2 (1.5%)
<i>Urogenital System</i>	
Oliguria/anuria	3 (2.2%)
<i>Cardiovascular System</i>	
Tachycardia	2 (1.5%)
<i>Nervous System</i>	
Convulsions	8 (5.9%)

Patients (≥3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values

Laboratory Parameter	Abnormality	No. of Patients With Abnormalities/ No. of Patients With Lab Done (%)
Hemoglobin	Age <5 mos.: <10 gm %	19/129 (14.7)
	6 mos.-12 yrs.: <11.5 gm %	
Hematocrit	Age <5 mos.: <30 vol %	23/129 (17.8)
	6 mos.-12 yrs.: <34.5 vol %	
Neutrophils	≤1000/mm ³ (absolute)	4/123 (3.3)
Eosinophils	≥7%	15/117 (12.8)
Platelet Count	≥500 ths/mm ³	16/119 (13.4)
Urine Protein	≥1	8/97 (8.2)
Serum Creatinine	>1.2 mg/dL	0/105 (0)
BUN	>22 mg/dL	0/108 (0)
AST (SGOT)	>36 IU/L	14/78 (17.9)
ALT (SGPT)	>30 IU/L	10/93 (10.8)

Patients (<3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values

Laboratory Parameter	No. of Patients With Abnormalities* (%)
Eosinophil Count↑	11 (9.0%)
Hematocrit↓	3 (2.0%)
Hematocrit↑	1 (1.0%)
Platelet Count↑	5 (4.0%)
Platelet Count↓	2 (2.0%)
Serum Creatinine↑	5 (5.0%)
Bilirubin↑	3 (3.0%)
Bilirubin↓	1 (1.0%)
AST (SGOT)↑	5 (6.0%)
ALT (SGPT)↑	3 (3.0%)
Serum Alkaline Phosphate↑	2 (3.0%)

*The denominator used for percentages was the number of patients for whom the test was performed during or post-treatment and, therefore, varies by test.

Examination of published literature and spontaneous adverse event reports suggested a similar spectrum of adverse events in adult and pediatric patients.

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.V., 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**Adults**

The dosage recommendations for PRIMAXIN I.V. represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 125 mg, 250 mg, or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 750 mg or 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

The total daily dosage for PRIMAXIN I.V. should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function, and body weight. Adult patients with impaired renal function, as judged by creatinine clearance ≤ 70 mL/min/1.73 m², require adjustment of dosage as described in the succeeding section of these guidelines.

Intravenous Dosage Schedule for Adults with Normal Renal Function and Body Weight ≥ 70 kg

Doses cited in Table I are based on a patient with normal renal function and a body weight of 70 kg. These doses should be used for a patient with a creatinine clearance of ≥ 71 mL/min/1.73 m² and a body weight of ≥ 70 kg. A reduction in dose must be made for a patient with a creatinine clearance of ≤ 70 mL/min/1.73 m² and/or a body weight less than 70 kg. (See Tables II and III.)

Dosage regimens in column A of Table I are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of Table I are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa*.

TABLE I
INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH
NORMAL RENAL FUNCTION AND BODY WEIGHT ≥ 70 kg

Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of <i>P. aeruginosa</i>
Mild	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)
Moderate	500 mg q8h (TOTAL DAILY DOSE = 1.5g) or 500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g) or 1 g q8h (TOTAL DAILY DOSE = 3.0g)
Severe, life threatening only	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	1 g q8h (TOTAL DAILY DOSE = 3.0g) or 1 g q6h (TOTAL DAILY DOSE = 4.0g)
Uncomplicated urinary tract infection	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	250 mg q6h (TOTAL DAILY DOSE = 1.0g)
Complicated urinary tract infection	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)

Due to the high antimicrobial activity of PRIMAXIN I.V., it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy. However, patients over twelve years of age with cystic fibrosis and normal renal function have been treated with PRIMAXIN I.V. at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

Reduced Intravenous Schedule for Adults with Impaired Renal Function and/or Body Weight < 70 kg

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² and/or body weight less than 70 kg require dosage reduction of PRIMAXIN I.V. as indicated in the tables below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

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

To determine the dose for adults with impaired renal function and/or reduced body weight:

1. Choose a total daily dose from Table I based on infection characteristics.
2. a) If the total daily dose is 1.0 g, 1.5 g, or 2.0 g, use the appropriate subsection of Table II and continue with step 3.
 b) If the total daily dose is 3.0 g or 4.0 g, use the appropriate subsection of Table III and continue with step 3.
3. From Table II or III:
 - a) Select the body weight on the far left which is closest to the patient's body weight (kg).
 - b) Select the patient's creatinine clearance category.
 - c) Where the row and column intersect is the reduced dosage regimen.

TABLE II
 REDUCED INTRAVENOUS DOSAGE OF PRIMAXIN I.V. IN ADULT PATIENTS WITH
 IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT <70 kg

and Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE I is:											
	1.0 g/day				1.5 g/day				2.0 g/day			
	and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:			
	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	250 q6h	250 q8h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q8h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q6h	125 q8h	125 q12h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h

TABLE III
 REDUCED INTRAVENOUS DOSAGE OF PRIMAXIN I.V. IN ADULT PATIENTS WITH
 IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT <70 kg

And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE I is:							
	3.0 g/day				4.0 g/day			
	and creatinine clearance (mL/min/1.73 m ²) is:				and creatinine clearance (mL/min/1.73 m ²) is:			
	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	1000 q8h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q8h	500 q6h	500 q12h
60	750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
50	500 q6h	500 q8h	250 q6h	250 q12h	750 q8h	500 q6h	500 q8h	500 q12h
40	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
30	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with PRIMAXIN I.V. 125 mg or 250 mg every 12 hours for most pathogens. There may be an increased risk of seizures when doses of 500 mg every 12 hours are administered to these patients.

Patients with creatinine clearance ≤ 5 mL/min/1.73 m² should not receive PRIMAXIN I.V. unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of PRIMAXIN I.V. for patients undergoing peritoneal dialysis.

Hemodialysis

When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 mL/min/1.73 m². (See *Reduced Intravenous Dosage Schedule for Adults with Impaired Renal Function and/or Body Weight <70 kg.*) Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive PRIMAXIN I.V. after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN I.V. is recommended only when the benefit outweighs the potential risk of seizures. (see **PRECAUTIONS.**)

Pediatric Patients

See **PRECAUTIONS, Pediatric Patients.**

For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections is 15-25 mg/kg/dose administered every six hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

For pediatric patients ≤ 3 months of age (weighing $\geq 1,500$ gms), the following dosage schedule is recommended for non-CNS infections:

<1 wk of age: 25 mg/kg every 12 hrs

1-4 wks of age: 25 mg/kg every 8 hrs

4 wks-3 mos. of age: 25 mg/kg every 6 hrs.

Doses less than or equal to 500 mg should be given by intravenous infusion over 15 to 30 minutes. Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes.

PRIMAXIN I.V. is not recommended in pediatric patients with CNS infections because of the risk of seizures.

PRIMAXIN I.V. is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.

PREPARATION OF SOLUTION

Infusion Bottles

Contents of the infusion bottles of PRIMAXIN I.V. Powder should be restored with 100 mL of diluent (see list of diluents under **COMPATIBILITY AND STABILITY**) and shaken until a clear solution is obtained.

Vials

Contents of the vials must be suspended and transferred to 100 mL of an appropriate infusion solution.

A suggested procedure is to add approximately 10 mL from the appropriate infusion solution (see list of diluents under **COMPATIBILITY AND STABILITY**) to the vial. Shake well and transfer the resulting suspension to the infusion solution container.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity. Therefore, diluents containing benzyl alcohol should not be used when PRIMAXIN I.V. is constituted for administration to pediatric patients in this age range.

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

Repeat with an additional 10 mL of infusion solution to ensure complete transfer of vial contents to the infusion solution. **The resulting mixture should be agitated until clear.**

ADD-Vantage®††† Vials

See separate INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage® VIALS. PRIMAXIN I.V. in ADD-Vantage® vials should be reconstituted with ADD-Vantage® diluent containers containing 100 mL of either 0.9% Sodium Chloride Injection or 100 mL 5% Dextrose Injection.

††† Registered trademark of Abbott Laboratories, Inc.

MONOVIAL® Vials

See separate INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN MONOVIAL® VIALS. PRIMAXIN I.V. in MONOVIAL® vials should be reconstituted using an appropriate diluent in an infusion bag, with a maximum port length of 14 mm.

The MONOVIAL® vial is not compatible with the ADD-Vantage® diluent bags.

COMPATIBILITY AND STABILITY*Before Reconstitution:*

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

Reconstituted Solutions:

Solutions of PRIMAXIN I.V. range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

PRIMAXIN I.V., as supplied in single use infusion bottles, vials and MONOVIAL® vials and reconstituted with the following diluents (see **PREPARATION OF SOLUTION**), maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (5°C). Solutions of PRIMAXIN I.V. should not be frozen.

- 0.9% Sodium Chloride Injection
- 5% or 10% Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose Injection with 0.225% or 0.45% saline solution
- 5% Dextrose Injection with 0.15% potassium chloride solution
- Mannitol 5% and 10%

PRIMAXIN I.V., as supplied in single dose ADD-Vantage® vials and reconstituted with the following diluents (see **PREPARATION OF SOLUTION**), maintains satisfactory potency for 4 hours at room temperature.

- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection

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

HOW SUPPLIED

PRIMAXIN I.V. is supplied as a sterile powder mixture in single dose containers including vials, infusion bottles, ADD-Vantage® vials, and MONOVIAL® vials containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

No. 3514 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer

NDC 0006-3514-58 in trays of 25 vials.

No. 3516 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer

NDC 0006-3516-59 in trays of 25 vials.

No. 3517 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer

NDC 0006-3517-75 in trays of 10 infusion bottles.

No. 3551 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer

NDC 0006-3551-58 in trays of 25 ADD-Vantage® vials.

No. 3552 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer

NDC 0006-3552-59 in trays of 25 ADD-Vantage® vials.

No. 3666 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer

NDC 0006-3666-59 in trays of 25 MONOVIAL® vials.

REFERENCES

1. 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.
 2. 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.
 3. 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.
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 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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PRIMAXIN® I.M. **(IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION)**

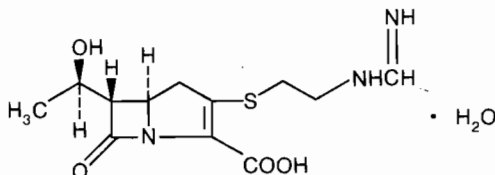
To reduce the development of drug-resistant bacteria and maintain the effectiveness of PRIMAXIN I.M.† and other antibacterial drugs, PRIMAXIN I.M. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intramuscular Injection Only

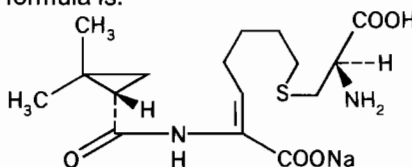
DESCRIPTION

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 cattleya*. 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 C₁₂H₁₇N₃O₄S•H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is [*R*-[*R'*, *S'*-(*Z*)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[2-(2,2-dimethylcyclopropyl)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 C₁₆H₂₅N₂O₅SNa, 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

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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 IMPENEM
(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 intermedius

(formerly *B. melaninogenicus intermedius*)

Bacteroides fragilis

Bacteroides thetaiotaomicron

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.

Capnocytophaga 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:

<u>Organism</u>	<u>MIC (µg/mL)</u>
<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:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥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:

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<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:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤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. intermedius** and *B. thetaiotaomicron**; *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**.

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

(4) **Gynecologic infections**, including postpartum endomyometritis, caused by Group D streptococcus including *Enterococcus faecalis**; *Escherichia coli*; *Klebsiella pneumoniae**; *Bacteroides intermedius**; 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 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 **DOSAGE 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 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

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

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.

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 papillar 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 Skin and skin structure Gynecologic	Mild/Moderate	500 or 750 mg q 12 h depending on the severity of infection
Intra-abdominal	Mild/Moderate	750 mg q 12 h

^{††} See INDICATIONS AND USAGE section.

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 (T_{cc}) may be estimated from the following equation:

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

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

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

1. 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.

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

2. 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.
 3. 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.
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 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-061

50-630 / S-023

MEDICAL REVIEW

Clinical Review of Labeling Supplements
NDA 50-587/S-061 and NDA 50-630/S-023

Date of Submission: November 25, 2003

Date CDER Received: November 26, 2003

Date Assigned to Reviewer: May 5, 2004

Date Review Initiated: May 10, 2004

Drugs: NDA 50-587: Primaxin IV (imipenem and cilastin) For Injection
NDA 50-605: Primaxin IM (imipenem and cilastin) Injectable Suspension

Applicant: Merck & Co., Inc.
Rahway, NJ 07065

Indications: NDA 50-587 (Primaxin IV for Injection) is approved for the following indications:

- lower respiratory tract infections
- urinary tract infections
- intra-abdominal infections
- gynecological infections
- bacterial septicemia
- bone and joint infections
- skin and skin structure infections
- endocarditis
- polymicrobial infections

NDA 50-630 (Primaxin IM Injectable Suspension) is approved for the following indications:

- lower respiratory tract infections
- intra – abdominal infections
- skin and skin structure infections
- gynecologic infections

Packaging: NDA 50-587: The product is provided in a variety of single-dose containers containing either 250 mg imipenem/250 mg cilastin or 500 mg/imipenem/500 mg cilastin for dilution with a number of standard diluents.

NDA 50-630: The product is provided in vials containing either 500 mg imipenem/500 mg cilastin or 750 mg imipenem/750 mg cilastin for dilution with lidocaine.

Reason for Supplements: These supplements were submitted to comply with FDA's requirements for labeling of systemic antibacterial drugs to include statements intended to reduce the development of resistant bacteria. The Final Rule for this regulation was published February 6, 2003.

Material Reviewed: The supplemental applications, as well as the February 6, 2003 Final Rule titled "Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use" were consulted in completing this review. The sponsor's submissions contain the presently approved label and the proposed labeling revision.

Review: The Final Rule requires the addition of specific statements concerning the necessity of using the drug to treat bacterial infections only (to prevent overuse). The statements are required:

- under the product name
- in the Indication section
- in the Precautions section, "General" subsection
- in the Precautions section, "Information for Patients" subsection.

The sponsor has included the required statements in the submitted draft labeling.

Conclusions and Recommendations: The supplements may be approved.

David C. Bostwick

Jean Mulinde, MD

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Bostwick
5/13/04 11:06:22 AM
MEDICAL OFFICER

Jean Mulinde
5/13/04 11:12:13 AM
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Janice Soreth
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