CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-587 / S-058
50-630 / S-021

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

Generic Name: **Imipenem and Cilastatin**

Sponsor: **Merck & Co.**

Approval Date: **March 4, 2003**

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50-630 / S-021

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058
50-630 / S-021

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-587/S-058
NDA 50-630/S-021

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

Dear Ms. Snyder:

Please refer to your supplemental new drug applications dated March 12, 2002, received March 13, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRIMAXIN™ IV for Injection (Imipenem and Cilastatin)[NDA 50-587/S-058] and PRIMAXIN™ IM Injectable Suspension (Imipenem and Cilastatin)[NDA 50-630/S-021].

These applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated May 7, 2002 and February 12, 2003.

These supplemental new drug applications provide for revisions to the **PRECAUTIONS** section, *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy: Teratogenic Effects Pregnancy Category C* subsections of the labels. Specifically, the labels have been revised to reflect the comparison between dose levels used in animal teratology and reproduction tests to those doses used in humans on the basis of body surface area (mg/m^2) rather than body weight (mg/kg).

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted February 12, 2003).

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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 50-587/S-058 and NDA 50-630/S-021**". Approval of these submissions by FDA is not required before the labeling is used.

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

If you have any questions, please contact 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
3/4/03 01:40:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058
50-630 / S-021

LABELING

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

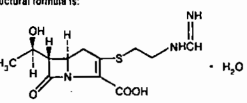
PRIMAXIN® I.V.
(IMIPENEM AND CILASTATIN FOR INJECTION)

For Intravenous Injection Only

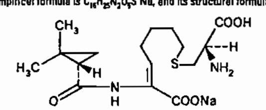
DESCRIPTION

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 $C_{12}H_{17}N_3O_4S \cdot H_2O$, 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 $C_{16}H_{25}N_2O_5S\,Na$, 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 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:

[†] Registered trademark of MERCK & CO., Inc.

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 method[1] (broth, agar, or microdilution) or equivalent with imipenem powder.

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

MIC (μg/mL)	Interpretation
≤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:

Microorganism	MIC (μg/mL)
E. coli ATCC 25922	0.06–0.25
S. aureus ATCC 29213	0.015–0.06
E. faecalis ATCC 29212	0.5–2.0
P. aeruginosa 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 procedure[2] 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:

Zone Diameter (mm)	Interpretation
≥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:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	26–32
P. aeruginosa 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:

MIC (μg/mL)	Interpretation
≤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:

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

Broth Microdilution Testing:

Microorganism	MIC (μg/mL)
B. thetaiotaomicron ATCC 29741	0.06–0.25
E. lentum 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,

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

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

Circular Number 7882127

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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) **Polymicrobic infections.** PRIMAXIN I.V. is indicated for polymicrobic 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.

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.

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 m^2, 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 m^2 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.

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/m^2 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/m^2 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 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/m^2 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/m^2 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/m^2 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

[††] Based on patient body surface area of 1.6 m^2 (weight of 60 kg).

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 0.8±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, 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 date 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 — 2.1%
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 (2.2%), 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

** Two patients were less than 3 months of age.
*** One patient was greater than 3 months of age.

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 (%)
Digestive System	
Diarrhea	7* (3.9)
Gastroenteritis	2 (1.1)
Vomiting	2* (1.1)
Skin	
Rash	4 (2.2)
Irritation, I.V. site	2 (1.1)
Urogenital System	
Urine discoloration	2 (1.1)
Cardiovascular System	
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 (%)
Digestive System	
Diarrhea	4 (3.0%)
Oral Candidiasis	2 (1.5%)
Skin	
Rash	2 (1.5%)
Urogenital System	
Hypertonia	3 (2.2%)
Cardiovascular System	
Tachycardia	2 (1.5%)
Nervous System	
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 Abnormality/ 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 %	23/128	(17.9)
	6 mos.-12 yrs.:	<34.5 vol %		
Neutrophils	≤1000/mm³ (absolute)		4/123	(3.3)
Eosinophils	≥7%		15/117	(12.8)
Platelet Count	≥500 thsn/mm³		10/119	(13.4)
Urine Protein	≥1		8/97	(8.2)
Serum Creatinine	>1.2 mg/dL		0/105	(0)
BUN	>20mg/dL		0/88	(0)
AST (SGOT)	>36 IU/L		14/78	(17.9)
ALT (SGPT)	>30 IU/L		10/92	(10.9)

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

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

*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 *P. aeruginosa*
Mild	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)
Moderate	500 mg q6h (TOTAL DAILY DOSE = 1.5g) or 500 mg q8h (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 q6h (TOTAL DAILY DOSE = 3.0g) or 1 g q8h (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:

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

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

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.

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.)

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 — and creatinine clearance (mL/min/1.73 m²) is: ≥71	41-70	21-40	6-20	1.5 g/day — and creatinine clearance (mL/min/1.73 m²) is: ≥71	41-70	21-40	6-20	2.0 g/day — and creatinine clearance (mL/min/1.73 m²) is: ≥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 q6h	250 q12h	250 q12h	500 q6h	250 q6h	250 q8h	250 q12h	500 q6h	500 q6h	250 q6h	250 q12h
60	250 q6h	250 q6h	250 q12h	125 q12h	250 q6h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
50	125 q6h	125 q6h	125 q6h	125 q12h	250 q6h	250 q6h	250 q8h	250 q12h	250 q6h	250 q6h	250 q6h	250 q12h
40	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q6h	125 q8h	125 q12h	250 q6h	250 q6h	125 q6h	125 q12h
30	125 q6h	125 q6h	125 q8h	125 q12h	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	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 — and creatinine clearance (mL/min/1.73 m²) is: ≥71	41-70	21-40	6-20	4.0 g/day — and creatinine clearance (mL/min/1.73 m²) is: ≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	1000 q6h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q6h	500 q8h	500 q12h
60	750 q6h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q6h	500 q8h	500 q12h
50	500 q6h	500 q6h	250 q6h	250 q12h	750 q6h	500 q6h	500 q8h	500 q12h
40	500 q6h	250 q6h	250 q6h	250 q12h	500 q6h	500 q6h	250 q6h	250 q12h
30	250 q6h	250 q6h	250 q6h	250 q12h	500 q6h	250 q6h	250 q6h	250 q12h

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 ≥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 date 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.

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 effect 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® viels 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. 3518 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3518-59 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. 3668 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3668-59 in trays of 25 MONOVIAL® vials.

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‡ Registered trademark of Becton Dickinson and Company.

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:* polyarthrelgia, asthenia/weaknass, 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 studiad in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxie was rapidly produced and clonic convulsions were noted in ebout 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 wes 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 showad tremors at all doses and clonic convulsions and ptosis were seen at the two highest doses (1130 and 1734 mg/kg). Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

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

DOSAGE AND ADMINISTRATION

PRIMAXIN I.M. is for intramuscular use only.

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

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

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

DOSAGE GUIDELINES

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

††See INDICATIONS AND USAGE section.

PRIMAXIN® I.M. (Imipenem and Cilastatin for Injectable Suspension)

Total daily IM dosagas 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 typa and severity of the infection. Generelly, PRIMAXIN I.M. should be continued for at least two days after the signs end 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 lerge muscle mass (such as the gluteel muscles or lateral part of the thigh) with a 21 gauge 2" needle. Aspiration is necessery to avoid inadvertent injection into a blood vessel.

ADULTS WITH IMPAIRED RENAL FUNCTION

The safety and efficecy of PRIMAXIN I.M. have not been studied in patients with creatinine clearance of less than 20 mL/min/1.73m^2. Serum creatinine alone may not be a sufficiently accurete meesure of renel function. Creatinine clearance (T_{cc}) mey 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 withdrew and inject the entire contents of viel 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 et 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 preperation.

PRIMAXIN I.M. should not be mixed with or physically added to other antibiotics. However, PRIMAXIN I.M. may be administered concomitantly but at seperate 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 treys 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, Villenova, 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, Villenova, 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.

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

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

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MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

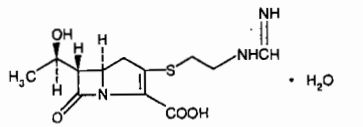
PRIMAXIN® I.M.
(IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION)

For Intramuscular Injection Only

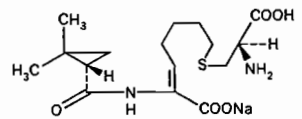
DESCRIPTION

PRIMAXIN† I.M. (Imipenem and Cilastatin for Injectable Suspension) is a formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (tha inhibitor of the renel 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*-[5α, 6α (*R**)]]-6-[1-hydroxyethyl) -3-[[2-[(iminomethyl) amino] ethyl]thio]-7-oxo-1-azebicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is en 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 $C_{12}H_{17}N_3O_4S{\cdot}H_2O$, 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-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 $C_{16}H_{25}N_2O_5SNa$, 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, end occur within 1 hour. When compared to intravenous administration of imipenem-cilastatin sodium, imipenem is approximately 75% bioavailable following intramuscular administration while cilastatin is approximately 95% bioavailable. The absorption of imipenem from the IM injection site continues for 6 to 8 hours while that for cilastatin is essentially complete within 4 hours. This prolonged absorption of imipenem following the administration of the intramuscular formulation of imipenem-cilastatin sodium results in an effective plasma half-life of imipenem of approximately 2 to 3 hours and plasma levels of the antibiotic which remain above 2 μg/mL for at least 6 or 8 hours, following a 500 mg or 750 mg dose, respectively. This plasma profile for imipenem permits IM administration of the intramuscular formulation of imipenem-cilastatin sodium every 12 hours with no accumulation of cilastatin and only slight accumulation of imipenem.

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

PRIMAXIN® I.M. (Imipenem and Cilastatin for Injectable Suspension)

PLASMA CONCENTRATIONS OF IMIPENEM (μg/mL)

	500 MG		750 MG	
TIME	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 eureus* 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*
- *Escherichie coli*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginose*
  (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 method[1] (broth, agar, microdilution) or equivalent with imipenem powder. The MIC values obtained should be interpreted according to the following criteria:

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

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

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

Organism	MIC (µg/mL)
E. coli ATCC 25922	0.06-0.25
S. aureus ATCC 29213	0.015-0.06
E. faecalis ATCC 29212	0.5-2.0
P. aeruginosa 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 procedure[2], which has been recommended for use with disks to test susceptibility of organisms to imipenem, uses the 10-µg imipenam disk. Interpretation involves the correletion of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for imipenem.

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

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

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

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

For anaerobic bacteria, the MIC of imipenem can be determined by ager or broth dilution (including microdilution) techniques[3].

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

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

INDICATIONS AND USAGE

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

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

(1) **Lower respiratory tract infections,** including pneumonia and bronchitis as an exacerbation of COPD, ceused 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**.

(4) **Gynecologic infections,** including postpartum endomyometritis, ceused 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.

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".

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

After the diagnosis of pseudomembranous colitis hes been established, therapeutic measures should be initiated. Mild ceses 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 antibecterial drug clinically effective against *C. difficile* colitis.

Lidocaine HCl — Refer to the package circuler 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 e 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 meesures should be taken.

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

Drug Interactions

Since concomitant administration of PRIMAXIN (Imipenem-Cilastatin Sodium) end 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 edded 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 variaty of bacterial end mammelian tests *in vivo* and *in vitro*. The tests used were: V79 mammelian cell mutagenesis essey (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 eny evidance 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/m^2 body surface area basis). Slight decreases in live fetal body weight were restricted to the highest dosege 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 end 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/m^2 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/m^2 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/m^2 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, diarrhee, end 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.

*** Based on patient body surface area of 1.6 m^2 (weight of 60 kg).

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 maternel toxicity including emesis, inappetence, body weight loss, diarrhea, abortion and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 1.3 times*** the maximum recommended daily human dose of the intramuscular formulation) were administered to pregnant cynomolgus monkeys et 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 tha 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/dey, 2.1 times the maximum recommended daily human dose (on a mg/m^2 body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN I.M. should be used during pregnency 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 eged 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 substantiellv 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 edverse local clinical reaction that wes 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 neusea (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 end 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 becteria in the urine.

Potential ADVERSE EFFECTS:

In addition, a variety of adverse effects, not observed in clinicel 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058
50-630 / S-021

MEDICAL REVIEW

Medical Officer's Review of NDA Supplements
NDA 50-587; NDA 50-630

NDA Numbers: 50-587 (SLR-058); 50-630 (SLR-021)

Sponsor Identification:

Merck & Co., Inc.
P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486
484-344-7984
Contact: Virginia Snyder, Manager, Regulatory Affairs

Submission and Review Dates

Dates of Submissions: 50-587 (SLR-058): 3/12/02
50-630 (SLR-021): 3/12/02
Date Review Completed: 4/1/02

Drug Identification

Generic Name: Imipenem and Cilastatin
Trade Names: PRIMAXIN® I.V. (NDA 50-587)
PRIMAXIN® I.M. (NDA 50-630)

These NDA supplements contain proposed labeling changes for the intravenous and intramuscular injection forms of imipenem and cilastatin. On 9/26/00, the Agency requested that the PRECAUTIONS section of the PRIMAXIN® I.M. label be revised to express comparisons between the drug doses used in animal reproductive tests and teratology studies and drug doses used in humans in terms of body surface area (mg/m^2) rather than body weight (mg/kg). The PRIMAXIN® I.V. label is being revised accordingly to maintain consistency in the labeling of these products.

The proposed changes are under review by Amy Ellis, Ph.D., Pharmacologist. There are no changes in other sections of these labels.

Thomas Smith, M.D.
Medical Officer, HFD-520

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

/s/

Thomas Smith
4/1/02 11:24:39 AM
MEDICAL OFFICER
Labeling supplement.
Please sign off.

Jean Mulinde
4/1/02 11:50:58 AM
MEDICAL OFFICER

Janice Soreth
4/17/02 04:09:28 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058
50-630 / S-021

PHARMACOLOGY REVIEW

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA#s: 50,587 (SLR 058) and 50,630 (SLR 021)

Date CDER Received/Type of Submission: original submissions rec'd 3/13/02 and additional information rec'd 5/8/02 (labeling supplements)
Reviewer: Amy L. Ellis, Ph.D.
Date Assigned: 3/26/02
Number of Volumes: 2
Date Review Started: 4/9/02
Date 1ST Draft Completed: 5/31/02
Scientific Literature Reviewed: Not necessary

KEY WORDS: Primaxin™, imipenem, cilastatin, label, reproduction toxicity

Sponsor: Merck
PO Box 4, BLA-20
West Point, PA 19486
(484) 344-7984

Review Contains Information to be Communicated to Sponsor: Yes

Submission Contains Any Integrated Tox Study Summaries in Lieu of Final Reports: No

Drug Information:

Class:	Carbapenem antimicrobial with renal dehydropeptidase I inhibitor
Generic Name:	imipenem/cilastatin
Trade Name:	Primaxin™

Introduction and Drug History: As requested by the Division, the sponsor has submitted labeling supplements to the IV and IM Primaxin™ NDAs to change the animal to human dose comparisons in the *Impairment of Fertility* and *Pregnancy* sections of the label from mg/kg to mg/m^2.

Studies reviewed within this submission: No new studies were submitted- the data used for the label is unchanged. The only change is that animal to human dose comparisons will be made on a body surface area basis instead of mg/kg.

SUMMARY/LABELING RECOMMENDATION:

It is not obvious to the pharmacologist why 2 different adult sizes (50 kg vs. 70 kg) were used when making dose comparisons for the IM and IV Primaxin™ labels, respectively. The sponsor should reconcile both labels using one size, preferably 60 kg. This is the adult human size assumption routinely used by CDER pharm/tox reviewers when making dose comparisons

with animal data (see draft internal document *A Harmonized Approach to Estimating the Safe Starting Dose for Clinical Trials of Therapeutics in Healthy Volunteers*). Additionally, the pharmacologist recommends that the dose comparisons in the IV label should consistently use the highest recommended human dose. Currently some of the comparisons in this label use the highest recommended human dose (50 mg/kg/day) and others use what is referred to as "the usual human dose" (30 mg/kg/day). For the IM label, FDA based the dose comparisons on a 60 kg person instead of 50 kg; thus, the highest recommended daily dose (up to 1500 mg/day) came out to 25 mg/kg/day. This was not a large enough change to significantly alter the dose comparison calculations when the sponsor and reviewer used the same body surface area conversion factors to transform the doses to mg/m^2. The pharmacologist and sponsor generally used the same conversion factors, but the one for rabbits did differ somewhat. The rabbit conversion factor routinely used by CDER pharm/tox reviewers is also found in the draft document mentioned above. It caused the pharmacologist's mg/m^2 dose calculated for rabbits to be higher than the sponsor's. Finally, the sponsor should mention in the label the routes of administration used in the animal studies described in the *Fertility* and *Pregnancy* sections.

The reviewer notes that most of her calculations of dose comparisons between animals and humans do not differ significantly differ from the sponsor's. The largest differences occur in the IV label because the pharmacologist consistently used the highest recommended human dose of 50 mg/kg/day to make the comparisons.

Conversion Factors, Body Surface Area Dose Calculations and Dose Comparisons Between Humans and Animal Species

Species	Dose (mg/kg/day)	Conversion Factor	Dose (mg/m^2/day)	Animal:Human Dose Comparison
Human* (IV)	50	37	1850	---
Human* (IM)	25	37	925	---
Rat	320	6	1920	Approx equal (IV); 2.1 (IM)
Rat	900	6	5400	2.9 (IV); 5.8 (IM)
Rat	1000	6	6000	3.2 (IV); 6.5 (IM)
Rabbit	60	12	720	0.4 (IV); 0.8 (IM)
Rabbit	300	12	3600	1.9 (IV); 3.9 (IM)
Monkey	100	12	1200	0.6 (IV); 1.3 (IM)
Mouse	320	3	960	0.5 IV; Approx. equal (IM)

*assumes 60 kg human and highest recommended doses of IM 1500 mg/day and IV 50 mg/kg/day)

Suggested labeling for NDA 50,587 (Primaxin™ IV):

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.

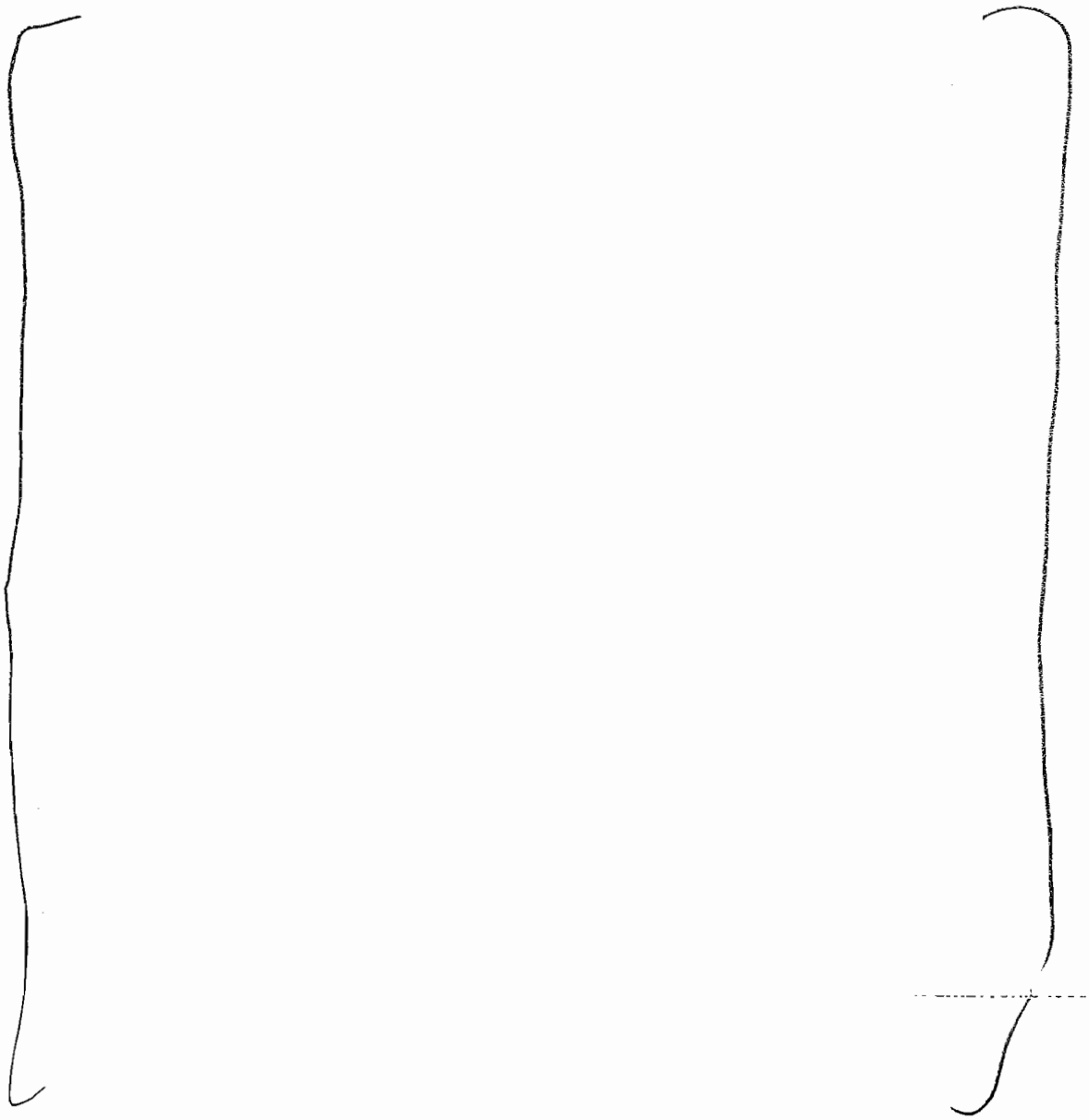
Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at (insert

Suggested labeling for NDA 50,630 (Primaxin™ IM):

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 **(insert**



The reviewer's recommendations for the labels should be conveyed to the sponsor, along with the table of calculated dose comparisons.

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Please initial below to indicate that you have seen the paper copy of this review and agree that it should be put into DFS as a final, archival document:

HFD-520/TSPeters
HFD-520/LGavrilovich

cc:
HFD-520/CSO/Dillon-Parker
HFD-520/MO/Smith

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

/s/

Amy Ellis
6/12/02 04:12:28 PM
PHARMACOLOGIST
The reviewer's recommendations for the label should be conveyed to the sponsor, along with the table of
calculated dose comparisons.
Terry- You signed the paper copy of this review on 6/10/02.

Terry Peters
6/17/02 09:56:14 AM
PHARMACOLOGIST

Lillian Gavrilovich
6/21/02 12:34:14 PM
MEDICAL OFFICER