CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 62-756 / S-005, S-007, S-008, and S-010

***Name*:** Primaxin® I.V. in ADD-Vantage® vials (Imipenem-Cilastatin Sodium for Injection)

***Sponsor*:** Merck Research Laboratories

***Approval Date*:** December 29, 1993

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APPROVAL LETTER

AADA 62-756/S-005, S-007, S-008, S-010

DEC 29 1993

Merck Sharp and Dohme Research Laboratories
Attention: Ronald A. Salerno, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Sir:

Reference is made to your supplemental antibiotic drug applications dated April 5, 1990, (S-005); September 26, 1990, (S-007); October 30, 1990, (S-008); and April 24, 1991, (S-010); submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated antibiotic applications for Primaxin® (Imipenem-Cilastatin Sodium for Injection), ADD-Vantage vials.

The supplemental applications provide for:

S-005: revised INDICATIONS AND USAGE and PRECAUTIONS sections;

S-007: change in name from INJECTION PRIMAXIN to PRIMAXIN I.V.;

S-008: revised ADVERSE REACTIONS section as well as editorial changes;

S-010: revised ADVERSE REACTIONS section.

We have completed the review of these supplemental applications and they are approved. Our letter of January 5, 1987, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained in our files.

Sincerely,
Yana Ruth Mille for/ 12/29/93
Robert W. Pollock
Director, Division of Labeling and
Program Support
Office of Generic Drugs
Center For Drug Evaluation and Research

cc: AADA 62-756/S-005, S-007, S-008, S-010
Dup/Division File
HFD-613/AVezza/JPhillips (no cc:) AVezza 12/29/93
HFD-600/RF mdsmith 12/29/93
HFC-130/JAllen
HFD-82
mpd 12/22/93/62756.S05
Approval Letter

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APPLICATION NUMBER:

ANDA 62-756 / S-005, S-007, S-008, and S-010

LABELING

S-005

APPROVED

DEC 29 1993

A.H.F.S. Category: 8:12.28

INJECTION

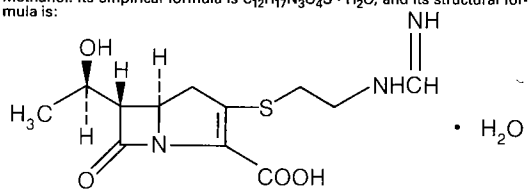
MSD | PRIMAXIN®
(IMIPENEM-CILASTATIN SODIUM, MSD)

PRIMAXIN®
(Imipenem-Cilastatin Sodium, MSD)

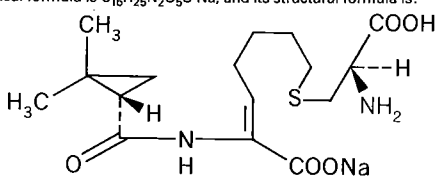
DESCRIPTION

PRIMAXIN* (Imipenem-Cilastatin Sodium, MSD) 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 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*-[5α, 6α (*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S \cdot H_2O$, 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 $C_{16}H_{25}N_2O_5S$ Na, and its structural formula is:



PRIMAXIN is buffered to provide solutions in the pH range of 6.5 to 7.5. There is no significant change in pH when solutions are prepared and used as directed. (See COMPATIBILITY AND STABILITY.) PRIMAXIN 250 contains 18.8 mg of sodium (0.8 mEq) and PRIMAXIN 500 contains 37.5 mg of sodium (1.6 mEq). Solutions of PRIMAXIN range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

Intravenous Administration

Intravenous infusion of PRIMAXIN over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose and from 41 to 83 mcg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN, range from 15 to 25 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose.

General

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 mcg/mL can be maintained for up to 8 hours with PRIMAXIN at the 500 mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN.

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

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.

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

Tissue or Fluid	N	Imipenem Level mcg/mL or mcg/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 to 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

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 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 *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

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.

In vitro, imipenem is active against most strains of clinical isolates of the following microorganisms:

Gram-positive:
- Group D streptococci (including enterococci e.g., *Streptococcus faecalis*)
  - NOTE: Imipenem is inactive against *Streptococcus faecium.*
- *Streptococcus pyogenes* (Group A streptococci)
- *Streptococcus agalactiae* (Group B streptococci)
- Group C streptococci
- Group G streptococci
- *Viridans streptococci*
- *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*)
- *Staphylococcus aureus* including penicillinase producing strains
- *Staphylococcus epidermidis* including penicillinase producing strains
  - NOTE: Many strains of methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:
- *Escherichia coli*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Morganella morganii*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Citrobacter* spp.
- *Klebsiella* spp. including *K. pneumoniae* and *K. oxytoca*
- *Enterobacter* spp.
- *Hafnia* spp. including *H. alvei*
- *Serratia marcescens*
- *Serratia* spp. including *S. liquefaciens*
- *Haemophilus parainfluenzae*
- *H. influenzae*
- *Gardnerella vaginalis*
- *Acinetobacter* spp.
- *Pseudomonas aeruginosa*
  - NOTE: Imipenem is inactive against *P. maltophilia* and some strains of *P. cepacia.*

Anaerobes:
- *Bacteroides* spp. including *Bacteroides bivius, Bacteroides fragilis, Bacteroides melaninogenicus*
- *Clostridium* spp. including *C. perfringens*
- *Eubacterium* spp.
- *Fusobacterium* spp.
- *Peptococcus* spp.
- *Peptostreptococcus* spp.
- *Propionibacterium* spp. including *P. acnes*
- *Actinomyces* spp.
- *Veillonella* spp.

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Imipenem has been shown to be active *in vitro* against the following microorganisms; however, clinical efficacy has not yet been established.

Gram-positive:
Listeria monocytogenes
Nocardia spp.
Gram-negative:
Salmonella spp.
Shigella spp.
Yersinia spp. including *Yersinia enterocolitica, Yersinia pseudotuberculosis*
Bordetella bronchiseptica
Campylobacter spp.
Achromobacter spp.
Alcaligenes spp.
Moraxella spp.
Pasteurella multocida
Aeromonas hydrophila
Plesiomonas shigelloides
Neisseria gonorrhoeae (including penicillinase-producing strains)
Anaerobes:
Bacteroides asaccharolyticus
Bacteroides disiens
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus

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

Susceptibility Testing

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 10 mcg imipenem disc should be interpreted according to the following criteria.

Fully susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to doses of 2 g per day or less (see DOSAGE AND ADMINISTRATION).

Moderately susceptible organisms produce zones of 14 to 15 mm and are expected to be susceptible if the maximum recommended dosage is used or if infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered fully susceptible if the MIC value for imipenem is equal to or less than 4 mcg/mL. Organisms are considered moderately susceptible if the MIC value is 8 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg imipenem disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	26-32 mm
Ps. aeruginosa	27853	20-28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.06-0.25
S. aureus	29213	0.015-0.06
S. faecalis	29212	0.5-2.0
Ps. aeruginosa	27853	1.0-4.0

Based on blood levels of imipenem achieved in man, breakpoint criteria have been adopted for imipenem.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Fully Susceptible	≥16	≤4
Moderately Susceptible	14-15	8
Resistant	≤13	≥16

INDICATIONS AND USAGE

PRIMAXIN is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

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

(2) **Urinary tract infections** (Complicated and uncomplicated). *Staphylococcus aureus* (penicillinase producing strains)*, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris*, Providencia rettgeri*, Morganella morganii*, Pseudomonas aeruginosa.*

(3) **Intra-abdominal infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus* species (indole positive and indole negative), *Morganella morganii*, Pseudomonas aeruginosa, Citrobacter* species, *Clostridium* species, Gram-positive anaerobes, including *Peptococcus* species, *Peptostreptococcus* species, *Eubacterium* species, *Propionibacterium* species*, *Bifidobacterium* species, *Bacteroides* species, including *B. fragilis, Fusobacterium* species.

(4) **Gynecologic infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group B streptococci, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species*, *Proteus* species (indole positive and indole negative), *Enterobacter* species*, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, *B. fragilis*, Gardnerella vaginalis.*

(5) **Bacterial septicemia.** *Staphylococcus aureus* (penicillinase producing strains), Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species*, *Enterobacter* species, *Bacteroides* species, *B. fragilis*.*

(6) **Bone and joint infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Enterobacter* species, *Pseudomonas aeruginosa.*

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

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

(9) **Polymicrobic infections.** PRIMAXIN is indicated for polymicrobic infections including those in which *S. pneumoniae* (pneumonia, septicemia), Group A beta-hemolytic streptococcus (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 is not indicated in patients with meningitis because safety and efficacy have not been established.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, PRIMAXIN 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 on treatment with PRIMAXIN. When clinically appropriate during therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done.

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

CONTRAINDICATIONS

PRIMAXIN 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', CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

PRECAUTIONS

General

CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, 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.

Patients with severe or marked impairment of renal function, whether or not

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

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

undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

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

For patients on hemodialysis, PRIMAXIN 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 re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN 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.

While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

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

Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN) and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. 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. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy

Pregnancy Category C. Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggests an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are underway to evaluate these findings.

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

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in infants and children below 12 years of age have not yet been established.

ADVERSE REACTIONS

PRIMAXIN 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.

Local Adverse Reactions

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

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

Systemic Adverse Reactions

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

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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 (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory*— chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Skin*—toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole*—polyarthralgia, asthenia/weakness; *Renal*—acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN 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 SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs test, decreased WBC and neutrophils including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, 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.

OVERDOSAGE

The intravenous LD_{50} of imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the mouse.

The intravenous LD_{50} of cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD_{50} of PRIMAXIN is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Information on overdosage in humans is not available.

DOSAGE AND ADMINISTRATION

The dosage recommendations for PRIMAXIN represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 250 mg or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 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 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. 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.

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

Doses cited in the Table below are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION

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 *Ps. aeruginosa*
Mild	250 mg q6h	500 mg q6h
Moderate	500 mg q8h 500 mg q6h	500 mg q6h 1 g q8h
Severe, life threatening	500 mg q6h	1 g q8h 1 g q6h
Uncomplicated urinary tract infection	250 mg q6h	250 mg q6h
Complicated urinary tract infection	500 mg q6h	500 mg q6h

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Due to the high antimicrobial activity of PRIMAXIN, 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 at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² require adjustment of the dosage of PRIMAXIN as indicated in the table below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

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

Column A of the following Table shows maximum dosages recommended in each category of impaired renal function for infections caused by fully susceptible organisms which represent the majority of pathogenic species. The maximum dosages in column B are recommended only for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *Ps. aeruginosa*. Doses cited are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

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

Maximum Recommended Intravenous Dosage of PRIMAXIN in Adults with Impaired Renal Function

Creatinine Clearance (mL/min/ 1.73 m2)	Renal Function	A Fully Susceptible Organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately Susceptible organisms, primarily some strains of *Ps. aeruginosa*
31-70	Mild Impairment	500 mg q8h	500 mg q6h
21-30	Moderate Impairment	500 mg q12h	500 mg q8h
6-20	Severe to Marked Impairment	250 mg q12h See Text Below	500 mg q12h See Text Below
0-5	None, but on Hemodialysis		

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

Similar dosage and safety considerations apply in the treatment of patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis. Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive PRIMAXIN 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 is recommended only when the benefit outweighs the potential risk of seizures (see PRECAUTIONS).

PREPARATION OF SOLUTION

Infusion Bottles

Contents of the infusion bottles of PRIMAXIN 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.

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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.

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' IN ADD-Vantage® VIALS. PRIMAXIN in ADD-Vantage® vials should be reconstituted with ADD-Vantage® diluent containers containing 100 mL of either 0.9 percent Sodium Chloride Injection or 100 mL 5 percent Dextrose Injection.

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 30°C.

Reconstituted solutions:

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

PRIMAXIN, as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature or for 24 hours under refrigeration (5°C) (note exception below). Solutions of PRIMAXIN should not be frozen.

0.9% Sodium Chloride Injection*
5% or 10% Dextrose Injection
5% Dextrose Injection with 0.02% sodium bicarbonate solution
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
NORMOSOL† – M in D5-W
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 2.5%, 5% and 10%

PRIMAXIN is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF 'PRIMAXIN' IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 100 mL of either 0.9 percent Sodium Chloride Injection or 5 percent Dextrose Injection. When prepared with either of these diluents, PRIMAXIN maintains satisfactory potency for 8 hours at room temperature.

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

HOW SUPPLIED

PRIMAXIN is supplied as a sterile powder mixture in vials and infusion bottles 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 0006-3514-74 in trays of 10 vials
(6505-01-232-3116 vial, 10's).

No. 3516—500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3516-75 in trays of 10 vials
(6505-01-232-3115 vial, 10's).

No. 3515—250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3515-74 in trays of 10 infusion bottles
(6505-01-246-4126 infusion bottle, 10's).

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
(6505-01-234-0240 infusion bottle, 10's).

No. 3551—250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3551-74 in trays of 10 ADD-Vantage® vials.
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 0006-3552-75 in trays of 10 ADD-Vantage® vials
(6505-01-276-4591 500 mg ADD-Vantage®, 10's).
NDC 0006-3552-59 in trays of 25 ADD-Vantage® vials
(6505-01-279-9627 500 mg ADD-Vantage®, 25's).

*PRIMAXIN has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature or 48 hours under refrigeration.
†Registered trademark of Abbott Laboratories, Inc.

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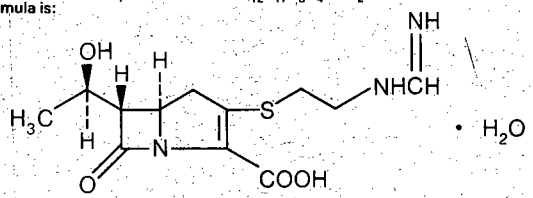
MSD | PRIMAXIN® I.V.

(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)

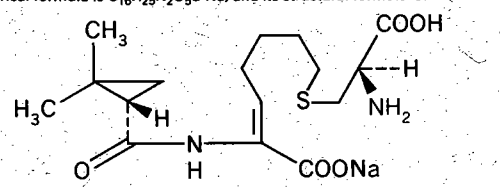
DESCRIPTION

PRIMAXIN* I.V. (Imipenem-Cilastatin Sodium for Injection, MSD) 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*-[5α, 6α (*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S \cdot H_2O$, 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 $C_{16}H_{25}N_2O_5S$ Na, and its structural formula is:



PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 7.5. 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

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 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose and from 41 to 83 mcg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/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 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose.

General

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 mcg/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 PRIMAXIN I.V. in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

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.

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

Tissue or Fluid	N	Imipenem Level mcg/mL or mcg/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 to 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

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 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 *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

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.

In vitro, imipenem is active against most strains of clinical isolates of the following microorganisms:

Gram-positive:
- Group D streptococci (including enterococci e.g., *Streptococcus faecalis*)
  - NOTE: Imipenem is inactive against *Streptococcus faecium.*
- *Streptococcus pyogenes* (Group A streptococci)
- *Streptococcus agalactiae* (Group B streptococci)
- Group C streptococci
- Group G streptococci
- *Viridans streptococci*
- *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*)
- *Staphylococcus aureus* including penicillinase producing strains
- *Staphylococcus epidermidis* including penicillinase producing strains
  - NOTE: Many strains of methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:
- *Escherichia coli*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Morganella morganii*
- *Providencia rettgeri*
- *Providencia stuartii*
- *Citrobacter* spp.
- *Klebsiella* spp. including *K. pneumoniae* and *K. oxytoca*
- *Enterobacter* spp.
- *Hafnia* spp. including *H. alvei*
- *Serratia marcescens*
- *Serratia* spp. including *S. liquefaciens*
- *Haemophilus parainfluenzae*
- *H. influenzae*
- *Gardnerella vaginalis*
- *Acinetobacter* spp.
- *Pseudomonas aeruginosa*
  - NOTE: Imipenem is inactive against *P. maltophilia* and some strains of *P. cepacia.*

Anaerobes:
- *Bacteroides* spp. including *Bacteroides bivius, Bacteroides fragilis, Bacteroides melaninogenicus*
- *Clostridium* spp. including *C. perfringens*
- *Eubacterium* spp.
- *Fusobacterium* spp.
- *Peptococcus* spp.
- *Peptostreptococcus* spp.
- *Propionibacterium* spp. including *P. acnes*
- *Actinomyces* spp.
- *Veillonella* spp.

Imipenem has been shown to be active *in vitro* against the following microorganisms; however, clinical efficacy has not yet been established.

Gram-positive:
- *Listeria monocytogenes*
- *Nocardia* spp.

Gram-negative:
Salmonella spp.
Shigella spp.
Yersinia spp. including *Yersinia enterocolitica, Yersinia pseudotuberculosis*
Bordetella bronchiseptica
Campylobacter spp.
Achromobacter spp.
Alcaligenes spp.
Moraxella spp.
Pasteurella multocida
Aeromonas hydrophila
Plesiomonas shigelloides
Neisseria gonorrhoeae (including penicillinase-producing strains)
Anaerobes:
Bacteroides asaccharolyticus
Bacteroides disiens
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus
In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa.*

Susceptibility Testing

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 10 mcg imipenem disc should be interpreted according to the following criteria.

Fully susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to doses of 2 g per day or less (see DOSAGE AND ADMINISTRATION).

Moderately susceptible organisms produce zones of 14 to 15 mm and are expected to be susceptible if the maximum recommended dosage is used or if infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered fully susceptible if the MIC value for imipenem is equal to or less than 4 mcg/mL. Organisms are considered moderately susceptible if the MIC value is 8 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg imipenem disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	26-32 mm
Ps. aeruginosa	27853	20-28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.06-0.25
S. aureus	29213	0.015-0.06
S. faecalis	29212	0.5-2.0
Ps. aeruginosa	27853	1.0-4.0

Based on blood levels of imipenem achieved in man, breakpoint criteria have been adopted for imipenem.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Fully Susceptible	≥16	≤4
Moderately Susceptible	14-15	8
Resistant	≤13	≥16

INDICATIONS AND USAGE

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

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

(2) **Urinary tract infections** (Complicated and uncomplicated). *Staphylococcus aureus* (penicillinase producing strains)*, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris*, Providencia rettgeri*, Morganella morganii*, Pseudomonas aeruginosa.*

(3) **Intra-abdominal infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus* species (indole positive and indole negative), *Morganella morganii*, Pseudomonas aeruginosa, Citrobacter* species, *Clostridium* species, Gram-positive anaerobes, including *Peptococcus* species, *Peptostreptococcus* species, *Eubacterium* species, *Propionibacterium* species*, *Bifidobacterium* species, *Bacteroides* species, including *B. fragilis, Fusobacterium* species.

(4) **Gynecologic infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group B streptococci, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species*, *Proteus* species (indole positive and indole negative), *Enterobacter* species*, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, *B. fragilis*, Gardnerella vaginalis.*

(5) **Bacterial septicemia.** *Staphylococcus aureus* (penicillinase producing strains), Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species*, *Enterobacter* species, *Bacteroides* species, *B. fragilis*.*

(6) **Bone and joint infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Enterobacter* species, *Pseudomonas aeruginosa.*

(7) **Skin and skin structure infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris, Providencia rettgeri*, Morganella morganii, Pseudomonas aeruginosa, Serratia* species, *Citrobacter* species, *Acinetobacter* species, Gram-positive anaerobes, including *Peptococcus* species and *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), Group A beta-hemolytic streptococcus (skin and skin structure), or non-penicillinase-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.

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 on treatment with PRIMAXIN I.V. When clinically appropriate during therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done.

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 TO 'PRIMAXIN I.V.' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN I.V.; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

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.

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

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

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

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

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

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

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

While PRIMAXIN I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions

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

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

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN I.V. alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN I.V.) and *in vivo* mouse cytogenicity test (PRIMAXIN I.V.). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN I.V. at dosage levels up to 8 times the usual human dose. 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. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN I.V. was administered to rats late in gestation.

Pregnancy

Pregnancy Category C. Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN I.V. at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggests an apparent intolerance to PRIMAXIN I.V. (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN I.V. was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are underway to evaluate these findings.

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 fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.V. is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in infants and children below 12 years of age have not yet been established.

ADVERSE REACTIONS

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

Local Adverse Reactions

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

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

PRIMAXIN® I.V.
(Imipenem-Cilastatin Sodium for Injection, MSD)

Systemic Adverse Reactions

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

Additional adverse systemic clinical reactions reported as possibly, probably or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory*— chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Skin*—toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole*—polyarthralgia, asthenia/weakness; *Renal*—acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN I.V. in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes

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

Hepatic: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs test, decreased WBC and neutrophils including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, 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.

OVERDOSAGE

The intravenous LD_{50} of imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the mouse.

The intravenous LD_{50} of cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD_{50} of PRIMAXIN I.V. is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Information on overdosage in humans is not available.

DOSAGE AND ADMINISTRATION

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 250 mg or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 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. 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.

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

Doses cited in the Table below are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION

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 *Ps. aeruginosa*
Mild	250 mg q6h	500 mg q6h
Moderate	500 mg q8h 500 mg q6h	500 mg q6h 1 g q8h
Severe, life threatening	500 mg q6h	1 g q8h 1 g q6h
Uncomplicated urinary tract infection	250 mg q6h	250 mg q6h
Complicated urinary tract infection	500 mg q6h	500 mg q6h

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.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² require adjustment of the dosage of PRIMAXIN I.V. as indicated in the table below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

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

Column A of the following Table shows maximum dosages recommended in each category of impaired renal function for infections caused by fully susceptible organisms which represent the majority of pathogenic species. The maximum dosages in column B are recommended only for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *Ps. aeruginosa*. Doses cited are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

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.

Maximum Recommended Intravenous Dosage of PRIMAXIN I.V. in Adults With Impaired Renal Function

Creatinine Clearance (mL/min/ 1.73 m²)	Renal Function	A Fully Susceptible Organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately Susceptible organisms, primarily some strains of *Ps. aeruginosa*
31-70	Mild Impairment	500 mg q8h	500 mg q6h
21-30	Moderate Impairment	500 mg q12h	500 mg q8h
6-20	Severe to Marked Impairment	250 mg q12h See Text Below	500 mg q12h See Text Below
0-5	None, but on Hemodialysis		

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

Similar dosage and safety considerations apply in the treatment of patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis. 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).

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.

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 percent Sodium Chloride Injection or 100 mL 5 percent Dextrose Injection.

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 30°C.

Reconstituted solutions:

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

PRIMAXIN I.V., as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature or for 24 hours under refrigeration (5°C) (note exception below). Solutions of PRIMAXIN I.V. should not be frozen.

0.9% Sodium Chloride Injection*
5% or 10% Dextrose Injection
5% Dextrose Injection with 0.02% sodium bicarbonate solution
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
NORMOSOL† – M in D5-W
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 2.5%, 5% and 10%

PRIMAXIN I.V. is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 100 mL of either 0.9 percent Sodium Chloride Injection or 5 percent Dextrose Injection. When prepared with either of these diluents, PRIMAXIN I.V. maintains satisfactory potency for 8 hours at room temperature.

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 vials and infusion bottles 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 0006-3514-74 in trays of 10 vials
(6505-01-232-3116 vial, 10's).

No. 3516 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3516-75 in trays of 10 vials
(6505-01-232-3115 vial, 10's).

No. 3515 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3515-74 in trays of 10 infusion bottles
(6505-01-246-4126 infusion bottle, 10's).

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
(6505-01-234-0240 infusion bottle, 10's).

No. 3551 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3551-74 in trays of 10 ADD-Vantage® vials.
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 0006-3552-75 in trays of 10 ADD-Vantage® vials
(6505-01-276-4591 500 mg ADD-Vantage®, 10's).
NDC 0006-3552-59 in trays of 25 ADD-Vantage® vials
(6505-01-279-9627 500 mg ADD-Vantage®, 25's).

*PRIMAXIN I.V. has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature or 48 hours under refrigeration.
†Registered trademark of Abbott Laboratories, Inc.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA

Issued August 1990

Printed in USA

S-007

APPROVED

INSTRUCTIONS FOR USE OF PRIMAXIN®† I.V. (Imipenem-Cilastatin Sodium for Injection, MSD) IN ADD-Vantage®* VIALS

For IV Use Only.

DEC 2 9 1993

INSTRUCTIONS FOR USE

To Open Diluent Container.

Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container.
(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening. (SEE FIGURE 1.) Pull the ring approximately half way around the cap and then pull straight up to remove the cap. (SEE FIGURE 2.) NOTE: DO NOT ACCESS VIAL WITH SYRINGE.

Fig. 1

Fig. 2

   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately ½ turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go. NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)

†Registered trademark of MERCK & CO., Inc.
*Registered trademark of ABBOTT LABORATORIES, Inc.

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Fig. 3

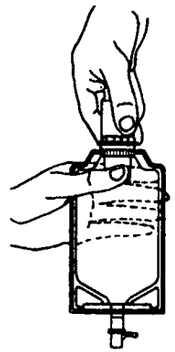

Fig. 4

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

N. B. If the rubber stopper is not removed from the vial and the antibiotic released on the first attempt, the inner cap should be manipulated back into the stopper without removing the drug vial from the diluent container and Step 3 repeated.

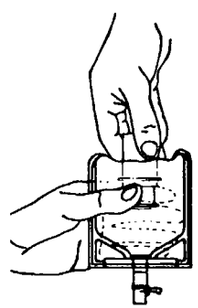

Fig. 5

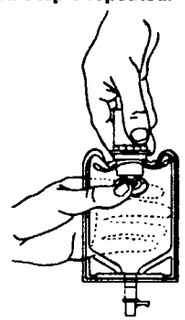

Fig. 6

Preparation for Administration
(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

Stability

PRIMAXIN I.V. (Imipenem - Cilastatin Sodium for Injection, MSD) 250 or 500 single dose ADD-Vantage® vials should be prepared with ADD-Vantage® diluent containers containing 100 mL of either 0.9 percent Sodium Chloride Injection or 5 percent Dextrose Injection. When prepared with either of these diluents, PRIMAXIN I.V. (Imipenem - Cilastatin Sodium for Injection, MSD) maintains satisfactory potency for 8 hours at room temperature.

Before administering, see accompanying package circular for PRIMAXIN I.V. (Imipenem - Cilastatin Sodium for Injection, MSD).

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ANDA 62-756

NDA 62-756

APPROVED

DEC 29 1993

For the Preparation of Intravenous Solutions and
USUAL ADULT DOSAGE:
See accompanying circular.
Store dry material below 30°C.
After constitution as directed, the solution maintains satisfactory potency for 8 hours at room temperature.
Consult accompanying INSTRUCTIONS FOR USE. Use only with ADD-Vantage® Diluent Containers.

[redacted]

Single-dose ADD-Vantage® vial
500

PRIMAXIN® I.V.

(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)
IMIPENEM 500 mg (Anhydrous Equivalent)
CILASTATIN EQUIVALENT 500 mg
CAUTION: SINGLE DOSE VIAL / FOR I.V. USE ONLY
NOT FOR DIRECT INFUSION
PRIMAXIN® is a registered trademark of MERCK & CO., Inc.
ADD-Vantage® is a registered trademark of ABBOTT LABORATORIES, Inc.

PRIMAXIN® I.V. 500

CAUTION: Federal (USA) law prohibits dispensing without prescription.
MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA
500 mg | No. 3552 7613403

Lot

Exp.

[redacted]

ANDA 62-756

NDA 62-756

APPROVED

DEC 29 1993

[redacted]

Lot No. & Exp. Date

500

6505-01-279-9627

PRIMAXIN® I.V.

Not to be divided.

(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)

IMIPENEM 500 mg (Anhydrous Equivalent) CILASTATIN EQUIVALENT 500 mg

Inactive ingredient: sodium bicarbonate 20 mg added to each vial as a buffer.

CAUTION: SINGLE DOSE VIAL / FOR I.V. USE ONLY / NOT FOR DIRECT INFUSION

For the Preparation of Intravenous Solutions and USUAL ADULT DOSAGE: See accompanying circular.

Consult accompanying INSTRUCTIONS FOR USE.

Store dry material below 30°C.

Color changes in solution from colorless to yellow do not affect potency.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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ADD-Vantage® is a registered trademark of ABBOTT LABORATORIES, Inc.

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MSD | PRIMAXIN® I.V.

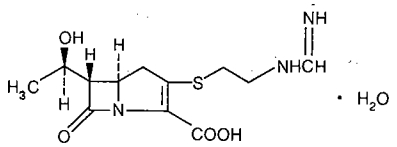
(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)

PRIMAXIN® I.V.
(Imipenem-Cilastatin Sodium for Injection, MSD)

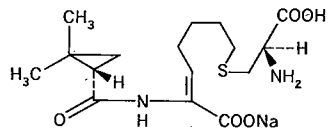
DESCRIPTION

PRIMAXIN* I.V. (Imipenem-Cilastatin Sodium for Injection, MSD) 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*-[5α, 6α (*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S \cdot H_2O$, 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 $C_{16}H_{25}N_2O_5S$ Na, and its structural formula is:



PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 7.5. 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

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 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose and from 41 to 83 mcg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/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 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose.

General

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 mcg/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 PRIMAXIN I.V. in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

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.

PRIMAXIN® I.V.
(Imipenem-Cilastatin Sodium for Injection, MSD)

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

Tissue or Fluid	n	Imipenem Level mcg/mL or mcg/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 to 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

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 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 *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

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.

In vitro, imipenem is active against most strains of clinical isolates of the following microorganisms:

Gram-positive:

Group D streptococci (including enterococci e.g., *Streptococcus faecalis*)
NOTE: Imipenem is inactive against *Streptococcus faecium.*
Streptococcus pyogenes (Group A streptococci)
Streptococcus agalactiae (Group B streptococci)
Group C streptococci
Group G streptococci
Viridans streptococci
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)
Staphylococcus aureus including penicillinase producing strains
Staphylococcus epidermidis including penicillinase producing strains
NOTE: Many strains of methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:

Escherichia coli
Proteus mirabilis
Proteus vulgaris
Morganella morganii
Providencia rettgeri
Providencia stuartii
Citrobacter spp.
Klebsiella spp. including *K. pneumoniae* and *K. oxytoca*
Enterobacter spp.
Hafnia spp. including *H. alvei*
Serratia marcescens
Serratia spp. including *S. liquefaciens*
Haemophilus parainfluenzae
H. influenzae
Gardnerella vaginalis
Acinetobacter spp.
Pseudomonas aeruginosa
NOTE: Imipenem is inactive against *P. maltophilia* and some strains of *P. cepacia.*

Anaerobes:

Bacteroides spp. including *Bacteroides bivius, Bacteroides fragilis, Bacteroides melaninogenicus*
Clostridium spp. including *C. perfringens*
Eubacterium spp.
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp. including *P. acnes*
Actinomyces spp.
Veillonella spp.

Imipenem has been shown to be active *in vitro* against the following microorganisms; however, clinical efficacy has not yet been established.

Gram-positive:

Listeria monocytogenes
Nocardia spp.

Gram-negative:
Salmonella spp.
Shigella spp.
Yersinia spp. including *Yersinia enterocolitica, Yersinia pseudotuberculosis*
Bordetella bronchiseptica
Campylobacter spp.
Achromobacter spp.
Alcaligenes spp.
Moraxella spp.
Pasteurella multocida
Aeromonas hydrophila
Plesiomonas shigelloides
Neisseria gonorrhoeae (including penicillinase-producing strains)
Anaerobes:
Bacteroides asaccharolyticus
Bacteroides disiens
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus

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

Susceptibility Testing

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 10 mcg imipenem disc should be interpreted according to the following criteria.

Fully susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to doses of 2 g per day or less (see DOSAGE AND ADMINISTRATION).

Moderately susceptible organisms produce zones of 14 to 15 mm and are expected to be susceptible if the maximum recommended dosage is used or if infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered fully susceptible if the MIC value for imipenem is equal to or less than 4 mcg/mL. Organisms are considered moderately susceptible if the MIC value is 8,mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg imipenem disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	26-32 mm
Ps. aeruginosa	27853	20-28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.06-0.25
S. aureus	29213	0.015-0.06
S. faecalis	29212	0.5-2.0
Ps. aeruginosa	27853	1.0-4.0

Based on blood levels of imipenem achieved in man, breakpoint criteria have been adopted for imipenem.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Fully Susceptible	≥16	≤4
Moderately Susceptible	14-15	8
Resistant	≤13	≥16

INDICATIONS AND USAGE

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

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

(2) **Urinary tract infections** (Complicated and uncomplicated). *Staphylococcus aureus* (penicillinase producing strains)*, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris*, Providencia rettgeri*, Morganella morganii*, Pseudomonas aeruginosa.*

(3) **Intra-abdominal infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus* species (indole positive and indole negative), *Morganella morganii*, Pseudomonas aeruginosa, Citrobacter* species, *Clostridium* species, Gram-positive anaerobes, including *Peptococcus* species, *Peptostreptococcus* species, *Eubacterium* species, *Propionibacterium* species*, *Bifidobacterium* species, *Bacteroides* species, including *B. fragilis, Fusobacterium* species.

(4) **Gynecologic infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group B streptococci, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species*, *Proteus* species (indole positive and indole negative), *Enterobacter* species*, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, *B. fragilis*, Gardnerella vaginalis.*

(5) **Bacterial septicemia.** *Staphylococcus aureus* (penicillinase producing strains), Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species*, *Enterobacter* species, *Bacteroides* species, *B. fragilis*.*

(6) **Bone and joint infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Enterobacter* species, *Pseudomonas aeruginosa.*

(7) **Skin and skin structure infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris, Providencia rettgeri*, Morganella morganii, Pseudomonas aeruginosa, Serratia* species, *Citrobacter* species, *Acinetobacter* species, Gram-positive anaerobes, including *Peptococcus* species and *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), Group A beta-hemolytic streptococcus (skin and skin structure), or non-penicillinase-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.

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 on treatment with PRIMAXIN I.V. When clinically appropriate during therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done.

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 TO 'PRIMAXIN I.V.' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN I.V.; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

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.

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

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

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

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

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

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

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

While PRIMAXIN I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions

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

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

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN I.V. alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN I.V.) and *in vivo* mouse cytogenicity test (PRIMAXIN I.V.). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN I.V. at dosage levels up to 8 times the usual human dose. 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. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN I.V. was administered to rats late in gestation.

Pregnancy

Pregnancy Category C. Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN I.V. at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggests an apparent intolerance to PRIMAXIN I.V. (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN I.V. was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are underway to evaluate these findings.

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 fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.V. is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in infants and children below 12 years of age have not yet been established.

ADVERSE REACTIONS

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

Local Adverse Reactions

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

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

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Systemic Adverse Reactions

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

Additional adverse systemic clinical reactions reported as possibly, probably or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *Hematologic*—agranulocytosis, thrombocytopenia, neutropenia, leukopenia; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory*— chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Skin*—toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole*—polyarthralgia, asthenia/weakness; *Renal*—acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN I.V. in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes

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

Hepatic: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, 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.

OVERDOSAGE

The intravenous LD_{50} of imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the mouse.

The intravenous LD_{50} of cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD_{50} of PRIMAXIN I.V. is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Information on overdosage in humans is not available.

DOSAGE AND ADMINISTRATION

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 250 mg or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 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. 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.

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

Doses cited in the Table below are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION

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 *Ps. aeruginosa*
Mild	250 mg q6h	500 mg q6h
Moderate	500 mg q8h 500 mg q6h	500 mg q8h 1 g q8h
Severe, life threatening	500 mg q6h	1 g q8h 1 g q6h
Uncomplicated urinary tract infection	250 mg q6h	250 mg q6h
Complicated urinary tract infection	500 mg q6h	500 mg q6h

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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.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² require adjustment of the dosage of PRIMAXIN I.V. as indicated in the table below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

T_{cc} (Females) = 0.85 x above value

Column A of the following Table shows maximum dosages recommended in each category of impaired renal function for infections caused by fully susceptible organisms which represent the majority of pathogenic species. The maximum dosages in column B are recommended only for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *Ps. aeruginosa*. Doses cited are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

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.

Maximum Recommended Intravenous Dosage of PRIMAXIN I.V. in Adults With Impaired Renal Function

Creatinine Clearance (mL/min/ 1.73 m²)	Renal Function	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of *Ps. aeruginosa*
31-70	Mild Impairment	500 mg q8h	500 mg q6h
21-30	Moderate Impairment	500 mg q12h	500 mg q8h
6-20	Severe to Marked Impairment	250 mg q12h See Text Below	500 mg q12h See Text Below
0-5	None, but on Hemodialysis		

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

Similar dosage and safety considerations apply in the treatment of patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis. 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).

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.

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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.

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.

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 30°C.

Reconstituted solutions:

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

PRIMAXIN I.V., as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature or for 24 hours under refrigeration (5°C) (note exception below). Solutions of PRIMAXIN I.V. should not be frozen.

0.9% Sodium Chloride Injection*
5% or 10% Dextrose Injection
5% Dextrose Injection with 0.02% sodium bicarbonate solution
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
NORMOSOL† – M in D5-W
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 2.5%, 5% and 10%

PRIMAXIN I.V. is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 100 mL of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. When prepared with either of these diluents, PRIMAXIN I.V. maintains satisfactory potency for 8 hours at room temperature.

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 vials and infusion bottles containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

No. 3514—250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3514-58 in trays of 25 vials.

No. 3516—500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3516-59 in trays of 25 vials.

No. 3515—250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3515-74 in trays of 10 infusion bottles
(6505-01-246-4126 infusion bottle, 10's).

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
(6505-01-234-0240 infusion bottle, 10's).

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
(6505-01-279-9627 500 mg ADD-Vantage®, 25's).

*PRIMAXIN I.V. has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature or 48 hours under refrigeration.
†Registered trademark of Abbott Laboratories, Inc.

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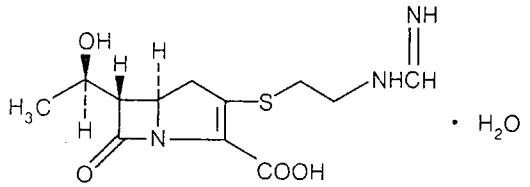
(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)

PRIMAXIN® I.V.
(Imipenem-Cilastatin Sodium for Injection, MSD)

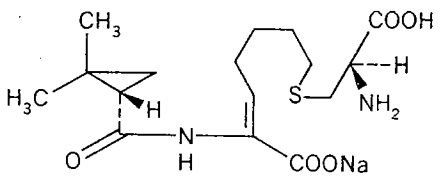
DESCRIPTION

PRIMAXIN* I.V. (Imipenem-Cilastatin Sodium for Injection, MSD) 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*-[5α, 6α (*R**)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water, and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S \cdot H_2O$, 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 $C_{16}H_{25}N_2O_5S$ Na, and its structural formula is:



PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 7.5. 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

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 mcg/mL for the 250 mg dose, from 21 to 58 mcg/mL for the 500 mg dose and from 41 to 83 mcg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/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 mcg/mL for the 250 mg dose, from 31 to 49 mcg/mL for the 500 mg dose and from 56 to 88 mcg/mL for the 1000 mg dose.

General

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 mcg/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 PRIMAXIN I.V. in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

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.

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

Tissue or Fluid	n	Imipenem Level mcg/mL or mcg/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 to 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

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin binding proteins (PBP) 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 *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

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.

In vitro, imipenem is active against most strains of clinical isolates of the following microorganisms:

Gram-positive:

Group D streptococci (including enterococci e.g., *Streptococcus faecalis*)
NOTE: Imipenem is inactive against *Streptococcus faecium.*
Streptococcus pyogenes (Group A streptococci)
Streptococcus agalactiae (Group B streptococci)
Group C streptococci
Group G streptococci
Viridans streptococci
Streptococcus pneumoniae (formerly *Diplococcus pneumoniae*)
Staphylococcus aureus including penicillinase producing strains
Staphylococcus epidermidis including penicillinase producing strains
NOTE: Many strains of methicillin-resistant staphylococci are resistant to imipenem.

Gram-negative:

Escherichia coli
Proteus mirabilis
Proteus vulgaris
Morganella morganii
Providencia rettgeri
Providencia stuartii
Citrobacter spp.
Klebsiella spp. including *K. pneumoniae* and *K. oxytoca*
Enterobacter spp.
Hafnia spp. including *H. alvei*
Serratia marcescens
Serratia spp. including *S. liquefaciens*
Haemophilus parainfluenzae
H. influenzae
Gardnerella vaginalis
Acinetobacter spp.
Pseudomonas aeruginosa
NOTE: Imipenem is inactive against *P. maltophilia* and some strains of *P. cepacia.*

Anaerobes:

Bacteroides spp. including *Bacteroides bivius, Bacteroides fragilis, Bacteroides melaninogenicus*
Clostridium spp. including *C. perfringens*
Eubacterium spp.
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp. including *P. acnes*
Actinomyces spp.
Veillonella spp.

Imipenem has been shown to be active *in vitro* against the following microorganisms; however, clinical efficacy has not yet been established.

Gram-positive:

Listeria monocytogenes
Nocardia spp.

Gram-negative:
Salmonella spp.
Shigella spp.
Yersinia spp. including *Yersinia enterocolitica, Yersinia pseudotuberculosis*
Bordetella bronchiseptica
Campylobacter spp.
Achromobacter spp.
Alcaligenes spp.
Moraxella spp.
Pasteurella multocida
Aeromonas hydrophila
Plesiomonas shigelloides
Neisseria gonorrhoeae (including penicillinase-producing strains)
Anaerobes:
Bacteroides asaccharolyticus
Bacteroides disiens
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus
In vitro tests show imipenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa.*

Susceptibility Testing

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

Reports from the laboratory giving results of the standard single-disc susceptibility test with a 10 mcg imipenem disc should be interpreted according to the following criteria.

Fully susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to doses of 2 g per day or less (see DOSAGE AND ADMINISTRATION).

Moderately susceptible organisms produce zones of 14 to 15 mm and are expected to be susceptible if the maximum recommended dosage is used or if infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered fully susceptible if the MIC value for imipenem is equal to or less than 4 mcg/mL. Organisms are considered moderately susceptible if the MIC value is 8 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg imipenem disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	26-32 mm
Ps. aeruginosa	27853	20-28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.06-0.25
S. aureus	29213	0.015-0.06
S. faecalis	29212	0.5-2.0
Ps. aeruginosa	27853	1.0-4.0

Based on blood levels of imipenem achieved in man, breakpoint criteria have been adopted for imipenem.

Category	Zone Diameter (mm)	Recommended MIC Breakpoint (mcg/mL)
Fully Susceptible	≥16	≤4
Moderately Susceptible	14-15	8
Resistant	≤13	≥16

INDICATIONS AND USAGE

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

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

(2) **Urinary tract infections** (Complicated and uncomplicated). *Staphylococcus aureus* (penicillinase producing strains)*, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris*, Providencia rettgeri*, Morganella morganii*, Pseudomonas aeruginosa.*

(3) **Intra-abdominal infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus* species (indole positive and indole negative), *Morganella morganii*, Pseudomonas aeruginosa, Citrobacter* species, *Clostridium* species, Gram-positive anaerobes, including *Peptococcus* species, *Peptostreptococcus* species, *Eubacterium* species, *Propionibacterium* species*, *Bifidobacterium* species, *Bacteroides* species, including *B. fragilis, Fusobacterium* species.

(4) **Gynecologic infections.** *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis,* Group B streptococci, Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species*, *Proteus* species (indole positive and indole negative), *Enterobacter* species*, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, *B. fragilis*, Gardnerella vaginalis.*

(5) **Bacterial septicemia.** *Staphylococcus aureus* (penicillinase producing strains), Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Pseudomonas aeruginosa, Serratia* species*, *Enterobacter* species, *Bacteroides* species, *B. fragilis*.*

(6) **Bone and joint infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Enterobacter* species, *Pseudomonas aeruginosa.*

(7) **Skin and skin structure infections.** *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis,* Group D streptococci (enterococci), *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Proteus vulgaris, Providencia rettgeri*, Morganella morganii, Pseudomonas aeruginosa, Serratia* species, *Citrobacter* species, *Acinetobacter* species, Gram-positive anaerobes, including *Peptococcus* species and *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), Group A beta-hemolytic streptococcus (skin and skin structure), or non-penicillinase-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.

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 on treatment with PRIMAXIN I.V. When clinically appropriate during therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done.

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 TO 'PRIMAXIN I.V.' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN I.V.; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

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.

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

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

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

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

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

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

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

While PRIMAXIN I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions

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

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

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN I.V. alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN I.V.) and *in vivo* mouse cytogenicity test (PRIMAXIN I.V.). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN I.V. at dosage levels up to 8 times the usual human dose. 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. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN I.V. was administered to rats late in gestation.

Pregnancy

Pregnancy Category C. Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN I.V. at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggests an apparent intolerance to PRIMAXIN I.V. (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN I.V. was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are underway to evaluate these findings.

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 fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.V. is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in infants and children below 12 years of age have not yet been established.

ADVERSE REACTIONS

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

Local Adverse Reactions

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

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

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Systemic Adverse Reactions

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

Additional adverse systemic clinical reactions reported as possibly, probably or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal*—pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *Hematologic*—agranulocytosis, thrombocytopenia, neutropenia, leukopenia; *CNS*—encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses*—transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory*— chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular*—palpitations, tachycardia; *Skin*—toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole*—polyarthralgia, asthenia/weakness; *Renal*—acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN I.V. in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes

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

Hepatic: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, 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.

OVERDOSAGE

The intravenous LD_{50} of imipenem is greater than 2000 mg/kg in the rat and approximately 1500 mg/kg in the mouse.

The intravenous LD_{50} of cilastatin sodium is approximately 5000 mg/kg in the rat and approximately 8700 mg/kg in the mouse.

The intravenous LD_{50} of PRIMAXIN I.V. is approximately 1000 mg/kg in the rat and approximately 1100 mg/kg in the mouse.

Information on overdosage in humans is not available.

DOSAGE AND ADMINISTRATION

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 250 mg or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 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. 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.

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

Doses cited in the Table below are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH NORMAL RENAL FUNCTION

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 *Ps. aeruginosa*
Mild	250 mg q6h	500 mg q6h
Moderate	500 mg q8h 500 mg q6h	500 mg q6h 1 g q8h
Severe, life threatening	500 mg q6h	1 g q8h 1 g q6h
Uncomplicated urinary tract infection	250 mg q6h	250 mg q6h
Complicated urinary tract infection	500 mg q6h	500 mg q6h

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.

INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² require adjustment of the dosage of PRIMAXIN I.V. as indicated in the table below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

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

Column A of the following Table shows maximum dosages recommended in each category of impaired renal function for infections caused by fully susceptible organisms which represent the majority of pathogenic species. The maximum dosages in column B are recommended only for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *Ps. aeruginosa*. Doses cited are based on a body weight of 70 kg. A further proportionate reduction in dose administered must be made for patients with a body weight less than 70 kg by multiplying the selected dose by the patient's weight in kg divided by 70.

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.

Maximum Recommended Intravenous Dosage of PRIMAXIN I.V. in Adults With Impaired Renal Function

Creatinine Clearance (mL/min/ 1.73 m²)	Renal Function	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of *Ps. aeruginosa*
31-70	Mild Impairment	500 mg q8h	500 mg q6h
21-30	Moderate Impairment	500 mg q12h	500 mg q8h
6-20	Severe to Marked Impairment	250 mg q12h	500 mg q12h
0-5	None, but on Hemodialysis	See Text Below	See Text Below

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

Similar dosage and safety considerations apply in the treatment of patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis. 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).

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.

PRIMAXIN® I.V.
(Imipenem-Cilastatin Sodium for Injection, MSD)

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.

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.

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 30°C.

Reconstituted solutions:

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

PRIMAXIN I.V., as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature or for 24 hours under refrigeration (5°C) (note exception below). Solutions of PRIMAXIN I.V. should not be frozen.

0.9% Sodium Chloride Injection*
5% or 10% Dextrose Injection
5% Dextrose Injection with 0.02% sodium bicarbonate solution
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
NORMOSOL† – M in D5-W
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 2.5%, 5% and 10%

PRIMAXIN I.V. is supplied in single dose ADD-Vantage® vials and should be prepared as directed in the accompanying INSTRUCTIONS FOR USE OF 'PRIMAXIN I.V.' IN ADD-Vantage® VIALS using ADD-Vantage® diluent containers containing 100 mL of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. When prepared with either of these diluents, PRIMAXIN I.V. maintains satisfactory potency for 8 hours at room temperature.

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 vials and infusion bottles 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
(6505-01-332-4793 250 mg, 25's).

No. 3516 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
NDC 0006-3516-59 in trays of 25 vials
(6505-01-332-4794 500 mg, 25's).

No. 3515 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer
NDC 0006-3515-74 in trays of 10 infusion bottles
(6505-01-246-4126 infusion bottle, 10's).

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
(6505-01-234-0240 infusion bottle, 10's).

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
(6505-01-279-9627 500 mg ADD-Vantage®, 25's).

*PRIMAXIN I.V. has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature or 48 hours under refrigeration.
†Registered trademark of Abbott Laboratories, Inc.

MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., INC., WEST POINT, PA 19486, USA

Issued March 1991

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-005, S-007, S-008, and S-010

CORRESPONDENCE

REJ

S-005 ✓
FPL

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
WEST POINT, PENNSYLVANIA 19486

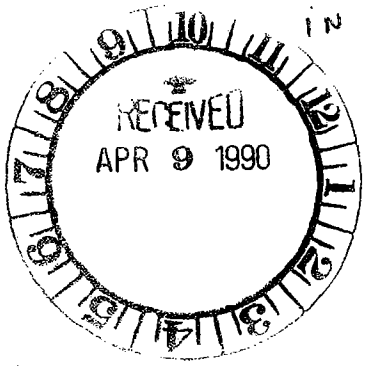
KENNETH R. BROWN, M.D.
GROUP DIRECTOR
REGULATORY AFFAIRS BIOLOGICS

(215) 834-2552
(215) 661-5000

approval letter 11/17/93 abs

April 5, 1990

LH filed on S-010 dated 4.27.91 → 5.1.91 in vol 3.1



Mr. John D. Harrison, Chief
Antibiotic Drug Review Branch, HFD-235
Division of Generic Drugs
Office of Drug Standards
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

000 3460

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

ANDA 62-756: Primaxin® ADD-Vantage® (Imipenem-Cilastatin Sodium, MSD)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c), we submit a supplement to ANDA 62-756.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 4.c. of the approved New Drug Application for Primaxin® ADD-Vantage®.

This supplement contains copies of the final printed package circular (No. 7362410), a summary of revisions and a draft revised annotated package circular. The labeling has been revised under DESCRIPTION editorially, under PRECAUTIONS, Drug Interactions based on adverse reaction reports, and under INDICATIONS AND USAGE to add a statement that Primaxin® ADD-Vantage® is not indicated in meningitis patients.

The changes will become effective on or about July 1, 1990 and will apply to all packages of Primaxin® ADD-Vantage® distributed from the company's manufacturing facilities at West Point, Pennsylvania.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

ORIGINAL

Questions concerning this supplemental application should be directed to Kenneth R. Brown, M.D. (215/834-2552) or, in his absence, to David W. Blois, Ph.D. (215/834-2304).

Sincerely yours,

K R Brown

Kenneth R. Brown, M.D.
Group Director
Regulatory Affairs, Biologics

WL/cat
4371H

Circular No. 7362410

Attachments

Certified No. P 529 432 712

S-007
ORIGINAL

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
WEST POINT, PENNSYLVANIA 19486

RONALD A. SALERNO, PH.D.
ASSOCIATE DIRECTOR
REGULATORY AFFAIRS

(215) 834-2958
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approval letter 11/17/93 atlr

September 26, 1990

Ltr filed on S-010 dated 4.2.91 5.1.91 in Vol 2.1

Mr. John D. Harrison, Chief
Antibiotic Drug Review Branch
HFD-635, Room 17B-31
Division of Generic Drugs
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

Supplemental Abbreviated New Drug Application: ANDA 62-756

Primaxin® I.V. ADD-Vantage® (Imipenem-Cilastatin Sodium For Injection, MSD)

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.55 and 21 CFR 314.70(b), we submit, for your approval, a supplement to ANDA 62-756.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 4.c. of the approved Abbreviated New Drug Application for Primaxin® I.V. ADD-Vantage®.

Reference is made to the Supplemental New Drug Application 50-587/S-025 for Primaxin® I.V. submitted on May 1, 1989 and to your letter dated August 24, 1990 approving the portion of that supplemental application which provides for the proprietary name change of Injection Primaxin® to Primaxin® I.V.

Reference is also made to a telephone conversation on September 14, 1990, between Dr. Rosemary Roberts and me concerning the format for the revised labels. During this conversation, it was agreed that examples of all revised labeling would be submitted for her review and approval. Attached are the following:

Draft Annotated Package Circular	- Tab 1
Draft Instructions For Use	- Tab 2
Final Printed Package Circular (No. 7362412)	- Tab 3
Final Printed Instructions For Use (No. 7482203)	- Tab 4
Representative Final Printed Labels	- Tab 5

Label No. 7613403 - 500 mg. Single-Dose ADD-Vantage® Vial
Label No. 7488203 - 500 mg. 25 ADD-Vantage® Vial Package

These copies are OFFICIAL FDA Copies
not desk copies.

The text of all printed components has been revised to reflect the name change of Injection Primaxin® to Primaxin® I.V. and to include the U.S.P. classification with the generic name, (Imipenem-Cilastatin Sodium For Injection, MSD). Additionally, the phrase "For I.V. Use Only" has been added to the labels.

I will be contacting Dr. Roberts shortly to obtain her concurrence on the label format as presented.

We consider the filing of this Supplemental Abbreviated New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Ronald A. Salerno, Ph.D. (215/834-2958) or, in my absence, to Kenneth R. Brown, M.D. (215/834-2552).

Sincerely yours,

Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Affairs

WL/cat
4371H

Attachments

Federal Express No. 7027218096

cc: Dr. Rosemary Roberts, HFD-520, Room 12B-45 (Desk Copy)
Federal Express No. 7027218100

Ms. Kathryn Huntley, HFD-521, Room 12B-03 (Letter Only)
Federal Express No. 7027218192

11/19/90 Send to labeling reviewer - J. Hannan

SL-008

MERCK SHARP & DOHME RESEARCH LABORATORIES
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WEST POINT, PENNSYLVANIA 19486

RONALD A. SALERNO, PH.D.
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approval letter 11/17/93 alg

October 30, 1990

Ltr filed on 5.0/0 dated 4.24.91 ⇒ 5.1.91 IN VOL 3.1

Mr. John D. Harrison, Chief
Antibiotic Drug Review Branch
HFD-635, Room 17B-31
Division of Generic Drugs
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

ANDA 62-756: Primaxin® I.V. ADD-Vantage® (Imipenem-Cilastatin Sodium, MSD)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c)(2), we submit a supplement to ANDA 62-756

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4.c. of the approved Abbreviated New Drug Application for Primaxin® I.V. ADD-Vantage®.

This supplement contains revised printed package circulars (No. 7362413), a summary of revisions, and an annotated draft package circular. The circular has been revised as follows:

- Editorially under CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, PREPARATION OF SOLUTION, and COMPATABILITY AND STABILITY.
- Under HOW SUPPLIED to change the package size.
- Under ADVERSE REACTIONS to add a new subsection, Hematologic, based on adverse reaction reports.

The changes will become effective on or about January 1, 1991 and will apply to all packages of Primaxin® I.V. ADD-Vantage® distributed from the company's manufacturing facilities at West Point, Pennsylvania.

ORIGINAL

RECEIVED
NOV 0 1 1990
GENERIC DRUGS

We consider the filing of this Supplemental Abbreviated New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Ronald A. Salerno, Ph.D. (215/834-2958) or, in my absence, to Kenneth R. Brown, M.D. (215/834-2552).

Sincerely yours,

Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Affairs

WL/cat
4371H

Attachments

Circular No. 7362413

Federal Express No. 7027218052

MERCK SHARP & DOHME RESEARCH LABORATORIES
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RONALD A. SALERNO, PH.D.
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April 24, 1991

Approval letter 11/17/93 ahp

NDA No. _____ REF. NO. 321-010
APPROVAL FOR Labeling

Mr. John D. Harrison, Chief
Antibiotic Drug Review Branch
HFD-635, Room 17B-31
Division of Generic Drugs
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

ANDA 62-756: Primaxin® I.V. in ADD-Vantage® Vials
(Imipenem-Cilastatin Sodium for Injection, MSD)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c), we submit a supplement to ANDA 62-756.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4.c. of the approved Abbreviated New Drug Application for Primaxin® I.V. in ADD-Vantage® Vials.

This supplement contains revised printed package circulars (No. 7362414), a summary of revisions, and an annotated draft package circular. The circular has been revised as follows:

- Under ADVERSE REACTIONS, Systemic Adverse Reactions

  Add "jaundice" to the Gastrointestinal subsection based on adverse experience reports.

- Under HOW SUPPLIED

  Add National Stock Numbers for Product Nos. 3514 and 3516.

The changes will become effective on or about July 1, 1991 and will apply to all packages of Primaxin® I.V. ADD-Vantage® distributed from the company's manufacturing facilities at West Point, Pennsylvania.

ORIGINAL

ORIGINAL

We consider the filing of this Supplemental Abbreviated New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Ronald A. Salerno, Ph.D. (215/834-2958) or, in my absence, to Kenneth R. Brown, M.D. (215/834-2552).

Sincerely yours,

Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Affairs

AS/cat
75H

Attachments

Circular No. 7362414

Certified No. P 856 788 759