CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 62-756 / S-014

***Name*:** Primaxin® ADD-Vantage®
(Imipenem-Cilastatin Sodium for Injection)

***Sponsor*:** Merck Research Laboratories

***Approval Date*:** February 3,1993

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-014

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Reviews	
Medical Review(s)	
Chemistry Review	
Bioequivalence Review(s)	
Statistical Review(s)	
Microbiology Review	
Administrative Documents	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-014

APPROVAL LETTER

AADA 62-756/S-014

FEB 3 1993

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

Dear Sir:

Reference is made to your supplemental antibiotic drug application dated October 4, 1991, submitted pursuant to Section 314.70(c)(Special Supplement - Changes Being Effected) of the Regulations, regarding your abbreviated antibiotic drug application for Primaxin® I.V. (Imipenem-Cilastatin Sodium for Injection), ADD-Vantage vials.

The supplemental application provides for revised package insert labeling reflecting revisions in the ADVERSE REACTIONS section.

We have completed the review of this supplemental application and it is 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 yours,

Kent L. Johnson /for

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

2-3-93

cc:
AADA 62-756/S-014
HFD_600/RF
HFC-130/JAllen
HFD-82
HFD-638/KRoberts/JPhillips
mw/1/30/93/62756S.014
APPROVAL

KRoberts 2.1.93

Jerry Phillips 2/2/93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-014

LABELING

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

7362415

MSD | PRIMAXIN® I.V.

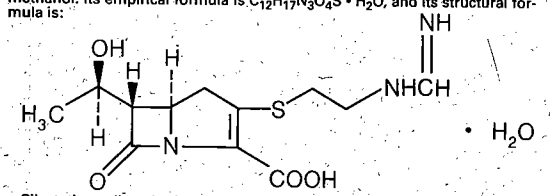
(IMIPENEM-CILASTATIN SODIUM FOR INJECTION, MSD)

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

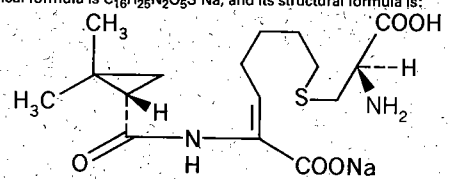
DESCRIPTION

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.

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:

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

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.

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

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

(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.

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 func-

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

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

tion; 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%

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, angioneurotic 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 August 1991

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-014

CORRESPONDENCE

ORIGINAL

These copies are OFFICIAL FDA Copies
not desk copies.

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
(215) 661-5000
FAX (215) 834-2962

FPL PI
Satisfactory
KLB
1-28-93
FPL

October 4, 1991

NDA NO. SLN 014 REF. NO.
NDA SUPPL FOR Final Label

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

OK for SCBE.
(I presume supplement was sent for the 50 numbers as well).
10/28/91
BY.

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

AADA 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 AADA 62-756.

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

This supplement contains a summary of revisions, an annotated draft package circular, a rationale for revisions, and a final printed package circular. The circular has been revised as follows:

- Under ADVERSE REACTIONS, Systemic Adverse Reactions, Skin

  Replace "facial edema" with "angioneurotic edema" in order to emphasize the presumed pathophysiology of the adverse experience

The changes will become effective on or about January 1, 1992 and will apply to all packages of PRIMAXIN® I.V. in ADD-Vantage® Vials 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.

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

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

ALS/cat
75H

Attachments

Circular No. 7362415

Certified No. P 712 126 910