# CENTER FOR DRUG EVALUATION AND RESEARCH

# Approval Package for:

***APPLICATION NUMBER:***

## ANDA 62-756/S-024

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

***Sponsor:*** Merck Sharp & Dohme Research Laboratories

***Approval Date:*** August 31, 2001

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 62-756/S-024

## CONTENTS

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

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 62-756/S-024**

# APPROVAL LETTER

ANDA 62-756/S-024 and S-031

AUG 31 2001

Merck Research Laboratories
Attention: Virgina G. Snyder
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

Dear Madam:

This is in reference to your new drug applications dated February 14, 1995 and August 27, 1999, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new applications for PRIMAXIN® I.V. (Imipenem and Cilastatin for Injection, USP) ADD-Vantage™ Vials. We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendment dated July 11, 2001.

The supplemental application [S-024] provides for revised package insert labeling reflecting changes in the TITLE, CLINICAL PHARMACOLOGY (Microbiology), INDICATIONS AND USAGE, and REFERENCES sections to be in accordance with the insert labeling for your NDA product (NDA 50-587). In addition, we note that you have further revised your insert labeling [# 7882125] reflecting the changes in the Microbiology subsection requested by the Agency in the approval letter for NDA 50-587/S-050 dated February 4, 1999.

The supplemental application [S-025] provides for revised package insert labeling reflecting changes in DESCRIPTION, PREPARATION OF SOLUTION, COMPATIBILITY AND STABILITY and HOW SUPPLIED sections reflecting addition of Primaxin® I.V. in MONOVIAL™ vials and some editorial revisions to ADVERSE REACTIONS and PREPARATION OF SOLUTION sections. We acknowledge that your supplemental application for MONOVIAL™ vials submitted to the Division of Anti-Infective Drug Products was approved on July 24, 1998 (NDA 50-587/S-049).

We have completed the review of these supplemental applications [# 7882125] and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

APPEARS THIS WAY
ON ORIGINAL

The material submitted is being retained in our files.

Sincerely yours,

8/30/0(

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 62-756/S-024, S-031
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APPROVAL LETTER – MULTIPLE SUPPLEMENTS

J. Council (MO) 8/29/01

8/30/01

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 62-756/S-024

# LABELING

MERCK & CO., INC.
West Point, PA 19486, USA

AUG 31 2001
APPROVED

# PRIMAXIN® I.V.

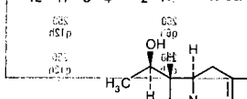
## (IMIPENEM AND CILASTATIN FOR INJECTION)

**For Intravenous Injection Only**

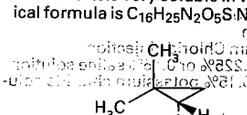
## DESCRIPTION

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

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water and slightly soluble in methanol. Its empirical formula is $C_{12}H_{17}N_3O_4S{\cdot}H_2O$, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoric acid. Its chemical name is sodium (*Z*)-7-[[(*R*)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5S{\cdot}Na$, and its structural formula is:



PRIMAXIN I.V. is buffered to provide solutions in the pH range of 6.5 to 8.5. There is no significant change in pH when solutions are prepared and used as directed. (See **COMPATIBILITY AND STABILITY.**) PRIMAXIN I.V. 250 contains 18.8 mg of sodium (0.8 mEq) and PRIMAXIN I.V. 500 contains 37.6 mg of sodium (1.6 mEq). Solutions of PRIMAXIN I.V. range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

## CLINICAL PHARMACOLOGY

*Adults*

*Intravenous Administration*

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

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

No accumulation of imipenem/cilastatin in plasma or urine was 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:

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

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

*Microbiology*

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

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

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

*Gram-positive aerobes:*
*Enterococcus faecalis* (formerly *S. faecalis*)
(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*].)
*Staphylococcus aureus* including penicillinase-producing strains
*Staphylococcus epidermidis* including penicillinase-producing strains
(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)
*Streptococcus agalactiae* (Group B streptococci)
*Streptococcus pneumoniae*
*Streptococcus pyogenes*

*Gram-negative aerobes:*
*Acinetobacter* spp.
*Citrobacter* spp.
*Enterobacter* spp.
*Escherichia coli*
*Gardnerella vaginalis*
*Haemophilus influenzae*
*Haemophilus parainfluenzae*
*Klebsiella* spp.
*Morganella morganii*
*Proteus vulgaris*
*Providencia rettgeri*
*Pseudomonas aeruginosa*
(NOTE: Imipenem is inactive *in vitro* against *Xanthomonas (Pseudomonas) maltophilia* and some strains of *P. cepacia*.)
*Serratia* spp. including *S. marcescens*

*Gram-positive anaerobes:*
*Bifidobacterium* spp.
*Clostridium* spp.
*Eubacterium* spp.
*Peptococcus* spp.
*Peptostreptococcus* spp.
*Propionibacterium* spp.

*Gram-negative anaerobes:*
*Bacteroides* spp., including *B. fragilis*
*Fusobacterium* spp.

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

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

*Gram-positive aerobes:*
*Bacillus* spp.
*Listeria monocytogenes*
*Nocardia* spp.
*Staphylococcus saprophyticus*
Group C streptococci
Group G streptococci
Viridans group streptococci

*Gram-negative aerobes:*
*Aeromonas hydrophila*
*Alcaligenes* spp.
*Capnocytophaga* spp.
*Haemophilus ducreyi*
*Neisseria gonorrhoeae* including penicillinase-producing strains
*Pasteurella* spp.
*Providencia stuartii*

*Gram-negative anaerobes:*
*Prevotella bivia*
*Prevotella disiens*
*Prevotella melaninogenica*
*Veillonella* spp.

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

*Susceptibility Tests:*

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

*Dilution Techniques:*

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such procedure uses a standardized dilution method[1] (broth, agar, or microdilution) or equivalent with imipenem powder.

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

| MIC (µg/mL) | Interpretation |
|---|---|
| ≤4 | Susceptible (S) |
| 8 | Intermediate (I) |
| ≥16 | Resistant (R) |

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

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

| Microorganism | MIC (µg/mL) |
|---|---|
| *E. coli* ATCC 25922 | 0.06–0.25 |
| *S. aureus* ATCC 29213 | 0.015–0.06 |
| *E. faecalis* ATCC 29212 | 0.5–2.0 |
| *P. aeruginosa* ATCC 27853 | 1.0–4.0 |

*Diffusion Techniques:*

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] that has been recommended for use with disks to test the susceptibility of microorganisms to imipenem uses the 10-µg imipenem disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for imipenem.

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

| Zone Diameter (mm) | Interpretation |
|---|---|
| ≥16 | Susceptible (S) |
| 14–15 | Intermediate (I) |
| ≤13 | Resistant (R) |

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

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

| Microorganism | Zone Diameter (mm) |
|---|---|
| *E. coli* ATCC 25922 | 26–32 |
| *P. aeruginosa* ATCC 27853 | 20–28 |

*Anaerobic Techniques:*

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

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

| MIC (µg/mL) | Interpretation |
|---|---|
| ≤4 | Susceptible (S) |
| 8 | Intermediate (I) |
| ≥16 | Resistant (R) |

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

Reference Agar Dilution Testing:

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

Broth Microdilution Testing:

| Microorganism | MIC (µg/mL) |
|---|---|
| *B. thetaiotaomicron* ATCC 29741 | 0.06–0.25 |
| *F. lentum* ATCC 43055 | 0.12–0.5 |

## INDICATIONS AND USAGE

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

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

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

[1] Efficacy for this organism in this organ system was studied in fewer than 10 infections.

**PRIMAXIN® I.V.**
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Circular Number 7882125

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

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

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

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

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

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

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

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

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

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

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

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

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

## CONTRAINDICATIONS

PRIMAXIN I.V. is contraindicated in patients who have shown hypersensitivity to any component of this product.

## WARNINGS

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

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH PRIMAXIN I.V., CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, PRIMAXIN SHOULD BE DISCONTINUED.

**SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE ADMINISTERED AS INDICATED.**

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

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

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

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

## PRECAUTIONS

*General*

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

When recommended doses were exceeded, adult patients with creatinine clearances of ≤20 mL/min/1.73 m$^2$, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended. (See **DOSAGE AND ADMINISTRATION**.)

Patients with creatinine clearances of ≤5 mL/min/1.73 m$^2$ should not receive PRIMAXIN I.V. unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, PRIMAXIN I.V. is recommended only when the benefit outweighs the potential risk of seizures. Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN I.V. reexamined to determine whether it should be decreased or the antibiotic discontinued.

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

*Laboratory Tests*

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

*Drug Interactions*

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

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

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

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

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

Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at dosage levels up to 11 times the usual human dose of the intravenous formulation (on a mg/kg basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups. Similarly, no adverse effects on the fetus or lactation were observed when imipenem-cilastatin sodium was administered to rats late in gestation.

*Pregnancy: Teratogenic Effects*

*Pregnancy Category C.* Teratology studies with cilastatin sodium in rabbits and rats at 6 to 20 times†† the maximum recommended human dose of the intravenous formulation of imipenem-cilastatin sodium (50 mg/kg/day††) respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits and rats given imipenem at doses up to 1 and 18 times†† the maximum recommended daily human dose of the intravenous formulation of imipenem-cilastatin sodium, respectively.

Teratology studies with imipenem-cilastatin sodium at doses up to 11 times†† the usual recommended human dose of the intravenous formulation (30 mg/kg/day††) in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Imipenem-cilastatin sodium, when administered to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher, caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some

††Based on patient weight of 70 kg.

cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 2 times the maximum recommended daily human dose of the intravenous formulation) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity but an increase in embryonic loss relative to control groups.

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

*Nursing Mothers*

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

*Pediatric Use*

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

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

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

In a published dose-ranging study of smaller premature infants (670-1,890 gms) in the first week of life, a dose of 20 mg/kg q12h by 15-30 minutes infusion was associated with mean peak and trough plasma imipenem concentrations of 43 µg/mL and 1.7 µg/mL after multiple doses, respectively. However, moderate accumulation of cilastatin in neonates may occur following multiple doses of PRIMAXIN I.V. The safety of this accumulation is unknown.

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

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

**ADVERSE REACTIONS**

*Adults*

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

*Local Adverse Reactions*

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

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

*Systemic Adverse Reactions*

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

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

*Adverse Laboratory Changes*

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

*Hepatic:* Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH.

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

*Electrolytes:* Decreased serum sodium, increased potassium, increased chloride.

*Renal:* Increased BUN, creatinine.

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

*Pediatric Patients*

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

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

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

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

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

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

| Adverse Experience | No. of Patients (%) |
|---|---|
| *Digestive System* | |
| Diarrhea | 13 (9.6%) |
| Candidiasis | 2 (1.5%) |
| *Skin* | |
| Rash | 2 (1.5%) |
| *Urogenital System* | |
| Oliguria/anuria | 3 (2.2%) |
| *Cardiovascular System* | |
| Tachycardia | 2 (1.5%) |
| *Nervous System* | |
| Convulsions | 8 (5.9%) |

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

| Laboratory Parameter | Abnormality | | No. of Patients With Abnormalities/ No. of Patients With Lab Done (%) |
|---|---|---|---|
| Hemoglobin | Age | <10 gm % | 19/129 (14.7) |
| | 6 mos.-12 yrs. | <11.5 gm % | |
| Hematocrit | Age | <30 vol % | 23/128 (17.8) |
| | 6 mos.-12 yrs. | <34.5 vol % | |
| Neutrophils | | ≤1000/mm³ (absolute) | 4/123 (3.3) |
| Eosinophils | | ≥7% | 15/117 (12.8) |
| Platelet Count | | ≥500 ths/mm³ | 15/119 (13.4) |
| Urine Protein | | ≥1+ | 8/97 (8.2) |
| Serum Creatinine | | ≥1.2 mg/dl | 9/105 (10) |
| BUN | | ≥27 mg/dl | 10/108 (9) |
| AST (SGOT) | | ≥36 IU/L | 14/78 (17.9) |
| ALT (SGPT) | | ≥30 IU/L | 10/93 (10.8) |

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

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

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

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

**OVERDOSAGE**

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

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

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

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

## DOSAGE AND ADMINISTRATION

*Adults*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*Hemodialysis*

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

PRIMAXIN® I.V. (Imipenem and Cilastatin for Injection)

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

| If TOTAL DAILY DOSE from TABLE I is: | 1.0 g/day | | | 1.5 g/day | | | 2.0 g/day | | |
|---|---|---|---|---|---|---|---|---|---|
| and Body Weight (kg) is: | and creatinine clearance (mL/min/1.73 m²) is: | | | and creatinine clearance (mL/min/1.73 m²) is: | | | and creatinine clearance (mL/min/1.73 m²) is: | | |
| | ≥71 | 41-70 | 21-40 | 6-20 | 41-70 | 21-40 | 6-20 | 41-70 | 21-40 | 6-20 |
| | then the reduced dosage regimen (mg) is: | | | | then the reduced dosage regimen (mg) is: | | | then the reduced dosage regimen (mg) is: | | |
| ≥70 | 250 q8h | 250 q8h | 250 q12h | 250 q12h | 500 q8h | 250 q6h | 250 q8h | 250 q12h | 500 q8h | 500 q6h | 250 q8h | 250 q12h |
| 60 | 250 q8h | 125 q6h | 250 q12h | 125 q12h | 250 q8h | 250 q8h | 250 q12h | | 500 q8h | 250 q6h | 250 q8h | 250 q12h |
| 50 | 125 q6h | 125 q6h | 125 q12h | 125 q12h | 250 q8h | 250 q12h | 250 q12h | | 250 q6h | 250 q6h | 250 q8h | 250 q12h |
| 40 | 125 q6h | 125 q8h | 125 q12h | 125 q12h | 250 q8h | 125 q6h | 125 q12h | | 250 q6h | 250 q8h | 250 q12h | 250 q12h |
| 30 | 125 q8h | 125 q8h | 125 q12h | 125 q12h | 125 q8h | 125 q6h | 125 q12h | | 250 q8h | 125 q6h | 125 q8h | 125 q12h |

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

| If TOTAL DAILY DOSE from TABLE I is: | 3.0 g/day | | | | 4.0 g/day | | | |
|---|---|---|---|---|---|---|---|---|
| and Body Weight (kg) is: | and creatinine clearance (mL/min/1.73 m²) is: | | | | and creatinine clearance (mL/min/1.73 m²) is: | | | |
| | ≥71 | 41-70 | 21-40 | 6-20 | 41-70 | 21-40 | 6-20 | |
| | then the reduced dosage regimen (mg) is: | | | | then the reduced dosage regimen (mg) is: | | | |
| ≥70 | 500 q6h | 1000 q8h | 500 q8h | 500 q12h | 750 q6h | 1000 q8h | 500 q6h | 500 q12h |
| 60 | 750 q8h | 500 q6h | 500 q8h | 500 q12h | 1000 q8h | 750 q8h | 500 q8h | 500 q12h |
| 50 | 500 q6h | 500 q8h | 250 q6h | 250 q12h | 750 q8h | 500 q6h | 500 q8h | 500 q12h |
| 40 | 500 q8h | 250 q6h | 250 q8h | 250 q12h | 500 q6h | 500 q8h | 250 q6h | 250 q12h |
| 30 | 250 q6h | 250 q8h | 250 q8h | 250 q12h | 500 q8h | 250 q6h | 250 q8h | 250 q12h |

disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN I.V. is recommended only when the benefit outweighs the potential risk of seizures. (See **PRECAUTIONS**.)

*Pediatric Patients*

See **PRECAUTIONS**, *Pediatric Patients*.

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

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

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

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

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

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

**PREPARATION OF SOLUTION**

*Infusion Bottles*

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

*Vials*

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

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

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

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

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

*ADD-Vantage®††† Vials*

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

*MONOVIAL®‡ Vials*

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

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

**COMPATIBILITY AND STABILITY**

*Before Reconstitution:*

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

†††Registered trademark of Abbott Laboratories, Inc.
‡Registered trademark of Becton Dickinson and Company.

*Reconstituted Solutions:*

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

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

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

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

0.9% Sodium Chloride Injection
5% Dextrose Injection

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

**HOW SUPPLIED**

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

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

No. 3666 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium bicarbonate as a buffer
**NDC** 0006-3666-59 in trays of 25 MONOVIAL® vials.

**REFERENCES**

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

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 62-756/S-024

# CORRESPONDENCE

Henrietta N. Ukwu, M.D.
Director
Regulatory Liaison

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S-043 NDA's

review deferred letter alezzo 3/3/95

MERCK
Research Laboratories

February 14, 1995

NDA NO. _____ REF. NO. S-004
NDA SUPPL FOR Revision
Draft
Labeling

Mr. John D. Harrison, Chief
Office of Generic Drugs, CDER, FDA
HFD-635, Room #MPN2
Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

Supplemental New Drug Application: AADA 62-756
PRIMAXIN® ADD-VANTAGE® Vials

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

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4c(i) of the approved New Drug Application for PRIMAXIN® ADD-VANTAGE® Vials.

The circular has been revised in response to the FDA letter of January 26, 1993, in which you request the standardization of the CLINICAL PHARMACOLOGY, Microbiology subsection for all approved antibiotic product labeling. This draft revision has been submitted to the Division of Anti-Infective Drug Products for NDA 50-587 on August 12, 1994.

The circular has been revised to conform to the text provided under Item #1 of the FDA's letter (page 3 of the letter). The list of organisms under Item #1 has previously been approved (Supplement S-026 for NDA 50-587, approved 11/4/93), and references for each organism are attached. The list of organisms under Item #2 is revised to conform to specifications set forth under Item #2. References for each organism are also attached. The text, as provided under Item #4 (page 5 of the letter), has previously been incorporated in circular #7882119, which was submitted on 5/31/94 as Final Printed Labeling for use in response to the Approval of Supplements S-026, S-033 and S-040 dated 3/7/94, 11/4/93 and 11/19/93, respectively, for NDA 50-587.

RECEIVED
FEB 21 1995
GENERIC DRUGS

AADA 62-756/S-024

Merck Research Laboratories
Attention: Henrietta Ukwu, M.D.
Sumneytown Pike
West Point, PA 19486

MAR 14 1995

Dear Madam:

Reference is made to your supplemental antibiotic drug application dated February 14, 1995, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated antibiotic application for Primaxin® I.V. (Imipenem-Cilastatin Sodium for Injection USP), ADD-Vantage vials 250 mg and 500 mg.

The supplemental application provides for insert labeling revisions in the CLINICAL PHARMACOLOGY, Microbiology subsection and the INDICATIONS AND USAGE section.

We have reviewed the insert labeling submitted and have the following comments:

> We acknowledge that you have submitted this draft revision to the Division of Anti-Infective Drug Products for NDA 50-587 on August 12, 1994. We thereby defer review of this supplement pending actions on your similar supplemental application. When you have received a response for the related supplemental application for NDA 50-587, please notify us and include a copy of the letter. Until that time, no further action will be taken on this supplement.

The material submitted is being retained as a part of your application.

Sincerely,

Jerry Phillips for/

3-14-95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

DS-93 NDA

cc: ANDA 62-756/S-024
Dup\Division File
HFD-613/AVezza/CZimmermann/JPhillips (nocc)
HFD-600/RF
FIELD COPY
njg/3/13/95/62756.S24
~~Letter Out~~
Review - Deferred

Allegra 3/13/95
CZimmermann 3/13/95
JPhillips 3/14/95

Henrietta N. Ukwu, M.D.
Director
Regulatory Liaison

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Merck & Co., Inc.
P.O. Box 4, BLA-30A
West Point PA 19486-0004
Fax 610 397 2962
Tel 610 397 7176
215 652 5000

June 12, 1996

NDA SUPPL AMENDMENT
SLOW AL 5:43

RECEIVED
JUN 14 1996
GENERIC DRUGS

MERCK Research Laboratories

Mr. John D. Harrison, Chief
Office of Generic Drugs, CDER, FDA
HFD-635, Room #MPN2
Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

**AADA 62-756/S-024: PRIMAXIN I.V™. ADD-VANTAGE™ Vials**

Amendment to a Abbreviated Antibiotic Drug Application

Reference is made to the Supplemental Abbreviated Antibiotic Drug Application 62-756/S-024 PRIMAXIN I.V.™ ADD-VANTAGE™ vials dated February 12, 1995 providing for the standardization of the CLINICAL PHARMACOLOGY, Microbiology subsection in response to the FDA letter dated January 26, 1993 to all approved antibiotic NDA holders. This amendment provides for deletion of Legionella organism from the above stated circular as current guidelines in the U.S. for the treatment of Legionella exclude the use of all beta-lactam agents including carbapenems. References are contained in the attached documentation. This revision has been made to page 3 of the draft circular #7882119, AADA 62-756/S-024 which is currently under your review.

Attached for your review are the following:

- Page 3 of draft circular #7882119 with annotations as replacement pages
- Supporting documentation

We consider the filing of this Abbreviated Antibiotic Drug Application to be a confidential matter, and request the Food and Drug Administration not 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 Henrietta N. Ukwu, M.D. (610/397-7176) or, in my absence, to Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

Henrietta Ukwu, M.D.
Director
Regulatory Liaison

Attachments

Certified No. P 914 178 947
Q/YARB/LAC/LTR/PRIM

AADA 62-756/S-024

Merck Research Laboratories
Attention: Henrietta N. Ukwu
Sumneytown Pike
West Point, PA 19486

SEP 5 1996

Dear Madam:

This is in reference to your supplemental antibiotic drug application dated February 14, 1995, submitted pursuant to Section 314.70 of the Regulations, regarding your abbreviated antibiotic application for PRIMAXIN® I.V.(Imipenem-Cilastatin Sodium for Injection) ADD-Vantage® Vials.

Reference is also made to your amendment dated June 12, 1996.

The supplemental application provides for revised package insert labeling reflecting changes in the CLINICAL PHARMACOLOGY (Microbiology) and INDICATIONS AND USAGE sections.

We have no information of similarly revised labeling being approved by the Division of Anti-Infective Drug Products (HFD-520). When similarly revised insert labeling is approved or is otherwise addressed for your NDA(50-587/S-043), please provide us with a copy of the approval letter so that we may respond to this supplement accordingly. Until that time no further action will be taken on this supplement.

Please keep us informed as to the status of your related NDA supplement.

The material submitted is being retained in our files.

Sincerely yours,

Jerry Phillips 9/6/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 62-756/S-024
Dup/Division File
HFD-600 R/F
FIELD COPY
HFD-613/APayne/AVezza (no cc) AVezza 9/4/96 A Payne 8/28/96
njg/8/27/96/x:|new\...Merck\lts&rev\62756s24.rdl
Review Deferred

APPEARS THIS WAY
ON ORIGINAL

Charles L. Hyman, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Tel 610 397 2850
215 652 5000
Fax 610 397 2516

July 28, 1999

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MERCK Research Laboratories

FPL

SUPPL AMENDMENT

SL-024 AL

Douglas L. Sporn, MD, Director
Division of Generic Drug Products
CDER, Bldg. MPN2, HFD-600, Room 286
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

**AADA 62-756/S-024 and S-028: PRIMAXIN™ I.V. in ADD-Vantage™ Vials (Imipenem and Cilastatin for Injection)**

**FINAL PRINTED LABELING**

Dear Dr. Sporn:

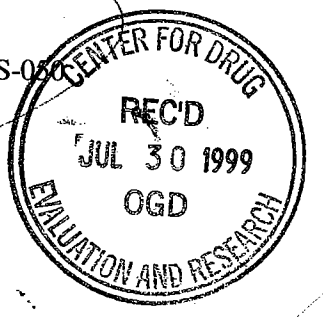
Reference is made to the supplemental Abbreviated Antibiotic New Drug Applications (AADA) 62-756/S-024 and S-028 for PRIMAXIN™ I.V. in ADD-Vantage™ Vials. In addition, reference is made to the parallel supplemental New Drug Applications (sNDA) for NDA 50-587/S-043 and S-047 for PRIMAXIN™ I.V., which were unified into S-050 by the Division of Anti-Infective Drug Products.

Reference is also made to an FDA letter dated September 5, 1996 indicating that no action will be taken on AADA 62-756/S-024 until the approval of NDA 50-587/S-043. Additional reference is made to an FDA approval letter dated March 17, 1998 for AADA 62-756/S-028.

NDA 50-587/S-050 was approved by the Division of Anti-Infective Drug Products on February 4, 1999, and a copy of this approval letter is attached. The Final Printed Label (FPL) for S-050 was submitted to the Anti-Infective Division on July 20, 1999. To ensure that the labels of AADA 62-756 and NDA 50-587 remain consistent, we are now submitting the corresponding FPL to AADA 62-756/S-024 and S-028.

Attached for submission are the following:

1. FDA approval letter dated February 4, 1999 for NDA 50-587/S-050
2. A summary of revisions
3. An annotated circular, illustrating the revisions
4. Printed package circular #7882124 (20 copies)



The circular has been revised under the HEADER, CLINICAL PHARMACOLOGY – Microbiology and REFERENCES sections as illustrated in the annotated circular and the Summary of Revisions in response to FDA letters of June 17, 1997 and June 30, 1997 concerning NDA 50-587.

As explained in the Summary of Revisions, additional editorial changes were made, incorporating text inadvertently omitted in subsequent amendments. Also, there was a deletion of a package no longer marketed due to discontinued sale of this product. Specifically, the 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium bicarbonate as a buffer and trays of 10 infusion bottles were omitted.

The revised labeling will not be used in production. It will be superseded by circular 7882125 which incorporates the approved MONOVIAL text.

As required by Section 306(k)(1) of the Generic Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

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

Please direct questions or need for additional information to Charles L. Hyman, MD (610/397-2850) or, in my absence, Robert E. Silverman, MD, PhD (610/397-2944).

Sincerely,

Charles L. Hyman, MD
Director, Regulatory Affairs

Attachments

FDA approval letter dated February 4, 1999 for NDA 50-587/S-050
A summary of revisions
An annotated circular, illustrating the revisions
Printed package circular #7882124 (20 copies)

Certified No. P 971 230 266

q:graz/amy/templates/62756FPL

ANDA 62-756/S-024

Merck Research Laboratories
Attention: Charles L. Hyman, MD
P.O. BOX 4
Sumneytown Pike, BLA-20
West Point, PA 19486

MAR 16 2000

Dear Sir:

This is in reference to your new drug application dated February 14, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new application for PRIMAXIN® I.V.(Imipenem and Cilastatin for Injection, USP) ADD-Vantage Vials™. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendment dated July 28, 1999.

The supplemental application provides for revised package insert labeling reflecting changes in the TITLE, CLINICAL PHARMACOLOGY (Microbiology), INDICATIONS AND USAGE, AND references sections to be in accordance with the insert labeling for your NDA product (NDA 50-587). In addition, we note that you have further revised your insert labeling reflecting the changes in the Microbiology subsection requested by the Agency in the approval letter for NDA 50-587/S-050 dated February 4, 1999.

Please be advised that your drug product is the subject of a USP monograph. We encourage you to include "USP" in association with the established name of your drug product. We refer you to USP 24 for further guidance.

We have completed the review of this supplemental application and it is approvable. However, before the supplemental application may be approved, it is necessary that you submit sufficient information to show that the proposed labeling is the same as the labeling approved for the reference listed drug as described in 21 CFR 314.127(a)(7). Submit this information as an amendment to this supplemental application.

The material submitted is being retained in our files.

Sincerely yours,

3/15/00

Robert L. West
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 62-756/S-024
Dup/Division File
FIELD COPY
HFD-613/CPark/CHoppes (no cc)
chp/2/22/00/V:\FIRMSAM\MERCK\LTRS&REV\62756s24.ael
Approvable letter

3/10/00

3/15/00

Virginia G. Snyder
Manager
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 7984
215 652 5000
Fax 610 397 2516

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November 17, 2000

MERCK
Research Laboratories

Gary L. Buehler, Acting Director
Division of Generic Drug Products
Bldg. MPN2, HFD-600, Room 286 (CDER)
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

**NDA SUPPL AMENDMENT**
SLO 24/AL

Dear Mr. Buehler:

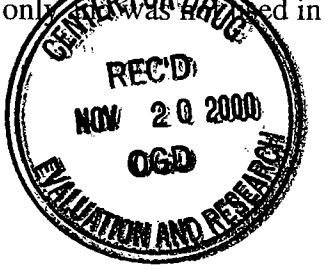
**AADA 62-756/S-024: PRIMAXIN ™ I.V. in ADD-Vantage ™ Vials**
**(Imipenem and Cilastatin for Injection)**

**AMENDMENT TO A PENDING APPLICATION**

Reference is made to the supplemental Abbreviated Antibiotic New Drug Application (AADA) 62-756/S-024 for PRIMAXIN™ I.V. in ADD-Vantage™ Vials, to an amendment to pending application submitted on July 28, 1999 and to the Approvable Letter from the Agency dated March 16, 2000. Additional reference is made to a telephone conversation between Dr. Jacqueline Council (FDA) and Ms. Snyder (MRL, a division of Merck & Co., Inc.) on March 31, 2000 concerning the supportive information that would be required for action to be taken on this supplement.

In the approvable letter of March 16, 2000 and in the conversation with Dr. Council, the Agency requested sufficient information to show that the proposed labeling for the AADA is the same as the labeling approved for the reference listed drug, PRIMAXIN™ I.V. (NDA 50-587). Both products are manufactured by Merck and Co., Inc. and share a single package circular entitled PRIMAXIN™ I.V.

Reference is also made to NDA 50-587/S-050 for PRIMAXIN™ I.V. Supplement S-050, which was approved by the Anti-Infective Division on February 4, 1999, provided for changes in the circular under the **MICROBIOLOGY** section. In order to insure that the labels for NDA 50-587 and AADA 62-756 remained consistent, identical final printed labeling (printed package circular #7882124) was submitted to both applications on July 20, 1999 and July 28, 1999, respectively. It should be noted that circular #7882124, which was printed for FDA use only, was revised in



production, was superseded by circular #7882125. Circular #7882125, which incorporated the approved changes in the MICROBIOLOGY section and the text related to the MONOVIAL configuration, was approved by the Anti-Infective Division on August 28, 2000. A copy of this approval letter is attached.

In accordance with the guidance, *Revising ANDA Labeling After Revision of RLD Labeling*, a side by side comparison of the labeling for NDA 50-587/S-050 and AADA 62-756 is provided (Attachment 1). In addition, we are providing the following information:

1. FDA approval letter dated February 4, 1999 for NDA 50-587/S-050
2. FDA approval letter dated August 28, 2000 for NDA 50-587/S-052

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

Please direct questions or need for additional information to Virginia G. Snyder (610/397-7984) or, in my absence, Dennis M. Erb, Ph.D. (610/397-7597).

Sincerely,

Virginia G. Snyder

Virginia G. Snyder
Manager, Regulatory Affairs

Attachments

Certified No. 7106 4575 1292 0797 6358

q:snyder/primaxin/62756s024

ANDA 62-756/S-024

MAY 21 2001

Merck Research Laboratories
Attention: Virgina G. Snyder
P.O. Box 4, BLA-20
Sumneytown PikeWest
Point, PA 19486

Dear Madam:

This is in reference to your new drug application dated February 14, 1995, submitted pursuant to 21 CFR 314.70 regarding your abbreviated new application for PRIMAXIN® I.V. (Imipenem and Cilastatin for Injection, USP) ADD-Vantage™ Vials. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendment dated November 17, 2000.

The supplemental application provides for revised package insert labeling reflecting changes in the TITLE, CLINICAL PHARMACOLOGY (Microbiology), INDICATIONS AND USAGE, and REFERENCES sections to be in accordance with the insert labeling for your NDA product (NDA 50-587). In addition, we note that you have further revised your insert labeling reflecting the changes in the Microbiology subsection requested by the Agency in the approval letter for NDA 50-587/S-050 dated February 4, 1999.

Please be advised that your drug product is the subject of a USP monograph. We encourage you to include "USP" in association with the established name of your drug product. We refer you to USP 24 for further guidance.

We have completed the review of this supplemental application and it is approvable. However, before the supplemental application may be approved, it is necessary that you submit twelve copies of final printed insert labeling as an amendment to this supplemental application.

We acknowledge that you submitted insert labeling #7882124 for FDA use only and not for production and that it is superseded by insert labeling #7882125 submitted to S-031, therefore if you prefer, you may request withdrawal of this supplement rather than submitting an amendment.

The material submitted is being retained in our files.

Sincerely yours,

5/16/01

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 62-756/S-024
Dup/Division File
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Approvable letter

5/16/01

Virginia G. Snyder
Manager
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 484 344 7984
215 652 5000
Fax 484 344 2516

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July 11, 2001

MERCK
Research Laboratories

Gary L. Buehler, Acting Director
Division of Generic Drug Products
Bldg. MPN2, HFD-600, Room 286 (CDER)
Food and Drug Administration
Metro Park North 2
7500 Standish Place
Rockville, Maryland 20855

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 17 2001
OGD

NDA SUPP AMEND
SL024 AL
SL031 AL

Dear Mr. Buehler:

**AADA 62-756/S-024 & S-031: PRIMAXIN™ I.V. in ADD-Vantage™ Vials**
**(Imipenem and Cilastatin for Injection)**

**AMENDMENT TO A PENDING APPLICATION**

Reference is made to the supplemental Abbreviated Antibiotic New Drug Applications (AADA) S-024 and S-031 for PRIMAXIN™ I.V. in ADD-Vantage™ Vials submitted on February 14, 1995 and August 27, 1999, respectively. Further reference is made to the Approvable Letters from the Agency dated May 21, 2001 for both S-024 and S-031 in which final printed labeling was requested.

The supplemental application S-024 provides for revised packet insert labeling reflecting changes in the Title, CLINICAL PHARMACOLOGY (Microbiology), INDICATIONS AND USAGE and REFERENCES in accordance with the insert labeling for our NDA product (NDA 50-587: PRIMAXIN™ I.V). As noted in the Approvable Letter of May 21, 2001, insert labeling #7882124 was submitted for FDA use only and was not for production and therefore it is superseded by insert labeling #7882125. All revisions submitted for S-024 have been incorporated into insert labeling #7882125.

The supplemental application S-031 provides for revised packet insert labeling reflecting changes in the DESCRIPTION, PREPARATION OF SOLUTION, COMPATIBILITY AND STABILITY and HOW SUPPLIED reflecting the addition of a new MONOVIAL image for PRIMAXIN™ I.V. All revisions submitted for S-031 have been incorporated into insert labeling #7882125.

As requested in the Approvable Letters for S-024 and S-031, final printed labeling (circular #7882125) is provided with this submission.

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

Please direct questions or need for additional information to Virginia G. Snyder (484-344-7984) or, in my absence, Dennis M. Erb, Ph.D. (484-344-7597).

Sincerely,

Virginia G. Snyder
Manager, Regulatory Affairs

Attachments

Certified No. 7106 4575 1292 0798 5381

q:graz/chris/primaxin/62756s24031fpl