CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 62-756 / S-028

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

***Sponsor*:** Merck Research Laboratories

***Approval Date*:** March 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 62-756/S-028

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

MAR 17 1998

Dear Madam:

This is in reference to your supplemental new drug application dated January 14, 1997, submitted pursuant to 21 CFR 314.70(c) (Special Supplement - Changes Being Effected) regarding your abbreviated new drug application for PRIMAXIN® I.V.(Imipenem-Cilastatin Sodium for Injection) ADD-Vantage® Vials.

Reference is also made to your correspondence dated September 2, 1997.

The supplemental application provides for revised package insert labeling reflecting additions to the Gastrointestinal and Body as a Whole subsections of the ADVERSE REACTIONS (Systemic Adverse Reactions) section, as well as editorial changes in the Header and INDICATIONS AND USAGE sections.

We have completed the review of this supplemental application and it is approved. However, at the time of next printing make the following revisions:

1. Make the revisions requested in the approval letter for NDA 50-587/S-047 approved June 30, 1997.

2. Replace the "CAUTION: Federal law ..." statement with the symbol "Rx only" or "℞ only" on your labels and labeling. We refer you to the Guidance for Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, **http://www.fda.gov/cder/guidance/index.htm** for guidance.

Submit revised insert labeling as a supplement to this approved application. We refer you to 21 CFR 314.70 for guidance.

Revised container labels and carton labeling to be in accord with the FDA Modernization Act of 1997 may be submitted in an annual

report provided the changes are described in full. We refer you to 21 CFR 314.70(d) for further guidance.

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

The material submitted is being retained in our files.

Sincerely yours,

3/16/98

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

cc: ANDA 62-756/S-028
Division File
HFD-92/with labeling
HFD-600/Reading File
HFD-610/JPhillips
Field Copy
See x:\new...62756s28.apl
APPROVAL LETTER - SINGLE SUPPLEMENT

Endorsements:
HFD-613/JWhite
HFD-613/CHoppes

3/16/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-028

LABELING

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

PRIMAXIN® I.V.

(IMIPENEM AND CILASTATIN FOR INJECTION)

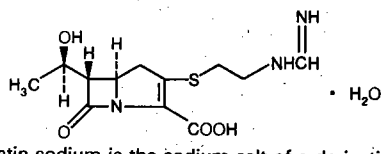
(Formerly called IMIPENEM-CILASTATIN SODIUM FOR INJECTION)

For Intravenous Injection Only

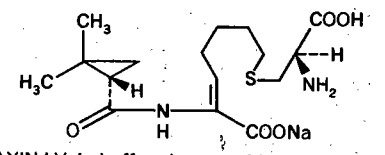
DESCRIPTION

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

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



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



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

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 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 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:

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

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

Microbiology

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

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

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem is active against most strains of the following microorganisms *in vitro* and in clinical infections treated with the intravenous formulation of imipenem-cilastatin sodium. (See **INDICATIONS AND USAGE.**)

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 streptococcus)
- *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 (MIC's) 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:
- *Listeria monocytogenes*
- *Nocardia* spp.
- Group C streptococcus
- Group G streptococcus
- Viridans group streptococci

Gram-negative aerobes:
- *Achromobacter* spp.
- *Aeromonas hydrophila*
- *Alcaligenes* spp.
- *Bordetella bronchiseptica*
- *Campylobacter* spp.
- *Hafnia alvei*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Moraxella* spp.
- *Neisseria gonorrhoeae* including penicillinase-producing strains
- *Pasteurella multocida*
- *Plesiomonas shigelloides*
- *Proteus mirabilis*
- *Providencia stuartii*
- *Salmonella* spp.
- *Serratia proteamaculans* (formerly *S. liquefaciens*)
- *Shigella* spp.
- *Yersinia* spp., including *Y. enterocolitica* and *Y. pseudotuberculosis*

Gram-positive anaerobes:
- *Actinomyces* spp.
- *Clostridium perfringens*
- *Propionibacterium acnes*

Gram-negative anaerobes:
- *Bacteroides* spp., including *B. bivius, B. disiens, B. distasonis, B. intermedius* (formerly *B. melaninogenicus intermedius*), *B. ovatus, B. thetaiotaomicron,* and *B. vulgatus*
- *Porphyromonas asaccharolytica* (formerly *B. asaccharolyticus*)
- *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.)

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[1] 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)

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. 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

Dilution Techniques:

Quantitative methods that are used to determine MIC's provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such procedure uses a standardized dilution method[2] (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)

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

As with standard diffusion techniques, dilution methods 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

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]

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

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

Broth Microdilution Testing:

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

INDICATIONS AND USAGE

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

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

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

(3) **Intra-abdominal infections.** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains)*, *Staphylococcus epidermidis, Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii**, *Proteus* species (indole positive and indole negative), *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 streptococcus), *Enterobacter* species*, *Escherichia coli, Gardnerella vaginalis, Klebsiella* species*, *Proteus* species (indole positive and indole negative), *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), Group A beta-hemolytic streptococcus (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

PRIMAXIN 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 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.

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

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

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

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

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

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

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

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

PRECAUTIONS

General

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

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

Patients with creatinine clearances of ≤5 mL/min/1.73 m^2 should not receive PRIMAXIN I.V. unless hemodialysis is instituted within 48 hours.

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

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

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

Laboratory Tests

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

Drug Interactions

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Adverse Laboratory Changes

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

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

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

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

Renal: Increased BUN, creatinine.

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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. 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 q6h (TOTAL DAILY DOSE = 2.0g) or 1 g q8h (TOTAL DAILY DOSE = 3.0g)
Severe, life threatening only	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	1 g q8h (TOTAL DAILY DOSE = 3.0g) or 1 g q6h (TOTAL DAILY DOSE = 4.0g)
Uncomplicated urinary tract infection	250 mg q6h (TOTAL DAILY DOSE = 1.0g)	250 mg q6h (TOTAL DAILY DOSE = 1.0g)
Complicated urinary tract infection	500 mg q6h (TOTAL DAILY DOSE = 2.0g)	500 mg q6h (TOTAL DAILY DOSE = 2.0g)

††Based on patient weight of 70 kg.

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

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

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

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

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

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

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

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

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

Hemodialysis

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

PREPARATION OF SOLUTION

Infusion Bottles

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

Vials

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

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

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

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

ADD-Vantage®††† Vials

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

†††Registered trademark of Abbott Laboratories, Inc.

COMPATIBILITY AND STABILITY

Before Reconstitution:

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

Reconstituted Solutions:

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

PRIMAXIN I.V., as supplied in 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). 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. 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 4 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).

REFERENCES

1. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24 NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically-Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, 1993.
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.

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued August 1996
Printed in USA

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	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	250 q6h	250 q8h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q8h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q6h	125 q8h	125 q12h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h

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

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	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	1000 q8h	500 q6h	500 q8h	500 q12h	1000 q6h	750 q8h	500 q6h	500 q12h
60	750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
50	500 q6h	500 q8h	250 q6h	250 q12h	750 q8h	500 q6h	500 q8h	500 q12h
40	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
30	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-028

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/24/97

FROM: John Grace, Consumer Safety Officer

SUBJECT: Special Supplement - Changes Placed into Effect

TO: Document Room

Please make the following entry in the MIS concerning the status of this Special Supplement - Changes Placed into Effect.

ANDA(s)	SUPPLEMENTS(s)	APPL	GRANTED	DENIED
62756	SL 028			

This form is to accompany the action package/jacket.

Thank you,

John Grace

Signature of CSO and Date

cc:

ANDA
DIVISION FILE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-028

CORRESPONDENCE

Henrietta N. Ukwu
Senior Director
Worldwide Regulatory Liaison
Biologics/Vaccines

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2962
Tel 610 397 7176

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January 14, 1997

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

NDA NO. _____ REF. 62028
NDA SUPPL FOR Label rev
S028K1

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

AADA 62-756: PRIMAXIN® I.V. in ADD-Vantage® Vials
(Imipenem-Cilastatin Sodium for Injection)

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 4cii of the approved New Drug Application for PRIMAXIN® I.V. in ADD-Vantage® Vials.

The package circular has been revised under HEADER, based on USP injectable nomenclature requirements, as requested by the FDA in a letter dated October 2, 1995, and under INDICATIONS AND USAGE, and ADVERSE REACTIONS.

Editorial

Attached for submission are 15 mounted copies of the printed package circular No. 7882122, a summary of revisions and a paste-up of the package circular annotated for revisions.

The changes will become effective on or about February 1, 1997 and will apply to all packages of PRIMAXIN® I.V. in ADD-Vantage® Vials distributed from the company's manufacturing facilities at West Point, PA.

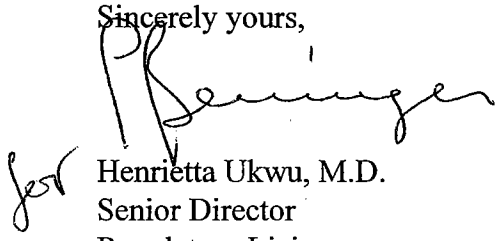
As required by Section 306(k)(1) of the Generic Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

RECEIVED
JAN 17 1997
GENERIC DRUGS

We consider the filing of this Supplemental New 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 David W. Blois, Ph.D. (610/397-2304).

Sincerely yours,



for Henrietta Ukwu, M.D.
Senior Director
Regulatory Liaison

Attachments

Certified No. P 914 177 430
Q/YAR/SAR/LTR/62756SS

AADA 62-756/S-028

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

APR 30 1997

Dear Madam:

This is in reference to your supplemental antibiotic drug application dated January 14, 1997, submitted pursuant to Section 314.70(c) (Special Supplement - Changes Being Effected) of the Regulations, regarding your abbreviated antibiotic application for PRIMAXIN® I.V.(Imipenem-Cilastatin Sodium for Injection) ADD-Vantage® Vials.

The supplemental application provides for revised package insert labeling reflecting additions to the Gastrointestinal and Body as a Whole subsections of the ADVERSE REACTIONS (Systemic Adverse Reactions) section, as well as editorial changes in the Header 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-047), 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,

John Grace for 4-30-97

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

APPEARS THIS WAY
ON ORIGINAL

cc: AADA 62-756/S-028
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Review Deferred

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

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

September 2, 1997

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

MERCK Research Laboratories

NEW CORRESP
(5028)

AADA 62-756/S-028: PRIMAXIN® in ADD-Vantage® Vials

GENERAL CORRESPONDENCE

Dear Mr. Harrison:

Reference is made to the above cited supplemental antibiotic drug application submitted January 14, 1997, providing for revisions to the label. Reference is also made to the FDA letter dated April 30, 1997, stating that you had not received information of similarly revised labeling being approved by the Division of Anti-Infective Drug Products (HFD-520) for NDA 50-587/S-047, and requesting that when the similarly revised labeling is addressed to please provide the Office of Generic Drugs with a copy of the action letter.

Attached, as requested, is a copy of the approval letter from the Division of Anti-Infective Drug Products (HFD-520) for NDA 50-587/S-047.

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

Sincerely yours,

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

Attachments
Q/YAR/SAR/LTR/62756028R

Certified No. P 963 213 465

RECEIVED
SEP 5 - 1997
GENERIC DRUGS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-587/S-047

Merck & Co., Inc.
Attention: Charles Hyman, M.D.
Director, Regulatory Affairs
P.O. Box 4, BLA-20
West Point, PA 19486

JUN 30 1997

Dear Dr. Hyman:

We acknowledge your supplemental new drug application dated January 14, 1997, received January 16, 1997, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Primaxin® I.V. (imipenem and cilastatin for injection).

We also acknowledge receipt of your amendment dated April 3, 1997.

This supplemental application provides for revisions to the **HEADER, INDICATIONS AND USAGE,** and **ADVERSE REACTIONS** sections of the labeling.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated January 14, 1997. Accordingly, this supplemental application is approved effective on the date of this letter.

However, it is requested that at the next printing of the labeling the following revisions be made:

CLINICAL PHARMACOLOGY section, *Microbiology* subsection

This subsection should be updated according to the January 26, 1993 letter from the DAIDP to all NDA holders.

PRECAUTIONS section, *Pediatric Use* subsection

"Safety and effectiveness" in infants and children below..." should be changed to "Safety and effectiveness in pediatric patients below...". This is to comply with the Pediatric Final Rule 21 CFR 201.57(f)(9).

REFERENCES section

References 1 and 2 should be updated according to 1997 approved standard documents.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 50-587/S-047. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug become available, revision of the labeling may be required.

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Kim Roche, Project Manager, at (301) 827-2125.

Sincerely yours,

Gary K Chikami

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research