CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-630 / S-009

Trade Name: **Primaxin**

Generic Name: **Cilastatin sodium; imipenem**

Sponsor: **Merck and Co.**

Approval Date: **October 2, 1996**

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APPLICATION NUMBER:

50-630 / S-009

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APPLICATION NUMBER:

50-630 / S-009

APPROVAL LETTER

HFD 520
Division file

NDA 50-630/S-009

OCT 2 1996

MERCK & Co., Inc.
Attention: Henrietta N. Ukwu, M.D.
Director, Regulatory Liaison
P.O. Box 4, BLA-30A
West Point, PA 19486-0004

Dear Dr. Ukwu:

We acknowledge your March 11, 1993 supplemental new drug application received on March 18, 1993, under section 507 of the Federal Food, Drug, and Cosmetic Act for PRIMAXIN® I.M. (Imipenem-Cilastatin Sodium for Suspension).

The original supplemental application provides for revisions to the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections of the labeling.

We acknowledge receipt of your amendment dated June 10, 1994, which provides for revisions in the following sections: **HEADING, DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **REFERENCES**.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on June 10, 1994. Accordingly, the supplemental application is approved effective on the date of this letter. However, at the next printing of the labeling, the following revisions should be made:

DESCRIPTION

The word "formimidoylamino" in the chemical name of imipenem, should be revised to read "Formimidoylamino", and the word "sodium" in the chemical name of cilastatin sodium, should be revised to read "Sodium".

CLINICAL PHARMACOLOGY

1. In the sixth paragraph, revise "...is questionable (see OVERDOSAGE)." to read "...is questionable. (See **OVERDOSAGE.**)"

2. In the third paragraph of the *Microbiology* subsection, revise "...sodium (see INDICATIONS AND USAGE)." to read "...sodium. (See **INDICATIONS AND USAGE.**)"

3. In the first paragraph of the *Susceptibility Tests* subsection, revise "(See CLINICAL PHARMACOLOGY section for...)" to read "(See **CLINICAL PHARMACOLOGY** section for....)"

PRECAUTIONS

In the *General* subsection, third paragraph, revise "...vessel (see DOSAGE AND ADMINISTRATION)." to read "...vessel. (See **DOSAGE AND ADMINISTRATION.**)"

ADVERSE REACTIONS

These comments are specific to the *Potential ADVERSE EFFECTS* subsection:

1. The heading "*Potential ADVERSE EFFECTS*:" should be revised to read "*Potential ADVERSE REACTIONS*:".

2. In the first paragraph, the word "effects" should be revised to read "reactions".

3. In the *Systemic Adverse Reactions* subsection, revise "(see PRECAUTIONS)" to read "(see **PRECAUTIONS**)" and revise "..., see WARNINGS),..." to read "..., see **WARNINGS**),...".

DOSAGE AND ADMINISTRATION

In the **DOSAGE GUIDELINES** table, revise "†See INDICATIONS AND USAGE section." to read "†See **INDICATIONS AND USAGE** section."

Please submit one market package of the drug when it is available.

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 Maureen P. Dillon-Parker, Project Manager at (301) 827-2125.

Sincerely yours,

10.1.96

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Original NDA 50-630/S-009
HF-2/Medwatch (with labeling)
HFD-2/Lumpkin
HFD-80 (with labeling)
HFD-104/D.Feigal
HFD-520/Div. files
HFD-520/PMS/M.Dillon-Parker
HFD-520/TL/Roberts/rd 9/20/96 pa 9/25/96
HFD-520/MO/Thompson
HFD-520/Pharm/Buko
HFD-520/Micro/Altaie
HFD-830/Chem/Dunn
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling)
DISTRICT OFFICE
HFD-222/ONDC/DivDir

drafted: mdp/September 12, 1996/N50630.LS9
r/d Initials:mpd
final:September 24, 1996

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630 / S-009

LABELING

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

STERILE

PRIMAXIN® I.M.

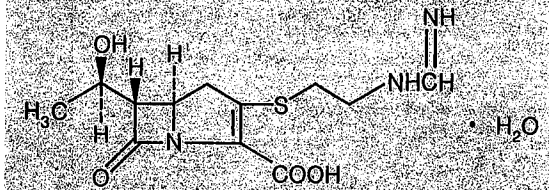
(IMIPENEM-CILASTATIN SODIUM FOR SUSPENSION)

For Intramuscular Injection Only

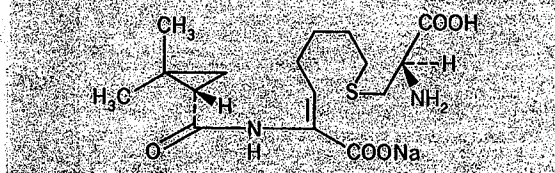
DESCRIPTION

Sterile PRIMAXIN† I.M. (Imipenem-Cilastatin Sodium for Suspension) is a formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I). PRIMAXIN I.M. is a potent broad-spectrum antibacterial agent for intramuscular administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (5*R*,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 380.44. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$, and its structural formula is:



PRIMAXIN I.M. 500 contains 32 mg of sodium (1.4 mEq) and PRIMAXIN I.M. 750 contains 48 mg of sodium (2.1 mEq). Prepared PRIMAXIN I.M. suspensions are white to light tan in color. Variations of color within this range do not affect the potency of the product.

CLINICAL PHARMACOLOGY

Following intramuscular administrations of 500 or 750 mg doses of imipenem-cilastatin sodium in a 1:1 ratio with 1% lidocaine, peak plasma levels of imipenem antimicrobial activity occur within 2 hours and average 10 and 12 µg/mL, respectively. For cilastatin, peak plasma levels average 24 and 33 µg/mL, respectively, and occur within 1 hour. When compared to intravenous administration of imipenem-cilastatin sodium, imipenem is approximately 75% bioavailable following intramuscular administration while cilastatin is approximately 95% bioavailable. The absorption of imipenem from the IM injection site continues for 6 to 8 hours while that for cilastatin is essentially complete within 4 hours. This prolonged absorption of imipenem following the administration of the intramuscular formulation of imipenem-cilastatin sodium results in an effective plasma half-life of imipenem of approximately 2 to 3 hours and plasma levels of the antibiotic which remain above 2 µg/mL for at least 6 or 8 hours, following a 500 mg or 750 mg dose, respectively. This plasma profile for imipenem permits IM administration of the intramuscular formulation of imipenem-cilastatin sodium every 12 hours with no accumulation of cilastatin and only slight accumulation of imipenem.

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

PLASMA CONCENTRATIONS OF IMIPENEM
(µg/mL)

	500 MG		750 MG	
TIME	I.V.	I.M.	I.V.	I.M.
25 min	45.1	6.0	57.0	6.7
1 hr	21.6	9.4	28.1	10.0
2 hr	10.0	9.9	12.0	11.4
4 hr	2.6	5.6	3.4	7.3
6 hr	0.6	2.5	1.1	3.8
12 hr	ND†	0.5	ND†	0.8

†ND: Not Detectable (<0.3 µg/mL)

Imipenem urine levels remain above 10 µg/mL for the 12 hour dosing interval following the administration of 500 mg or 750 mg doses of the intramuscular formulation of imipenem-cilastatin sodium. Total urinary excretion of imipenem averages 50% while that for cilastatin averages 75% following either dose of the intramuscular formulation of imipenem-cilastatin sodium.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly increased levels of imipenem are achieved in the urine. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%.

In a clinical study in which a 500 mg dose of the intramuscular formulation of imipenem-cilastatin sodium was administered to healthy subjects, the average peak level of imipenem in interstitial fluid (skin blister fluid) was approximately 5.0 µg/mL within 3.5 hours after administration.

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

Microbiology

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

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

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem is active against most strains of the following microorganisms *in vitro* and in clinical infections treated with the intramuscular 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
(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans group streptococci

Gram-negative aerobes:
Acinetobacter spp., including *A. calcoaceticus*
Citrobacter spp.
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Pseudomonas aeruginosa
(NOTE: Imipenem is inactive *in vitro* against *Xanthomonas (Pseudomonas) maltophilia* and *P. cepacia*.)

Gram-positive anaerobes:
Peptostreptococcus spp.

Gram-negative anaerobes:
Bacteroides spp., including
Bacteroides distasonis
Bacteroides intermedius
(formerly *B. melaninogenicus intermedius*)
Bacteroides fragilis
Bacteroides thetaiotaomicron
Fusobacterium spp.

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

Imipenem exhibits *in vitro* minimal 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.

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PRIMAXIN® I.M.
(Imipenem-Cilastatin Sodium for Suspension)

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic:* increased LDH; *Hemic:* positive Coombs test, decreased neutrophils, agranulocytosis, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes:* decreased serum sodium, increased potassium, increased chloride; *Urinalysis:* presence of urine protein, urine bilirubin, and urine urobilinogen.

Lidocaine HCl: Refer to the package circular for lidocaine HCl.

OVERDOSAGE

The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was 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 1593 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.M., treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

DOSAGE AND ADMINISTRATION

PRIMAXIN I.M. is for intramuscular use only.

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

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

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

DOSAGE GUIDELINES

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

†See INDICATIONS AND USAGE section.

Total daily IM dosages greater than 1500 mg per day are not recommended.

The dosage for any particular patient should be based on the location of and severity of the infection, the susceptibility of the infecting pathogen(s), and renal function.

The duration of therapy depends upon the type and severity of the infection. Generally, PRIMAXIN I.M. should be continued for at least two days after the signs and symptoms of infection have resolved. Safety and efficacy of treatment beyond fourteen days have not been established.

PRIMAXIN® I.M.
(Imipenem-Cilastatin Sodium for Suspension)

PRIMAXIN I.M. should be administered by deep intramuscular injection into a large muscle mass (such as the gluteal muscles or lateral part of the thigh) with a 21 gauge 2" needle. Aspiration is necessary to avoid inadvertent injection into a blood vessel.

ADULTS WITH IMPAIRED RENAL FUNCTION

The safety and efficacy of PRIMAXIN I.M. have not been studied in patients with creatinine clearance of less than 20 mL/min/1.73m². Serum creatinine alone may not be a sufficiently accurate measure of renal function. Creatinine clearance (T_{cr}) may be estimated from the following equation:

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

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

PREPARATION FOR ADMINISTRATION

PRIMAXIN I.M. should be prepared for use with 1.0% lidocaine HCl solution††† (without epinephrine). PRIMAXIN I.M. 500 should be prepared with 2 mL and PRIMAXIN I.M. 750 with 3 mL of lidocaine HCl. Agitate to form a suspension then withdraw and inject the entire contents of vial intramuscularly. The suspension of PRIMAXIN I.M. in lidocaine HCl should be used within one hour after preparation. **Note: The IM formulation is not for IV use.**

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 30°C (86°F).

Suspensions for IM Administration

Suspensions of PRIMAXIN I.M. are white to light tan in color. Variations in color within this range do not affect the potency of the product.

The suspension of PRIMAXIN I.M. in lidocaine HCl should be used within one hour after preparation.

PRIMAXIN I.M. should not be mixed with or physically added to other antibiotics. However, PRIMAXIN I.M. may be administered concomitantly but at separate sites with other antibiotics, such as aminoglycosides.

HOW SUPPLIED

PRIMAXIN I.M. is supplied as a sterile powder mixture in vials for IM administration as follows:

No. 3582 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent
NDC 0006-3582-75 in trays of 10 vials
(6505-01-337-3131 500 mg, 10's)

No. 3583 — 750 mg imipenem equivalent and 750 mg cilastatin equivalent
NDC 0006-3583-76 in trays of 10 vials
(6505-01-337-3130 750 mg, 10'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, 1993.
2. National Committee for Clinical Laboratory Standards. Methods ... tion Antimicrobial Susceptibility Tests for Bacteria that Grow Aer... Third Edition; Approved Standard NCCLS Document M7-A3, Vol. ... NCCLS, Villanova, PA, 1993.
3. National Committee for Clinical Laboratory Standards. Method... microbial Susceptibility Testing of Anaerobic Bacteria - Third E... proved Standard NCCLS Document M11-A3, Vol. 13, No. ... Villanova, PA, 1993.

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

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

Issued January 1994

Printed in US

WITH BETA-LACTAMS, THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM BEFORE INITIATING THERAPY WITH PRIMAXIN® I.M. CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, PRIMAXIN® SHOULD BE DISCONTINUED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including 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.

Lidocaine HCl - Refer to the package circular for lidocaine HCl.

PRECAUTIONS

General

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN I.V. (Imipenem-Cilastatin Sodium for Injection). These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) who also have compromised renal function. However, there were reports in which there was no recognized or documented underlying CNS disorder. These adverse CNS effects have not been seen with PRIMAXIN I.M.; however, should they occur during treatment, PRIMAXIN I.M. should be discontinued. Anticonvulsant therapy should be continued in patients with a known seizure disorder.

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

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

Laboratory Tests

While PRIMAXIN I.M. 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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin. Genetic toxicity studies were performed in a 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[1] the maximum daily recommended human dose of the intramuscular 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 10 and 33 times[1] the maximum recommended daily human dose of the intramuscular formulation (30 mg/kg/day) of PRIMAXIN, respectively, showed no evidence of adverse effects on the fetus. No evidence of teratogenicity was observed in rabbits and rats given imipenem at doses up to 2 and 30 times[1] the maximum recommended daily human dose of the intramuscular formulation of PRIMAXIN, respectively.

Teratology studies with imipenem-cilastatin sodium at doses up to 11 times[1] the maximum recommended human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

[1]Based on patient weight of 50 kg.

PRIMAXIN® I.M.
(Imipenem-Cilastatin Sodium for Suspension)

Imipenem-cilastatin sodium, when administered to pregnant rabbits at dosages above the usual human dose of the intramuscular formulation (1000-1500 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 100 mg/kg/day or approximately 3 times[1] the maximum daily recommended human dose of the intramuscular 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 the control groups.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN I.M. 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 or lidocaine HCl (diluent) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN I.M. is administered to a nursing woman.

Pediatric Use

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

ADVERSE REACTIONS

PRIMAXIN I.M.

In 686 patients in multiple dose clinical trials of PRIMAXIN I.M., the following adverse reactions were reported:

Local Adverse Reactions

The most frequent adverse local clinical reaction that was reported as possibly, probably or definitely related to therapy with PRIMAXIN I.M. was pain at the injection site (1.2%).

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN I.M. were nausea (0.6%), diarrhea (0.6%), vomiting (0.3%) and rash (0.4%).

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hemic: decreased hemoglobin and hematocrit, eosinophilia, increased and decreased WBC, increased and decreased platelets, decreased erythrocytes, and increased prothrombin time.

Hepatic: increased AST, ALT, alkaline phosphatase, and bilirubin.

Renal: increased BUN and creatinine.

Urinalysis: presence of red blood cells, white blood cells, casts, and bacteria in the urine.

Potential ADVERSE EFFECTS:

In addition, a variety of adverse effects, not observed in clinical trials with PRIMAXIN I.M., have been reported with intravenous administration of PRIMAXIN I.V. (Imipenem-Cilastatin Sodium for Injection). Those listed below are to serve as alerting information to physicians.

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably or definitely related to PRIMAXIN I.V. (Imipenem-Cilastatin Sodium for Injection) were fever, hypotension, seizures (see PRECAUTIONS), dizziness, pruritus, urticaria, and somnolence.

Additional adverse systemic clinical reactions reported possibly, probably or definitely drug related or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal:* pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment; see WARNINGS), hemorrhagic colitis, hepatitis, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of the teeth, heartburn, pharyngeal pain, increased salivation; *Hematologic:* thrombocytopenia, neutropenia, leukopenia; *CNS:* encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses:* hearing loss, tinnitus, taste perversion; *Respiratory:* chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular:* palpitations, tachycardia; *Renal:* acute renal failure, oliguria/anuria, polyuria, urine discoloration; *Skin:* toxic epidermal necrolysis, erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole:* polyarthralgia, asthenia/weakness.

Gram-positive aerobes:
Listeria monocytogenes
Nocardia spp.
Staphylococcus epidermidis including penicillinase-producing strains
(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)
Streptococcus agalactiae (Group B streptococcus)
Group C streptococcus
Group G streptococcus
Gram-negative aerobes:
Achromobacter spp.
Aeromonas hydrophila
Alcaligenes spp.
Bordetella bronchiseptica
Campylobacter spp.
Enterobacter spp.
Gardnerella vaginalis
Haemophilus parainfluenzae
Hafnia alvei
Klebsiella spp., including *K. oxytoca*
Moraxella spp.
Morganella morganii
Neisseria gonorrhoeae including penicillinase-producing strains
Pasteurella multocida
Plesiomonas shigelloides
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella spp.
Serratia spp., including *S. marcescens* and *S. proteamaculans* (formerly *S. liquefaciens*)
Shigella spp.
Yersinia spp., including *Y. enterocolitica* and *Y. pseudotuberculosis*
Gram-positive anaerobes:
Actinomyces spp.
Clostridium spp., including *C. perfringens*
Eubacterium spp.
Peptococcus niger
Propionibacterium acnes
Gram-negative anaerobes:
Bacteroides bivius
Bacteroides disiens
Bacteroides ovatus
Bacteroides vulgatus
Porphyromonas asaccharolytica (formerly *Bacteroides 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

PRIMAXIN® I.M.
(Imipenem-Cilastatin Sodium for Suspension)

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, 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 techniques.[2]

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

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

(1) **Lower respiratory tract infections**, including pneumonia and bronchitis as an exacerbation of COPD, caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

(2) **Intra-abdominal infections**, including acute gangrenous or perforated appendicitis and appendicitis with peritonitis, caused by *Enterococcus faecalis**; Viridans group streptococci*; *Escherichia coli*; *Klebsiella pneumoniae**; *Pseudomonas aeruginosa**; *Bacteroides* species including *B. fragilis*; *B. distasonis**; *B. intermedius** and *B. thetaiotaomicron**; *Fusobacterium* species and *Peptostreptococcus** species.

(3) **Skin and skin structure infections**, including abscesses, cellulitis, infected skin ulcers and wound infections caused by *Staphylococcus aureus*, including penicillinase-producing strains; *Streptococcus pyogenes**; *Enterococcus faecalis*; *Acinetobacter* species* including *A. calcoaceticus**; *Citrobacter* species*; *Escherichia coli*; *Enterobacter cloacae*; *Klebsiella pneumoniae*; *Pseudomonas aeruginosa** and *Bacteroides* species* including *B. fragilis*.

(4) **Gynecologic infections**, including postpartum endomyometritis caused by *Enterococcus faecalis**; *Escherichia coli*; *Klebsiella pneumoniae*; *Bacteroides intermedius** and *Peptostreptococcus* species*.

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

CONTRAINDICATIONS

PRIMAXIN I.M. is contraindicated in patients who have shown hypersensitivity to any component of this product. Due to the use of lidocaine hydrochloride diluent, this product is contraindicated in patients with known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block. (Refer to the package circular for lidocaine hydrochloride.)

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERA

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630 / S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DFile

SEP 24 1996

Division of Anti-Infective Drug Products

PROJECT MANAGER REVIEW OF SUPPLEMENT AND FINAL PRINTED LABELING (FPL)

Application Number: NDA 50-630/S-009

Name of Drug: PRIMAXIN I.M. (Imipenem-Cilastatin Sodium for Suspension)

Sponsor: Merck & Co., Inc.

Material Reviewed

Submission Date(s): June 10, 1994

Receipt Date(s): June 14, 1994

Background and Summary Description:

Final printed labeling (FPL) submitted in response to the Agency's not-approvable letter of November 4, 1993. Supplement 009 was originally submitted March 11, 1993.

The package insert has been revised in the following areas: **HEADING, DESCRIPTION, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **REFERENCES**. Also, there is a new Corporate logotype and signature resulting from the new Corporate Identity Program.

Review

The labeling was revised according to the not-approvable letter of November 4, 1993, and the NDA Holders letter of January 26, 1993, as well as a few additional changes as specified below:

HEADING

1.

2. The product name has been replaced with the new corporate logotype and signature added as a result of the new Corporate Identity Program.

   This is acceptable.

DESCRIPTION

1. As requested in the approval letter dated November 19, 1993, for NDA 50-587/S-040, Primaxin® I.V., the chemical names for imipenem and cilastatin sodium have been revised to the uninverted IUPAC name.

   This is acceptable, per the November 19, 1993 request. However, at the next printing the word "formimidoylamino" in the chemical name of imipenem, should be revised to read "Formimidoylamino", and the word "sodium" in the chemical name of cilastatin sodium, should be revised to read "Sodium", per the uninverted IUPAC name as found in the USP Dictionary of USAN and International Drug Names, 1996.

2. The molecular weight of cilastatin sodium has been revised fror ___ " to "380.44", due to a change in the molecular weight of sulfur.

   This change is acceptable per the USP Dictionary of USAN and International Drug Names, 1996.

CLINICAL PHARMACOLOGY

1. The abbreviation for microgram,"mcg", has been replaced with "μg" wherever it appears in the labeling.

   This change was requested in the November 4, 1993 letter and is acceptable.

2. In the first listing of microorganisms, under Gram-positive aerobes:

   a.
   b. 

   These changes were requested in the November 4, 1993 letter and are acceptable.

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

Imipenem exhibits *in vitro* minimal 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."

This change was requested in the November 4, 1993 letter and is acceptable.

4. In the second listing of microorganisms, under Gram-negative aerobes, " ——— ., including ——— has been revised to read "*Hafnia alvei*".

This change was requested in the approval letter for S-006 and S-007 dated November 23, 1992, and is acceptable.

5. The *Susceptibility Tests* subsection has been revised according to the NDA Holders letter of January 26, 1993.

This change was requested in the November 4, 1993 letter and is acceptable per the microbiology review dated June 21, 1996 for NDA 50-630/S-013.

INDICATIONS AND USAGE

In **Intra-abdominal infections,** ——— has been revised to read "Viridans group streptococci*".

This change was requested in the November 4, 1993 letter and is acceptable.

WARNINGS

1. In the second paragraph of the pseudomembranous colitis warning, "imipenem-cilastatin sodium" has replaced the word "PRIMAXIN".

2. [redacted]

has been revised to read "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."

This change was requested in the November 4, 1993 letter and is acceptable.

PRECAUTIONS

[redacted]

been revised to read:

"*Laboratory Tests*

While PRIMAXIN I.M. 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."

This change was requested in the November 4, 1993 letter and is acceptable.

2. The dagger (†) in this subsection has been replaced with a double-dagger (††).

This change is acceptable as the single dagger had already been used earlier in the labeling to identify PRIMAXIN as a registered trademark of MERCK & CO., Inc. The double dagger identifies animal data based on patient weight of 50 kg.

ADVERSE REACTIONS

In the [redacted] pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment, see WARNINGS),...."

This change was requested in the November 4, 1993 letter and is acceptable. However, at the next printing the word "WARNINGS" should be bolded.

PREPARATION FOR ADMINISTRATION

The dagger (†) in this subsection has been replaced with a triple-dagger (†††).

The single dagger and double-daggers have been used earlier in the labeling. See #2 in the **PRECAUTIONS** section above. This change is acceptable.

REFERENCES

The references have been revised in accordance with the December 1993 NCCLS publications.

These are acceptable as written.

Conclusions

An approval letter should be issued for the supplement, acknowledging the FPL. The letter should request that the following changes be made at the next printing:

DESCRIPTION

The word "formimidoylamino" in the chemical name of imipenem, should be revised to read "Formimidoylamino", and the word "sodium" in the chemical name of cilastatin sodium, should be revised to read "Sodium", per the uninverted IUPAC name as found in the USP Dictionary of USAN and International Drug Names, 1996.

CLINICAL PHARMACOLOGY

1. In the sixth paragraph, revise "...is questionable (see OVERDOSAGE)." to read "...is questionable. (See **OVERDOSAGE**.)"

2. In the third paragraph of the *Microbiology* subsection, revise "...sodium (see INDICATIONS AND USAGE)." to read "...sodium. (See **INDICATIONS AND USAGE**.)"

3. In the first paragraph of the *Susceptibility Tests* subsection, revise "(See CLINICAL PHARMACOLOGY section for...)" to read "(See **CLINICAL PHARMACOLOGY** section for...)".

PRECAUTIONS

In the *General* subsection, third paragraph, revise "...vessel (see DOSAGE AND ADMINISTRATION)." to read "...vessel. (See **DOSAGE AND ADMINISTRATION.**)"

ADVERSE REACTIONS

These comments are specific to the *Potential ADVERSE EFFECTS* subsection:

1. The heading "*Potential ADVERSE EFFECTS*:" should be revised to read "*Potential ADVERSE REACTIONS*:".

2. In the first paragraph, the word "effects" should be revised to read "reactions".

3. In the *Systemic Adverse Reactions* subsection, revise "(see PRECAUTIONS)" to read "(see **PRECAUTIONS**)" and revise "..., see WARNINGS),..." to read "..., see **WARNINGS**),...".

DOSAGE AND ADMINISTRATION

In the **DOSAGE GUIDELINES** table, revise "†See INDICATIONS AND USAGE section." to read "†See **INDICATIONS AND USAGE** section."

Project Manager

Concurrence:

Supervisory Clinical Team Leader

cc:
Original NDA
HFD-520/Div. Files
HFD-520/PM/Dillon-Parker
HFD-520/TL/Roberts/rd 9/20/96
HFD-520/MO/Thompson
HFD-520/Pharm/Buko
HFD-830/Chem/Dunn
HFD-520/Micro/Altaie
HFD-520/PMS/Roche

draft: mdp/September 11, 1996/N50630.S09
final: September 24, 1996

FPL REVIEW