CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-630 / S-014

Trade Name: **Primaxin**

Generic Name: **Cilastatin sodium; imipenem**

Sponsor: **Merck and Co.**

Approval Date: **June 30, 1997**

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APPLICATION NUMBER:

50-630 / S-014

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APPLICATION NUMBER:

50-630 / S-014

APPROVAL LETTER

D.N file

[redacted]

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.M. (imipenem and cilastatin for injectable suspension).

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

This supplemental application provides for revisions to the **HEADER, ADVERSE REACTIONS,** and **COMPATABILITY AND STABILITY** 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

The abbreviation mcg should be changed to μ wherever it appears in the labeling. In the second sentence of the last paragraph, a period should be placed after "questionable", and "(see OVERDOSAGE)." should be changed to "(See **OVERDOSAGE.**)"

Microbiology subsection

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

WARNINGS

The last sentence of the third paragraph regarding pseudomembranous colitis should be revised to read "...treatment with an antibacterial drug clinically effective against *C. difficile* colitis."

PRECAUTIONS section, *General* subsection

In the third paragraph, a period should be placed after "vessel", and "(See **DOSAGE AND ADMINISTRATION).**" should be changed to read "(See **DOSAGE AND ADMINISTRATION.)**"

REFERENCES section

All NCCLS references need to be updated. References 1 and 2 according to 1997 approved standard documents and reference 3 according to 1993 approved standard document.

Additionally, the stability data did not report testing for pH and particulate matter at each test station. The stability data should also include testing for sterility and pyrogen content at the initial test station as well as at the expiration period test station. The complete stability data with appropriate testing should be provided.

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 50-630/S-014. 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

cc:
Original NDA 50-630
HFD-520/Div. files
HFD-520/PMS/Roche
HFD-520/CTL/Roberts
HFD-520/MO/Thompson
HFD-520/DepDir/Gavrilovich
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Concurrence:
HFD-520/CTL/Albuerne 6/26/97
HFD-520/CPMS/Bona 6/30/97

Drafted by: kr/6/26/97/N50587.S47
Initialed by:
final: 6/27/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630 / S-014

LABELING

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

76329067

~~STERILE~~

PRIMAXIN® I.M.

(IMIPENEM AND CILASTATIN ~~SODIUM~~
FOR INJECTABLE SUSPENSION)

(Formerly called IMIPENEM-CILASTATIN SODIUM FOR SUSPENSION)

For Intramuscular Injection Only

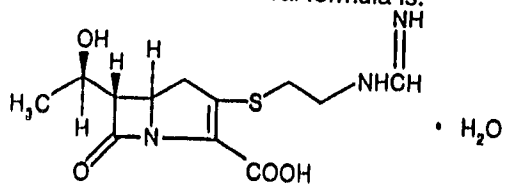
Title revision based on October 2, 1995 FDA letter requesting implementation of USP (23-NF 18), Supplement 1, revised injectable nomenclature requirements (also noted throughout text).
A "flag" has been added to assist practitioners in becoming familiar with the revised title, as requested in 10/2/95 FDA letter.

APPROVED JUN 30 1997

DESCRIPTION

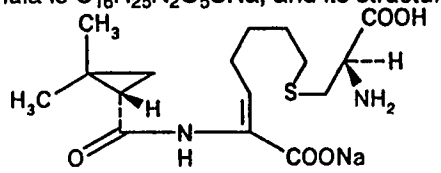
~~Sterile~~ PRIMAXIN† I.M. (Imipenem and Cilastatin ~~Sodium~~ for Injectable Suspension) is a formulation of imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I). PRIMAXIN I.M. is a potent broad spectrum antibacterial agent for intramuscular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

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



† Registered trademark of MERCK & CO., Inc.

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is [*R*-[*R**, *S**-(*Z*)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[(2,2-dimethylcyclopropyl)carbonyl]amino]-2-heptenoic acid, monosodium salt. It is an off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$, 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 mcg/mL, respectively. For cilastatin, peak plasma levels average 24 and 33 mcg/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 mcg/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
(mcg/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 mcg/mL)

Imipenem urine levels remain above 10 mcg/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 mcg/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:

Staphylococcus aureus including penicillinase-producing strains

(NOTE: Methicillin-resistant staphylococci should be reported as resistant to imipenem.)

Group D streptococcus including *Enterococcus faecalis* (formerly *S. faecalis*)

(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*].)

Streptococcus pneumoniae

Streptococcus pyogenes (Group A streptococcus)

Streptococcus viridans group

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.

Imipenem has been shown to be active *in vitro* against the following microorganisms; however, the clinical significance of these data is unknown.

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* spp., including *H. 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* spp., including *P. 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:

Diffusion techniques:

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such standard procedure[1], which has been recommended for use with disks to test susceptibility of organisms to imipenem, uses the 10-mcg imipenem disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for imipenem.

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

Zone Diameter (mm)	Interpretation
≥16	Susceptible
14 - 15	Moderately Susceptible
≤13	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "moderately susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 10-mcg imipenem disk should give the following zone diameters:

Organism	Zone Diameter (mm)
E. coli ATCC 25922	26 - 32
P. aeruginosa ATCC 27853	20 - 28

Dilution techniques:

Use 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 (mcg/mL)	Interpretation
≤4	Susceptible
8	Moderately Susceptible
≥16	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard imipenem powder should provide the following MIC values:

Organism	MIC (mcg/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

For anaerobic bacteria, the MIC of imipenem can be determined by agar or broth dilution (including microdilution) techniques[3].

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 instances 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 Group D streptococcus including *Enterococcus faecalis** ; *Streptococcus viridans* group*, *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**; Group D streptococcus including *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 Group D streptococcus including *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 a 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.)

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

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY 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 PRIMAX in severity from mild to life-threatenin important to consider this diagnosis in pa with diarrhea subsequent to the antibacterial agents.

Treatment with antibacterial agents alter the colon and may permit overgrowth o indicate that a toxin produced by *Clostri* primary cause of "antibiotic-associated colitis

After the diagnosis of pseudomembran established, therapeutic measures should b of pseudomembranous colitis usually discontinuation alone. In moderate to severe ca should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile*.

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.

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*** 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*** 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 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*** the maximum recommended human dose 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 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.

*** Based on patient weight of 50 kg.

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*** 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.

It was changed to pediatric patients in final "blue" insert.

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 and 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 and 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 antibiotic 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; *Renal:* acute renal failure, oliguria/anuria, polyuria, urine discoloration; *Skin:* toxic epidermal necrolysis, Stevens-Johnson syndrome , erythema multiforme, angioneurotic edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a whole:* polyarthralgia, asthenia/weakness, drug fever.

MRL proposal based on WAES reports (see attached p. 15a.)

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.

MRL proposal based on WAES reports (see attached p. 15b.)

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.

Tongue Discoloration
(Cutoff:September 20, 1995)

WAES#	DATE SUBMITTED TO FDA
+ 88040610	06/08/88
+ 89030974	✲
+ 91020896	✲
+ 93065529	✲
+ 93071242	01/26/94
+ 93101280	01/26/94
	01/30/95
+ 94040102	01/30/95

✲ Reported from overseas experience; not reportable under FDA regulations
+ WAES number repeated under more than one term.

Drug Fever

(Cutoff: September 21, 1995)

WAES#	DATE SUBMITTED TO FDA
+ 85030302	03/21/85
+ 87010593	01/18/84
+ 91120744	✲
89060292	12/26/89
+ 93021128	✲
+ 93100629	✲
94020768	02/14/94
+ 94090369	01/30/95
+ 95030197	01/24/96
+ 95060048	✲
+ 95060687	♦

✲ Reported from overseas experience; not reportable under FDA regulations.
+ WAES number repeated under more than one term.
♦ This was not submitted to FDA because this is a duplicate report of 95030197.

NDA 50-630
Merck & Co., Inc.
West Point, PA

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

NAME/STRENGTH:
PRIMAXIN I.M. 500 mg

BATCH/STUDY #:
800671 7039V

BATCH SIZE:
7556 vials

DATE MANUFACTURED:
2/10/92

MANUFACTURING SITE:

Merck, Elkton, VA

DATE PACKAGED:
2/20/92

PACKAGER/SITE:
Merck, Elkton, VA

DRUG SUBSTANCE MANUFACTURER/SITE:
Merck, Stonewall, VA

DRUG SUBSTANCE LOT #:
Imipenem - TEH831, TEH848
Cilastatin - VET014

CONTAINER SIZE/SUPPLIER:
20 mL Type I glass/Wheaton

CONTAINER RESIN:

NA

CLOSURE/SUPPLIER:
1816 rubber/West

SEAL/SUPPLIER:
Aluminum/West

FILLER:
NA

DATE STUDY STARTED:
2/10/92

PURPOSE OF STUDY:
Annual report

STORAGE CONDITIONS (INCLUDE ORIENTATION):
25°C ±1°C/Upright

DATE OF EXPIRY:
1/94

			TIME (months)						
ATTRIBUTES	METHODS	SPECIFICATIONS	0*	3*	6*	9*	12*	18*	24*
Imipenem	HPLC	90.0 - 115.0%	108.0	111.1	108.8	110.0	109.6	109.4	107.9
Cilastatin	HPLC	90.0 - 115.0%	109.2	110.7	110.6	109.1	112.3	110.4	106.4
Actual test dates	---	---	2/12/92	5/4/92	7/31/92	11/17/92	2/19/93	8/8/93	2/4/94

DF

NDA SUPPLEMENT REVIEW

MAY 23 1997

CHEMIST'S REVIEW Review #1

1. **ORGANIZATION** DAIDP (HFD-520)

2. **NDA NUMBER** 50-630

3. **NAME & ADDRESS OF APPLICANT**
Merck & Co., Inc.
PO Box 4, BLA-20
West Point, PA 19486

4. **AF NUMBER**

5. **SUPPLEMENT(s) NUMBER(s) DATE(s)** SLR-014; 1/14/97

6. **NAME OF DRUG** Primaxin

7. **NONPROPRIETARY NAME** Imipenem and Cilastatin sodium

8. **SUPPLEMENT(s) PROVIDES FOR:**

adoption labeling descriptions to conform to the USP 23 supplement 1 regarding drug product name and instructions for storage temperature as well as clarification to the ADVERSE REACTIONS section of the labeling.

9. **AMENDMENTS AND OTHER (REPORTS, etc.) DATES**

10. **PHARMACOLOGICAL CATEGORY** Antimicrobial

11. **HOW DISPENSED** XXX Rx OTC

12. **RELATED IND/NDA/DMF(s)**

13. **DOSAGE FORM(s)** IM injection

14. **POTENCY(ies)** 500 and 750 mg

15. **CHEMICAL NAME AND STRUCTURE**
Imipenem $C_{12}H_{17}N_3O_4S.H_2O$, 317.37 CAS-74431-23-5
Cilastatin Sodium
$C_{16}H_{25}N_2NaO_5S$, 380.44
CAS-81129-83-1

16. **RECORDS AND REPORTS**
CURRENT
Yes
REVIEWED
Yes

17. **COMMENTS**
This supplement is for changes being effected to comply with directions given in the USP 23 supplement 1. **The stability data provided is incomplete and a comment should be included in the approval letter requesting stability data showing all test results in addition to the assay results. See stability section of this review.**

18. **CONCLUSIONS AND RECOMMENDATIONS**
Recommend approval letter to issue for this supplement with request for more stability data.
Orig: NDA 50-630
HFD-520 HFD-520/Thompson/MO
HFD-520/Roche/CSO
HFD-520/JTimper/Chem, HFD-520/Katague: initialed DBK 5/23/97

19. **REVIEWER NAME** J. Timper

SIGNATURE 5/22/97

DATE COMPLETED 5/22/97

DISTRIBUTION ORIGINAL JACKET REVIEWER DIVISION FILE

20. **Components and Composition n/a**
21. **Facilities and Personnel** n/a
22. **Synthesis n/a**
23. **Raw Material Controls n/a**
24. **Other Firm(s) n/a**
25. **Manufacturing and Processing n/a**
26. **Container/Closure n/a**

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27. **Packaging and Labeling Adequate**

The changes to the labeling, except for the two adverse reactions added to that section, were submitted in order to conform to the USP 23 Supplement 1 guidances.

The labeling, in the drug product title, the word "Sterile" and "Sodium" have been deleted. The word "Injectable" has been added before "Suspension".

The COMPATIBILITY AND STABILITY section has been revised by the following change:

- The storage temperature for the dry powder has been revised from 30°C to 25°C.

The ADVERSE REACTIONS section has been revised by the following:

- "staining of teeth" has been revised to read "staining of the teeth and/or tongue"
- "drug fever" has been added after "asthenia/weakness".

28. **Laboratory Controls (In-process and Finished Dosage Form) n/a**
29. **Stability** Inadequate (not warranting to withhold approval of the supplement)

There was provided with the labeling supplement a report of the stability data for assay only up to 36 months test data.

The stability data did not report testing for pH, particulate matter, sterility, and pyrogen testing. The firm should provide the complete stability data.

The following comment should be addressed to the firm with the approval letter for the changes being effected supplement:

> **The stability data did not report testing for pH and particulate matter at each test station. The stability data should also include testing for sterility and pyrogen content at the initial test station as well as at the expiration period test station. Provide the complete stability data with appropriate testing.**

30. **Control Numbers n/a**
31. **Samples and Results n/a**
32. **Labeling n/a**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630 / S-014

MEDICAL REVIEW(S)

JUN 30 1997

Medical Review of Supplement

NDA 50-630/SLR-014

Date of Submission: January 14, 1997

Applicant: Merck & Co., Inc., West Point, PA 19486

Drug Name: Primaxin I.M.

Category: Imipenem-Carbapenem Antimicrobial
Cilastatin-Dehydropeptidase I Inhibitor

Dosage Form: Injection

Route of Administration: Intravenous

Date Review Started: June 20, 1997

Date Review Completed: June 20, 1997

Type of Submission: Special Supplement - Changes Being Effected

Material Submitted:

Fifteen mounted copies of the printed package circular No. 7632907, a summary of revisions, a paste-up of the package circulars annotated for revisions, and supporting documentation for storage temperature.

Summary of Revisions:

Header

The Word "Sterile" has been deleted; the word "Sodium" has been deleted; the hyphen between the words Imipenem-Cilastatin has been replaced by the word "and"; the word "Injectable" has been added before "Suspension". The header will now read "PRIMAXIN I.M. (IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION").

These revisions have been also implemented throughout the text.

A "flag", formerly called IMIPENEM-CILASTATIN SODIUM FOR INJECTION", has been added under the title to assist practitioners in becoming familiar with the revised title.

Justification

The revised title is based on USP injectable nomenclature requirements, as requested in the FDA letter dated October 2, 1995, and outlined in United States Pharmacopeia USP 23-NF18, Supplement 1.

Comment: These revisions are acceptable.

Adverse Reactions

Two adverse reactions have been added based on overseas experience reports. Under Gastrointestinal, staining of the teeth" has been revised to read "staining of the teeth and/or tongue".
Under Body as a whole, "drug fever" has been added after "asthenia/weakness".

Justification

Staining of the tongue was added based on seven overseas experience reports. Drug fever was added based on ten overseas experience reports.

Comment: The additions are acceptable.

Compatibility and Stability

Before reconstitution:

The storage temperature for the dry powder was changed from "below 30°C (77°F)".

Justification

Worldwide Stability requested this change in storage temperature for consistency with Merck's stability testing procedures.

Comment:

The revision is acceptable. However, the stability data provided are incomplete, and the chemist, J. Timper, recommends that a comment should be included in the approval letter requesting stability data showing all test results in addition to the assay results. This stability deficiency does not warrant withholding approval of this supplement. (See chemist's review.)

Additional Revisions to be Implemented at the Next Printing of the Package Insert

Clinical Pharmacology

The abbreviation mcg should be changed to μ wherever it appears. In the second sentence of the last paragraph, a period should be placed after "questionable", and "(see OVERDOSAGE)." Should be changed to "(See OVERDOSAGE.)"

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

Warnings

The last sentence of the third paragraph regarding pseudomembranous colitis should be revised to read "...treatment with an antibacterial drug clinically effective against C. difficile colitis.

Precautions
General

In the third paragraph, a period should be placed after "vessel", and "See DOSAGE AND ADMINISTRATION)." Should be changer to "(See DOSAGE AND ADMINISTRATION.)"

References

All NCCLS references need to be updated. References 1 and 2 according to 1997 approved standard documents and reference 3 according to 1993 approved standard document.

Recommendations:

It is recommended that this supplemental application be approved. The sponsor should be notified to make the above mentioned revisions at the time of the next printing of the package insert. In addition, the following comment from the chemist reviewer should be included in the approval letter:
"The stability data did not report testing for pH and particulate matter at each test station. The stability data should also include testing for sterility and pyrogen content at the initial test station as well as at the expiration period test station. The complete stability data with appropriate testing should be provided."

MS Albuerne
Mercedes S. Albuerne
Team Leader

cc: Orig NDA 50-630

Concurrence Only:

HFD-520/Div Files
HFD-520/MO/SThompson
HFD-520/PMS/KRoche
HFD-520/TLMO/RRoberts

HFD-520/Act.Dir/GChikami
Gary K Chikami 6/30/97