CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 50-630/S-015

Food and Drug Administration
Rockville MD 20857

FEB 4 1999

Merck & Company, Inc.
Attention: Charles L. Hyman, M.D.
Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

Dear Dr. Hyman:

Please refer to your supplemental new drug application dated August 19, 1998, received August 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Primaxin® I.M (imipenem and cilastatin for injectable suspension). We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

The supplemental new drug application provides for revisions to the **HEADER**, and the **CLINICAL PHARMACOLOGY – Microbiology**, **WARNINGS**, **PRECAUTIONS** and **REFERENCES** sections in response to our letters dated June 17, 1997 and June 30, 1997.

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 product is safe and effective for use as recommended in the submitted draft labeling dated August 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

At the next printing revise the **Microbiology** subsection to address the following issues.

1. The description of the Diffusion and Dilution techniques are out of order. Dilution should be listed before Diffusion techniques.

2. The Susceptibility testing technique for anaerobic bacteria should describe the interpretive criteria and quality control ranges for imipenem.

The final printed labeling (FPL) must be identical to the labeling (text for the package insert, immediate container and carton labels) dated August 1998. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, the submission should be designated "FPL for approved supplement NDA 50-630/S-015." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

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, contact Ms. Frances V. LeSane, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630/S015

FINAL PRINTED LABELING

NDA 50-630/S.015
5-19-98

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

7632908

PRIMAXIN® I.M.

(IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION)

APPROVED

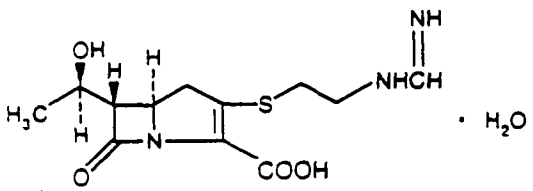
FEB 4 1999

For Intramuscular Injection Only

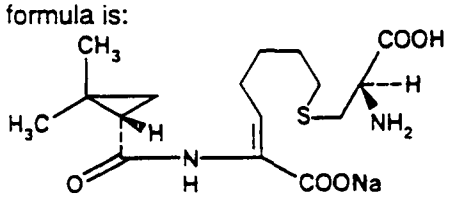
DESCRIPTION

PRIMAXIN† I.M. (Imipenem and Cilastatin 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:



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 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

† Registered trademark of MERCK & CO., Inc.

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:

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

Gram-positive aerobes:
Bacillus spp.
Listeria monocytogenes
Nocardia spp.
Group C streptococci
Group G streptococci
Gram-negative aerobes:
Aeromonas hydrophila
Alcaligenes spp.
Capnocytophaga spp.
Enterobacter agglomerans
Haemophilus ducreyi
Klebsiella oxytoca
Neisseria gonorrhoeae including penicillinase-producing strains
Pasteurella spp.
Proteus mirabilis
Providencia stuartii
Gram-positive anaerobes:
Clostridium perfringens
Gram-negative anaerobes:
Prevotella bivia
Prevotella disiens
Prevotella melaninogenica
Veillonella spp.

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

Susceptibility Tests:
Diffusion techniques: ⇒ why is this not first ??

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-µg 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-µg 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-µg 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 (µg/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 (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

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 PRIMAXIN, 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 and Cilastatin 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

*** Based on patient weight of 50 kg.

(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.

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 pediatric patients 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 and Cilastatin 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 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.

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 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.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. 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/1.73m^2. Serum creatinine alone may not be a sufficiently accurate measure of renal function. Creatinine clearance (T_{cc}) may be estimated from the following equation:

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

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

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 25°C (77°F).

Suspensions for IM Administration

Suspensions of PRIMAXIN I.M. are white to light tan in color. Variations of 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 — Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1 NCCLS, Villanova, PA. 1997.

[†††] Refer to the package circular for lidocaine HCl for detailed information concerning CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

2. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically — Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2 NCCLS, Villanova, PA, 1997.

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 1998
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630/S015

MICROBIOLOGY REVIEW

Division of Anti-Infective Drug Products DEC 23 1998
Clinical Microbiological Review

NDA NUMBER	REVIEW DATE	SUBMISSION/TYPE
50630,SLR-015	11-2-98	Labeling Supplement

DOCUMENT DATE	CDER DATE	ASSIGNED DATE
8-19-98	8-20-98	8-25-98

NAME & ADDRESS OF APPLICANT:
Merck Research Laboratories
Sumneytown Pike
P.O. Box 4, BLA-10
West Point, PA 19486

CONTACT PERSON:
Charles L. Hyman, Director
Regulatory Affairs
Merck Research Laboratories
Sumneytown Pike
P.O. Box 4, BLA-10
West Point, PA 19486
Phone Number: (610) 397-2850

DRUG PRODUCT NAME

Proprietary:	Primaxin™ I.M.
Nonproprietary/USAN:	Imipenem-Cilastatin Sodium
Code Names/#'s:	
Chemical Type/ Therapeutic Class:	Carbapenem, antimicrobial

DOSAGE FORM: I.M. solutions
STRENGTHS: I.M., 500 &750 mg

ROUTE OF ADMINISTRATION: I.M.

DISPENSED: _X_ Rx ___ OTC

RELATED DOCUMENTS (if applicable):
No reference given to other documents

REMARKS/COMMENTS:
This supplemental application provides for changes in the labeling of the approved NDA 50630 for Primaxin ™ I.M. The Microbiology subsection of the label has been revised based on the NDA holders' letter of January 26, 1993 and the recommendations given to the applicant in a regulatory letter dated 6-17-98 (SLR-013). The label was reviewed for accuracy and implementation of action items described in the regulatory letter of 6-17-98.

The microbiology subsection of the label is in compliance with the recommendations made by the agency in the letter dated 6-17-97. However, two additional revisions are necessary in order to bring the label in line with the current practices of the division. The recommended revisions are as follows:

1. The descriptions of the Diffusion and Dilution techniques are out of order. In the division's current practice the Dilution techniques are listed before the Diffusion techniques.
2. The susceptibility testing technique for anaerobic bacteria should describe the interpretive criteria and quality control ranges for imipenem.

CONCLUSIONS & RECOMMENDATIONS:

The revised label is in compliance with the agency's recommendations of 6-17-97. However, the applicant is encouraged to revise the label one additional time to address the following two issues:

3. The descriptions of the Diffusion and Dilution techniques are out of order. In the division's current practice the Dilution techniques are listed before the Diffusion techniques.
4. The susceptibility testing technique for anaerobic bacteria should describe the interpretive criteria and quality control ranges for imipenem.

/S/

Sousan Sayahtaheri Altaie, Ph.D.
Clinical Microbiology Review Officer

cc: [redacted]
HFD-520/Division File
HFD-520/Micro/S. Altaie
HFD-520/ TL MO/ R. Roberts
HFD-520/CSO/F. LeSane

Concurrence Only:
HFD-520/Dep Dir/L. Gavrilovich
HFD-520/TL Micro/A.T. Sheldon
RD# 1 and Final Initialed 12/22/98 AES

12/23/98
12/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-630/S015

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-630/S-015

Merck Research Laboratories
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

AUG 31 1998

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

Dear Dr. Hyman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Primaxin® I.M. (Imipenem-cilastatin) Powder for Suspension, 500mg,750mg

NDA Number: 50-630

Supplement Number: S-015

Date of Supplement: August 19, 1998

Date of Receipt: August 20, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 19, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/ 8/27/98

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

These copies are
OFFICIAL FDA
our desk copies

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

NDA NO. [illegible]
NDA SUPPL. NO. S-[illegible]
ORIGINAL

August 19, 1998

MERCK
Research Laboratories

Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation IV, HFD-520
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG. 20. 1998
MEGA DOC RM

Dear Dr. Chikami:

Supplemental New Drug Application

NDA 50-630: PRIMAXIN™ I.M. (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 (b), we submit a supplement to NDA 50-630.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the ***Labeling*** Section of the approved New Drug Application for PRIMAXIN™ I.M.

Attached for submission to the FDA as draft for approval [314.70 (b)], in response to FDA letters dated June 17, 1997 (**CLINICAL PHARMACOLOGY,** ***Microbiology***, S-013) and June 30, 1997 (**HEADER, ADVERSE REACTIONS, AND COMPATABILITY AND STABILITY,** S-014), are the following:

Tab 1. Mock-up of package circular #7632908

Tab 2. Summary of Revisions

Tab 3. Clean running text

The circular has been revised under the **CLINICAL PHARMACOLOGY,** ***Microbiology*** subsection based on the NDA holders letter dated January 26, 1993, our draft submission of December 8, 1994, and the FDA Approvable letter dated June 17, 1997. The **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS** and **REFERENCES** sections have been revised based on the FDA letter dated June 30, 1997, for **HEADER, ADVERSE REACTIONS,** and **COMPATIBILITY AND STABILITY.**

In addition, the circular has also been revised to comply with the FDA letter of October 2, 1995 to implement new injectable product nomenclature, which states that the "flag" alerting practitioners to the name change should be kept for a six month period. As this time period has been met, the "flag" is now being deleted.

In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997, as indicated in the attached Form 3397 , no user fee is required for this supplemental application.

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

We consider the filing of this 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 Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

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

Attachments
Q/YAR/HER/LTR/SS-I.M.

Federal Express

Desk Copy to: Ms. Frances LeSane, HFD-520, Rm. N355, Federal Express