

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-587 / S-058

50-630 / S-021

**Trade Name: Primaxin IV for Injection
Primaxin IM Injectable Suspension**

Generic Name: Imipenem and Cilastatin

Sponsor: Merck & Co.

Approval Date: March 4, 2003

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APPLICATION NUMBER:

50-587 / S-058

50-630 / S-021

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-587/S-058
NDA 50-630/S-021

Merck & Co., Inc.
Attention: Virginia G. Snyder
Manager, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Ms. Snyder:

Please refer to your supplemental new drug applications dated March 12, 2002, received March 13, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRIMAXIN™ IV for Injection (Imipenem and Cilastatin)[NDA 50-587/S-058] and PRIMAXIN™ IM Injectable Suspension (Imipenem and Cilastatin)[NDA 50-630/S-021].

These applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated May 7, 2002 and February 12, 2003.

These supplemental new drug applications provide for revisions to the **PRECAUTIONS** section, *Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy: Teratogenic Effects Pregnancy Category C* subsections of the labels. Specifically, the labels have been revised to reflect the comparison between dose levels used in animal teratology and reproduction tests to those doses used in humans on the basis of body surface area (mg/m^2) rather than body weight (mg/kg).

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted February 12, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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, these submissions should be designated "**FPL for approved supplements NDA 50-587/S-058 and NDA 50-630/S-021**". Approval of these submissions by FDA is not required before the labeling is used.

NDA 50-587/S-058
NDA 50-630/S-021
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We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Maureen Dillon-Parker, Regulatory Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Janice Soreth
3/4/03 01:40:08 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058

50-630 / S-021

LABELING

PRIMAXIN® I.M. (Imipenem and Cilastatin for Injectable Suspension)

Systemic Adverse Reactions

The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN I.M. (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 papillary hyperplasia, staining of the teeth and/or tongue, hemoarrhythm, pharyngitis, pen, increased salivation; **Hematologic/pancreatic:** bone marrow depression, thrombocytopenia, neutropenia, leukopenia, myeloperoxidase, hemolytic anemia, CNS; **Neurologic:** tremor, confusion, ataxia, vertigo, vertigo, headache, psychomotor disturbances including hallucinations, **Sensory:** decreased hearing loss, tinnitus, taste perversion; **Respiratory:** chest discomfort, dyspnea, hyperinflation, thoracic spine pain; **Cardiovascular:** palpitations, tachycardia, epidermal necrolysis, Stevens-Johnson syndrome, urticaria, discoloration; **Skin:** toxic epidermal necrolysis, flushing, rashes, hypotension, hypotension, severe allergic reactions, pruritus, urticaria; **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; **Urinanalysis:** presence of urine protein, urine bilirubin, and urine urobilinogen.

Overdosage

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

The acute intravenous toxicity of imipenem-cilastatin sodium was produced within 5-10 minutes in rats at doses of 771 to 1563 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 (1560 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.

DOSE 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.)

DOSSAGE GUIDELINES

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

†See INDICATIONS AND USAGE section.

PRIMAXIN® I.M. (Imipenem and Cilastatin for Injectable Suspension)

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 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/1.73m². Serum creatinine alone may not be a sufficiently accurate measure of renal function. Creatinine clearance (Cl_{cr}) may be estimated from the following equation:

$$Cl_{cr} (\text{Males}) = \frac{(wt. \text{ in kg}) (1.40 - age)}{(72) (\text{creatinine in mg/dL})}$$

$$Cl_{cr} (\text{Females}) = 0.85 \times \text{above value}$$

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. 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 0006-3362-15 in trays of 10 vials.
 No. 3583 — 750 mg imipenem equivalent and 750 mg cilastatin equivalent
 NDC 0006-3363-16 in trays of 10 vials.

REFERENCES

- National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Edition 6, Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Villanova, PA, 1991.
- National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition, Approved Standard NCCLS Document M2-A8, Vol. 17, No. 1, NCCLS, Villanova, PA, 1991.
- 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, 1985.

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

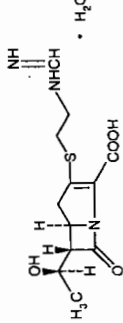
MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

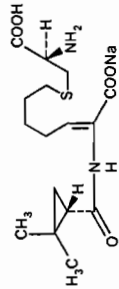
PRIMAXIN® I.M. (IMIPENEM AND CILASTATIN FOR INJECTABLE SUSPENSION)

For Intramuscular Injection Only

PRIMAXIN I.M. (Imipenem and Cilastatin for Injectable Suspension) is a combination of imipenem (a carbapenem 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-formimidazolidinone) is a crystalline derivative of thienamycin, which is produced by *Streptomyces carnosus*. Its chemical name is 6R-(5a, 6a, 7R)-6-[4-(1-hydroxyethyl)-3-(2-[(1-iminoethyl)amino]ethylthio)-2-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 C₁₇H₂₄N₄O₄·H₂O, and its structural formula is:



Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. Its chemical name is (R)-[R', S'-(2Z)]-7-[(2-amino-2-carboxyethylthio)-2-[(2Z)-dimethylpropionyl]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 C₁₄H₁₉N₂O₄Na, 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). 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 bioavailable 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 1 µg/mL for at least 6 to 8 hours, following a 500 mg or 750 mg dose, respectively. In a study comparing imipenem plasma levels after administration of the intramuscular injection of PRIMAXIN I.M. every 12 hours with no accumulation of cilastatin and only slight accumulation of imipenem, plasma levels of imipenem were 750 mg of imipenem-cilastatin (intravenous formulation) administered intravenously or of imipenem-cilastatin sodium (intramuscular formulation) diluted with 1% lidocaine and administered intramuscularly is as follows:

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 †† PRAIGHT © MERCK & CO., Inc., 1985, 1989
 All rights reserved

PRIMAXIN® I.M. (Imipenem and Cilastatin for Injectable Suspension)

PLASMA CONCENTRATIONS OF IMIPENEM (µg/mL)

TIME	500 MG		750 MG	
	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	5.9	12.0	11.4
4 hr	2.5	3.6	3.4	7.3
6 hr	0.5	2.5	1.1	3.8
12 hr	ND**	0.3	ND**	0.8

**ND: Not Detectable (<3.3 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 15% 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 a relatively low renal clearance of sodium salt. This enzyme is inhibited by cilastatin sodium, 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 50 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 6 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 has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections treated with the intramuscular formulation of imipenem-cilastatin sodium as described in the INDICATIONS AND USAGE section.

Gram-positive aerobes:

Staphylococcus aureus including penicillinase-producing strains resistant to imipenem.)
 (NOTE: Methicillin-resistant staphylococci should be reported as Group D streptococci including *Enterococcus faecalis* (formerly *S. faecalis*)

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

Streptococcus pneumoniae

Streptococcus pyogenes (Group A streptococci)

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:

Ferrous sulfate spp.

Gram-negative anaerobes:

Bacteroides spp., including *Bacteroides fragilis*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058

50-630 / S-021

MEDICAL REVIEW

**Medical Officer's Review of NDA Supplements
NDA 50-587; NDA 50-630**

NDA Numbers: 50-587 (SLR-058); 50-630 (SLR-021)

Sponsor Identification:

Merck & Co., Inc.
P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486
484-344-7984
Contact: Virginia Snyder, Manager, Regulatory Affairs

Submission and Review Dates

Dates of Submissions: 50-587 (SLR-058): 3/12/02
50-630 (SLR-021): 3/12/02
Date Review Completed: 4/1/02

Drug Identification

Generic Name: Imipenem and Cilastatin
Trade Names: PRIMAXIN[®] I.V. (NDA 50-587)
PRIMAXIN[®] I.M. (NDA 50-630)

These NDA supplements contain proposed labeling changes for the intravenous and intramuscular injection forms of imipenem and cilastatin. On 9/26/00, the Agency requested that the PRECAUTIONS section of the PRIMAXIN[®] I.M. label be revised to express comparisons between the drug doses used in animal reproductive tests and teratology studies and drug doses used in humans in terms of body surface area (mg/m²) rather than body weight (mg/kg). The PRIMAXIN[®] I.V. label is being revised accordingly to maintain consistency in the labeling of these products.

The proposed changes are under review by Amy Ellis, Ph.D., Pharmacologist. There are no changes in other sections of these labels.

Thomas Smith, M.D.
Medical Officer, HFD-520

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/s/

Thomas Smith
4/1/02 11:24:39 AM
MEDICAL OFFICER
Labeling supplement.
Please sign off.

Jean Mulinde
4/1/02 11:50:58 AM
MEDICAL OFFICER

Janice Soreth
4/17/02 04:09:28 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-587 / S-058

50-630 / S-021

PHARMACOLOGY REVIEW

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520**

NDA#s: 50,587 (SLR 058) and 50,630 (SLR 021)

Date CDER Received/Type of Submission: original submissions rec'd 3/13/02 and additional information rec'd 5/8/02 (labeling supplements)

Reviewer: Amy L. Ellis, Ph.D.

Date Assigned: 3/26/02

Number of Volumes: 2

Date Review Started: 4/9/02

Date 1ST Draft Completed: 5/31/02

Scientific Literature Reviewed: Not necessary

KEY WORDS: Primaxin™, imipenem, cilastatin, label, reproduction toxicity

Sponsor: Merck
PO Box 4, BLA-20
West Point, PA 19486
(484) 344-7984

Review Contains Information to be Communicated to Sponsor: Yes

Submission Contains Any Integrated Tox Study Summaries in Lieu of Final Reports: No

Drug Information:

Class:	Carbapenem antimicrobial with renal dehydropeptidase I inhibitor
Generic Name:	imipenem/cilastatin
Trade Name:	Primaxin™

Introduction and Drug History: As requested by the Division, the sponsor has submitted labeling supplements to the IV and IM Primaxin™ NDAs to change the animal to human dose comparisons in the *Impairment of Fertility* and *Pregnancy* sections of the label from mg/kg to mg/m².

Studies reviewed within this submission: No new studies were submitted- the data used for the label is unchanged. The only change is that animal to human dose comparisons will be made on a body surface area basis instead of mg/kg.

SUMMARY/LABELING RECOMMENDATION:

It is not obvious to the pharmacologist why 2 different adult sizes (50 kg vs. 70 kg) were used when making dose comparisons for the IM and IV Primaxin™ labels, respectively. The sponsor should reconcile both labels using one size, preferably 60 kg. This is the adult human size assumption routinely used by CDER pharm/tox reviewers when making dose comparisons

with animal data (see draft internal document *A Harmonized Approach to Estimating the Safe Starting Dose for Clinical Trials of Therapeutics in Healthy Volunteers*). Additionally, the pharmacologist recommends that the dose comparisons in the IV label should consistently use the highest recommended human dose. Currently some of the comparisons in this label use the highest recommended human dose (50 mg/kg/day) and others use what is referred to as “the usual human dose” (30 mg/kg/day). For the IM label, FDA based the dose comparisons on a 60 kg person instead of 50 kg; thus, the highest recommended daily dose (up to 1500 mg/day) came out to 25 mg/kg/day. This was not a large enough change to significantly alter the dose comparison calculations when the sponsor and reviewer used the same body surface area conversion factors to transform the doses to mg/m². The pharmacologist and sponsor generally used the same conversion factors, but the one for rabbits did differ somewhat. The rabbit conversion factor routinely used by CDER pharm/tox reviewers is also found in the draft document mentioned above. It caused the pharmacologist’s mg/m² dose calculated for rabbits to be higher than the sponsor’s. Finally, the sponsor should mention in the label the routes of administration used in the animal studies described in the *Fertility and Pregnancy* sections.

The reviewer notes that most of her calculations of dose comparisons between animals and humans do not differ significantly from the sponsor’s. The largest differences occur in the IV label because the pharmacologist consistently used the highest recommended human dose of 50 mg/kg/day to make the comparisons.

Conversion Factors, Body Surface Area Dose Calculations and Dose Comparisons Between Humans and Animal Species

Species	Dose (mg/kg/day)	Conversion Factor	Dose (mg/m²/day)	Animal:Human Dose Comparison
Human* (IV)	50	37	1850	---
Human* (IM)	25	37	925	---
Rat	320	6	1920	Approx equal (IV); 2.1 (IM)
Rat	900	6	5400	2.9 (IV); 5.8 (IM)
Rat	1000	6	6000	3.2 (IV); 6.5 (IM)
Rabbit	60	12	720	0.4 (IV); 0.8 (IM)
Rabbit	300	12	3600	1.9 (IV); 3.9 (IM)
Monkey	100	12	1200	0.6 (IV); 1.3 (IM)
Mouse	320	3	960	0.5 IV; Approx. equal (IM)

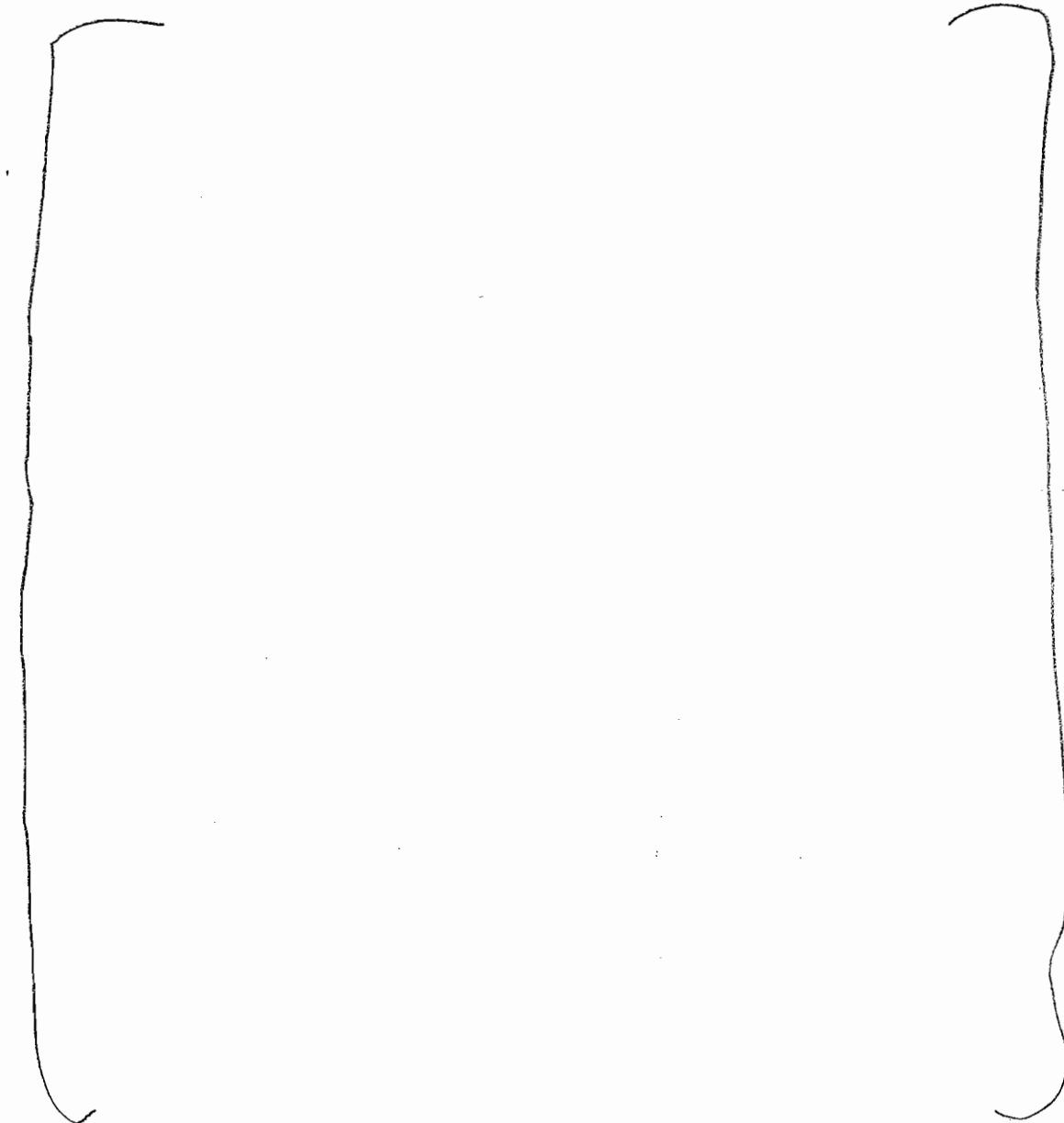
*assumes 60 kg human and highest recommended doses of IM 1500 mg/day and IV 50 mg/kg/day)

Suggested labeling for NDA 50,587 (Primaxin™ IV):

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 **insert**

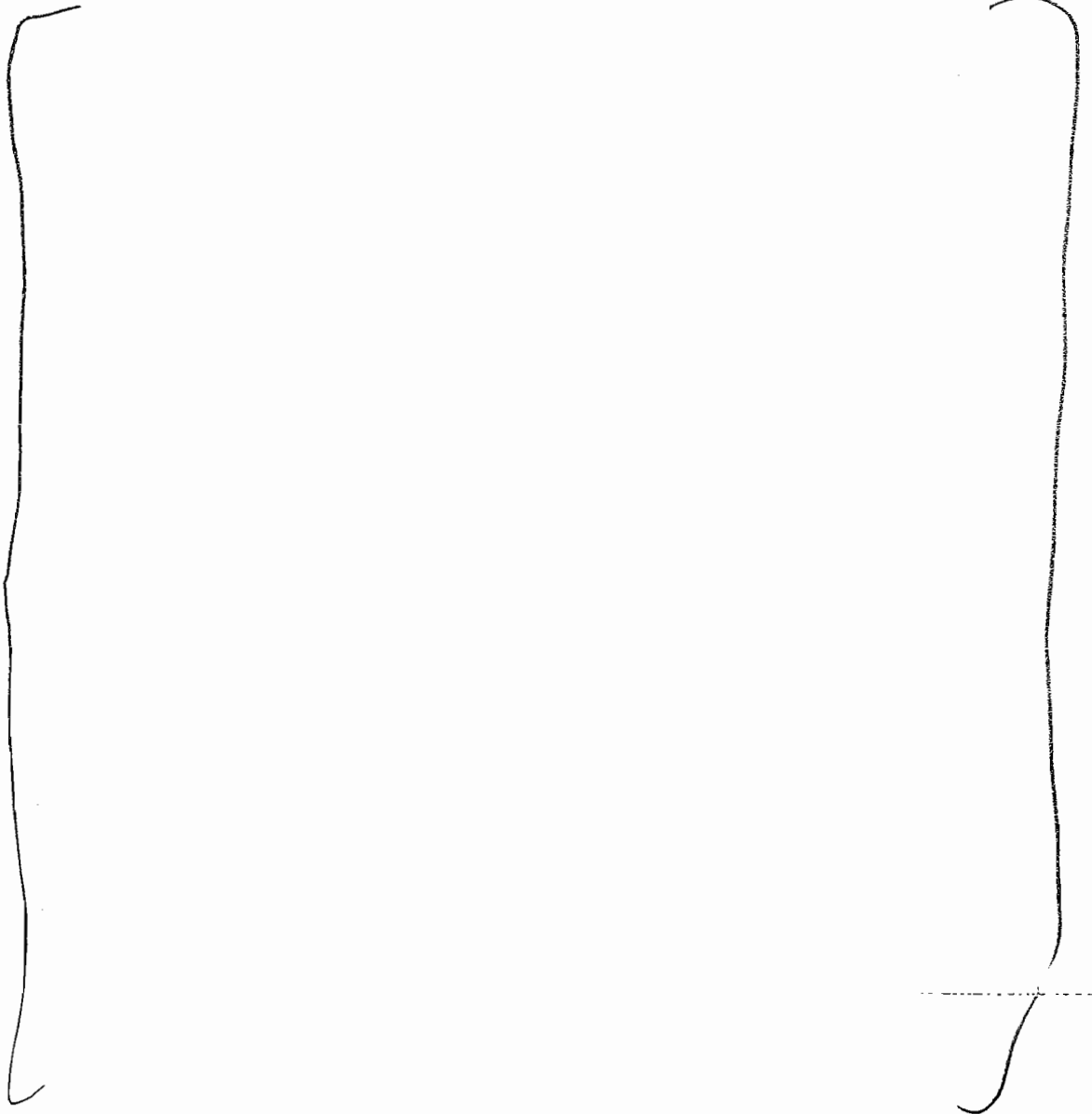


Suggested labeling for NDA 50,630 (Primaxin™ IM):

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 (insert



The reviewer's recommendations for the labels should be conveyed to the sponsor, along with the table of calculated dose comparisons.

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Please initial below to indicate that you have seen the paper copy of this review and agree that it should be put into DFS as a final, archival document:

HFD-520/TSPeters
HFD-520/LGavrilovich

cc:
HFD-520/CSO/Dillon-Parker
HFD-520/MO/Smith

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this page is the manifestation of the electronic signature.**

/s/

Amy Ellis

6/12/02 04:12:28 PM

PHARMACOLOGIST

The reviewer's recommendations for the label should be conveyed to the sponsor, along with the table of calculated dose comparisons.

Terry- You signed the paper copy of this review on 6/10/02.

Terry Peters

6/17/02 09:56:14 AM

PHARMACOLOGIST

Lillian Gavrilovich

6/21/02 12:34:14 PM

MEDICAL OFFICER