NDA: 50-507   TRADE: PRIMAXIN

SPONSOR: MERCK SHARP & DOHME   GENERIC: IMIPENEM

APPROVAL LETTER: Y   STATISTICIAN'S REVIEW: Y

SBA: N   BIO/DISSOLUTION REVIEW: Y

FINAL PRINTED LABEL: Y   MICROBIOLOGIST'S REVIEW: N

MEDICAL OFFICER'S REVIEW: Y   NAS/NRC REVIEW: N

CHEMIST'S REVIEW: Y   FEDERAL REGISTER NOTICE: N

PHARMACOLOGIST'S REVIEW: Y   DATE: 11/12/87

APRVL LTR

NO. 2 6 1985

David W. Blois, Ph.D.
Senior Director, Regulatory Affairs
Merck, Sharp & Dohme Research Laboratories
Division of Merck & Company, Inc.
West Point, PA 19486

Dear Dr. Blois:

Please refer to your Antibiotic Form 5 dated January 31, 1984, submitted
pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for
Primaxin 250/250 mg and 500/500 mg (Imipenem and Cilastatin Sodium) for
Injection.

We acknowledge receipt of your additional communications dated May 3, 15 and
23, June 11, July 2, August 24, September 7, and November 11, 1984 and January
2 and 23, February 13, 14, 20, 22 and 26, March 14, and 15, April 8, 12 and
16, May 1, 3, 13, and 21, June 7, 19, and 21, July 18, August 16, 22, and 27,
September 4 and 20, and October 1, 1985.

We have completed the review of this application as amended with draft
labeling and have concluded that the drug is safe and effective for use as
recommended in the submitted labeling. However, prior to marketing, the
following changes must be made in the labeling and twelve copies of the
labeling should be submitted to us:

1. Under the section "INTRAVENOUS DOSING SCHEDULE FOR ADULTS WITH NORMAL
    RENAL FUNCTION" in the next to last sentence change "4.0g day." to
    read " 4.0 g/day."

2. In the INDICATIONS AND USAGE section, the third to the last paragraph
    (which begins "Because of the broad spectrum...") should be deleted.

3. Omit "Pseudomonas aeruginosa**" from the list of organisms under
    "LOWER RESPIRATORY TRACT INFECTIONS" in the INDICATIONS AND USAGE
    section; also, omit its accompanying footnote.

4. Insert the following sentence as a separate paragraph before the last
    two paragraphs in the INDICATIONS AND USAGE section:

        Although clinical improvement has been noted in patients with
        cystic fibrosis or other chronic lung disease and lower
        respiratory tract infection due to Pseudomonas aeruginosa,
        bacterial eradication may not necessarily be achieved.

5. In the ADVERSE REACTIONS section, paragraph 1, delete the second
    sentence, which reads as follows:

        In a controlled clinical trial the safety of PRIMAXIN was
        similar to that of cefazolin.

The labeling should be revised exactly as we have requested above.   If
additional information relating to the safety or effectiveness of this drug
becomes available before the final printed labeling is submitted to the Food
and Drug Administration (FDA), further revision of that labeling may be
required.

It is noted that you have submitted commitments to do the following studies
and submit the results after approval:

1.   A study in animals to evaluate the possible interaction between
      imipenem and theophylline, with specific attention to CNS adverse
      events.   The results are to be reported by October 1986.

2.   A study that will directly compare the toxicity of
      imipenem/cilastatin in pregnant and non-pregnant rabbits.   The
      results of this study will be submitted as soon as possible.

In addition, please submit in duplicate, the advertising copy which you intend
to use in your proposed introductory promotional or advertising campaign.
Please submit one of the copies directly to the Division of Drug Advertising
with a copy of the package insert.

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

Your cooperation is appreciated.

                                       Sincerely yours,

                                       Elaine C. Esber, M.D.
                                       Director
                                       Office of Biologics Research and Review
                                       Center for Drugs and Biologics

cc: PHI-DO
ORIG. NDA 50-587
HFN-82   HFN-220
HFN-535   HFN-710
HFN-815   HFN-800/JMinor
HFN-815/CSO/DAFowler/sdj/9/20/85/10/4/85
R/D init. by: ETabor/10/8/85
              JKing/10/7/85
              RNorton/10/4/85
              LBuko/9/25/85
              MSAlbuerne/10/7/85
              JMDavitt/10/7/85
              GRStanley/10/4/85
F/T: smc/11/25/85

APPROVAL   0117u

FPL

James R. King
12/9/85

A.H.F.S. Category: 8-12.28

INJECTION

MSD | PRIMAXIN®
(IMIPENEM-CILASTATIN SODIUM, MSD)

PRIMAXIN®
(Imipenem-Cilastatin Sodium, MSD)

DESCRIPTION

PRIMAXIN® (imipenem-cilastatin sodium, MSD) is a formulation of imipenem, a thienamycin antibiotic, and cilastatin sodium, the inhibitor of the renal dipeptidase, dehydropeptidase I, with sodium bicarbonate added as a buffer. PRIMAXIN is a potent broad spectrum antibacterial agent for intravenous administration.

CLINICAL PHARMACOLOGY

PRIMAXIN®
(Imipenem-Cilastatin Sodium, MSD)

Achromobacter spp.
Alcaligenes spp.
Moraxella spp.
Pasteurella multocida
Aeromonas hydrophila
Pseudomonas [illegible]
Neisseria gonorrhoeae (including penicillinase-producing strains)
Anaerobes:
Bacteroides asaccharolyticus
Bacteroides disiens
Bacteroides distasonis
Bacteroides ovatus
Bacteroides thetaiotaomicron
Bacteroides vulgatus

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

Susceptibility Testing

Quantitative methods that require measurement of zone diameters give the most precise estimate of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to imipenem.

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

Susceptible organisms produce zones of 16 mm or greater, indicating that the test organism is likely to respond to therapy.

Organisms that produce zones of 14 to 15 mm are expected to be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

A bacterial isolate may be considered susceptible if the MIC value for imipenem is equal to or less than 4 mcg/mL. Organisms are considered resistant if the MIC is equal to or greater than 16 mcg/mL.

The standardized quality control procedure requires use of control organisms. The 10 mcg imipenem disc should give the zone diameters listed below for the quality control strains.

Organism	ATCC	Zone Size Range
E. coli	25922	27-31 mm
Ps. aeruginosa	27853	20-28 mm

Dilution susceptibility tests should give MICs between the ranges listed below for the quality control strains.

Organism	ATCC	MIC (mcg/mL)
E. coli	25922	0.06-0.25
S. aureus	29213	0.015-0.06
S. faecalis	29212	0.25-1.0
Ps. aeruginosa	27853	1.0-4.0

Based on blood levels of imipenem achieved in man, breakpoint criteria have been established for imipenem.

Category	Zone Diameter (mm)	Recommended MIC Breakpoints (mcg/mL)
Susceptible	≥16	[illegible]
Moderately Susceptible	14-15	[illegible]
Resistant	≤13	[illegible]

INDICATIONS AND USAGE

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

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

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

(3) Intra-abdominal infections. *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis**, Group D streptococci (enterococci), *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Proteus* species (indole positive and indole negative), *Morganella morganii**, *Pseudomonas aeruginosa*, *Citrobacter* species*, *Clostridium* species, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species*, *Eubacterium* species*, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, including *B. fragilis*, *Fusobacterium* species*.

(4) Gynecologic infections. *Staphylococcus aureus* (penicillinase producing strains)*, *Staphylococcus epidermidis*, Group B streptococci, Group D streptococci (enterococci), *Escherichia coli*, *Klebsiella* species*, *Proteus* species (indole positive and indole negative)*, *Enterobacter* species*, Gram-positive anaerobes, including *Peptococcus* species*, *Peptostreptococcus* species*, *Propionibacterium* species*, *Bifidobacterium* species*, *Bacteroides* species, *B. fragilis**, *Gardnerella vaginalis**.

(5) Bacterial septicemia. *Staphylococcus aureus* (penicillinase producing strains), Group D streptococci (enterococci)*, *Escherichia coli*, *Klebsiella* species*, *Pseudomonas aeruginosa**, *Serratia* species*, *Enterobacter* species*, *Bacteroides* species, *B. fragilis**.

(6) Bone and joint infections. *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis**, Group D streptococci (enterococci)*, *Enterobacter* species*, *Pseudomonas aeruginosa*.

(7) Skin and skin structure infections. *Staphylococcus aureus* (penicillinase producing strains), *Staphylococcus epidermidis*, Group D streptococci (enterococci), *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Proteus vulgaris**, *Providencia rettgeri**, *Morganella morganii*, *Pseudomonas aeruginosa*, *Serratia* species, *Citrobacter* species*, *Acinetobacter* species*, Gram-positive anaerobes, including *Peptococcus* species and *Peptostreptococcus* species, *Bacteroides* species, including *B. fragilis*, *Fusobacterium* species*.

(8) Endocarditis. *Staphylococcus aureus* (penicillinase producing strains).

(9) Polymicrobic infections. PRIMAXIN is indicated for polymicrobic infections including those in which *S. pneumoniae* (pneumonia, septicemia), Group A beta-hemolytic streptococcus (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G.

Although clinical improvement has been observed in patients with cystic fibrosis, chronic pulmonary disease, and lower respiratory tract infections caused by *Pseudomonas aeruginosa*, bacterial eradication may not necessarily be achieved.

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

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with PRIMAXIN.

CONTRAINDICATIONS

PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA-LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. [illegible] ALLERGENS. IF AN ALLERGIC REACTION TO PRIMAXIN OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life-threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

PRECAUTIONS

General

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN. These experiences have occurred most commonly in patients with CNS disorders [illegible] who also have compromised renal function. [illegible] Close adherence to recommended dosage schedules is urged, especially in patients with known factors that predispose to seizures (see DOSAGE AND ADMINISTRATION). Anticonvulsant therapy should be continued in patients with a known seizure disorder. [illegible] patients should be [illegible] on anticonvulsant therapy. [illegible] the dosage of PRIMAXIN should be decreased or discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's

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

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

James K. King
1/9/85

PRIMAXIN®
Imipenem-Cilastatin Sodium, MSD

condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pregnancy

Nursing Mothers

Pediatric Use

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

ADVERSE REACTIONS

SHARP & DOHME

PRIMAXIN®
Imipenem-Cilastatin Sodium, MSD

OVERDOSAGE

DOSAGE AND ADMINISTRATION

7362400

PRIMAXIN®
(Imipenem–Cilastatin Sodium, MSD)

Intravenous Dosage of PRIMAXIN in Adults With Impaired Renal Function

Creatinine Clearance (mL/min/ 1.73 m²)	Renal Function	Less Severe Infections or Presence of Highly Susceptible Organisms	Life Threatening Infections— Maximum Dosage
31–70	Mild Impairment	500 mg q8h	500 mg q6h
20–30	Moderate Impairment	500 mg q12h	500 mg q8h
5–20	Severe to Marked Impairment	250 mg q12h	500 mg q12h
0–5	... but no hemodialysis	250 mg q12h	500 mg q12h

PRIMAXIN is cleared by hemodialysis. In patients undergoing hemodialysis, a supplemental dose of PRIMAXIN should be given after hemodialysis unless the next dose is scheduled within four hours. The benefits over the risks should be considered in patients on hemodialysis. Dialysis patients, especially those with CNS background diseases, should be carefully monitored (see PRECAUTIONS).

PREPARATION OF SOLUTION

100 mL Infusion Bottles

Contents of the 100 mL infusion bottles of PRIMAXIN Powder should be reconstituted with 10 mL of diluent. (see list of diluents under COMPATIBILITY AND STABILITY) and shaken until a clear solution is obtained.

10 mL Vials

Contents of the 10 mL vials must be suspended and transferred to 100 mL of an appropriate infusion solution.

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

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

PRIMAXIN®
(Imipenem–Cilastatin Sodium, MSD)

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

COMPATIBILITY AND STABILITY

Before reconstitution:

The dry powder should be stored at a temperature below 25°C.

Reconstituted solutions:

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

PRIMAXIN, as supplied in infusion bottles and vials and reconstituted as above with the following diluents, maintains satisfactory potency for four hours at room temperature and for 24 hours under refrigeration (4°C) temperatures below. Solutions of PRIMAXIN should not be frozen.

0.9% Sodium Chloride Injection

5% or 10% Dextrose Injection

5% Dextrose Injection with 0.02% sodium bicarbonate solution

5% Dextrose and 0.9% Sodium Chloride Injection

5% Dextrose Injection with 0.45% or 0.9% Sodium Chloride NORMOSOL—M in D5-W

5% Dextrose Injection with 0.15% potassium chloride solution

Mannitol 2.5%, 5% and 10%

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

HOW SUPPLIED

PRIMAXIN is supplied as a sterile powder mixture in vials and infusion bottles containing imipenem (anhydrous equivalent) and cilastatin sodium as follows:

No. 3504 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium shown in a vial.
NDC 0006-3504-76 in trays of 25 vials.

No. 3516 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium in trays of 25 vials.
NDC 0006-3516-76 in trays of 25 vials.

No. 3505 — 250 mg imipenem equivalent and 250 mg cilastatin equivalent and 10 mg sodium in trays of 25 infusion bottles.
NDC 0006-3505-76 in trays of 25 infusion bottles.

No. 3517 — 500 mg imipenem equivalent and 500 mg cilastatin equivalent and 20 mg sodium as a buffer.
NDC 0006-3517-76 in trays of 25 infusion bottles.

PRIMAXIN has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature and 48 hours under refrigeration.

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MSD MERCK SHARP & DOHME
DIV OF MERCK & CO., Inc., WEST POINT, PA 19486, USA

MED
REV

Applicant: Merck Sharp and Dohne Research Laboratories
             West Point, Pennsylvania

Date of Applicant: May 3, 1984

Date Review Started: July 30, 1984

Date Review Completed: March 29, 1985

1. General Information

    A)   Name of Drug

         (1) Generic: Imipenem and Cilastatin Sodium
         (2) Trade: PRIMAXIN
         (3) Chemical:

         Imipenem
         [5R-[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.

         Cilastatin Sodium
         [Z, 7 (R), 7(S) -7- [(2 - Amino - 2 - carboxyethyl) thio]-2 -
         [[2,2 - dimethylcyclopropyl) carbonyl] amino] - 2 - heptenoic
         acid, monosodium salt

         A brief glossary is provided below in order to clarify
         nomenclature which has changed during the course of these
         studies.

         Imipenem, also known as MK0787, is the approved name (USAN) for
         N-formimidoyl thienamycin, a broad spectrum antibiotic.

         Cilaslatin, also know as MK0791, is an inhibitor of renal
         dehydropeptidase.

         Thienamycin now refers only to a specific class of carbapenem
         antibiotics of which imipenem is the first to be tested and used
         in man.

         Imipenide was transiently used to refer to N-formimidoyl
         thienamycin by USAN but has been dropped.

         Primaxin, also known as MK0787/MK0791, is a broad spectrum,
         antibiotic consisting of equal parts of imipenem and cilastatin.

(4) **Chemical Structure**

Imipenem

Cilastatin Sodium

B) **Pharmacologic Category**

Imipenem is a new broad spectrum beta-lactam antibiotic.

Cilastatin is an inhibitor of the renal dipeptidase, dehydropeptidase I.

C) **Proposed Indications:** Primaxin proposed indications are the treatment of the following infections caused by susceptible gram-positive and gram-negative aerobic and anaerobic microorganisms:

1. Lower respiratory tract infections
2. Genitourinary infections
3. Intra-abdominal infections
4. Gynecological infections
5. Bacterial septicemia
6. Endocarditis
7. Bone and Joint infections
8. Skin and Skin Structure infections

D) **Dosage Form:** Primaxin is supplied as a sterile powder mixture in vials and infusion bottles containing imipenem anhydrous 250 mg/250 mg cilastatin equivalent and imipenem anhydrous 500 mg/500 mg cilastatin equivalent.

E) **Route of Administration:** Intravenous infusion

F) **Related Drugs:** There are no pharmacologically or chemically analogous substances to imipenem or cilastatin sodium.

2. Manufacturing Controls: (Refer to Chemistry Review)

3. Pharmacology: (Refer to Pharmacology Review)

4. Microbiology: Thienamycin was discovered as a member of a complex of beta-lactam antibiotics produced in fermentation broths by the soil actinomycete, Streptomyces cattleya, itself a hitherto underscribed species.

    Structurally, thienamycin is dissimilar (see chemical structure) from all other natural and synthetic beta-lactam antibiotics in the following respects:

    (1) The five-membered fused ring lacks an S and, unlike the five-membered penicillins, has an enamine system typical of the six-membered cephalosporins. It is from the exocyclic S-substituent at C_3 that thienamycin derives its name.

    (2) The six-position is directly alkylated by the side chain, in contrast to the acylamino group present at that position in all penicillins and cephalosporins.

    (3) The configuration of the C6-side chain is trans with respect to the five-membered ring. In all other beta-lactam antibiotics, the relative configuration is cis.

    Thienamycin, however, resembles the classical beta-lactam antibiotics in its mode of action, being a specific inhibitor of bacterial peptidoglycan "cell-wall" biosynthesis. At inhibitory concentrations, it induces the formation of bacterial spheroplasts whose subsequent lysis accounts for the bactericidal nature of thienamycin activity. Biochemical studies indicate thienamycin acts at a late stage of cell-wall synthesis, probably by inactivating one or more of the transpeptidases that have been implicated in the mode of action of penicillins.

    Thienamycin and its derivative, imipenem, have a wide spectrum of antibacterial activity which includes bacteria inherently resistant to most beta-lactam antibiotics such as P. aeruginosa, the gram-negative anaerobes, and enterococci.
    The antibiotic potency is virtually unaffected by the presence of beta-lactamases directed against one or more of the penicillins and cephalosporins.

    The antibacterial spectra of imipenem, thienamycin, and several reference antibiotics are compared in Tables 1 and 2.

TABLE 1

AGAR DILUTION SUSCEPTIBILITY TEST
MIC (mcg/ml) of

STRAIN	(10 5CFU)	IMIPENEM	THM	CFX	CEF	CAB	GEN
S. aureus	2985	0.01	0.02	3.2	0.2	0.63	0.32
S. aureus	210	0.02	0.04	3.2	0.4	1.3	0.32
S. aureus	2874	0.02	0.04	3.2	0.2	1.3	0.16
S. aureus	2314	0.04	0.04	6.3	0.8	20.0	0.63
S. aureus	2867	0.02	0.04	6.3	0.8	20.0	0.63
S. aureus	4428[b]	20.0	40.0	>100	>100	80.0	5.0
Enterococcus	2864	0.63	1.3	> 100	25.0	40.0	10.0
Enterococcus	2862	1.3	2.5	>100	25.0	40.0	> 20
Enterococcus	2863	40.0	40.0	>100	> 100	> 80	20.0
E. coli	2482	0.32	0.63	6.3	12.5	5.0	0.32
E. coli	2884	0.08	0.16	6.3	6.3	5.0	1.3
E. coli	2964	0.32	0.32	6.3	100	> 80	> 20
E. coli	2891	0.16	0.16	50.0	>100	40.0	2.5
E. coli	2895	0.32	0.63	25.0	>100	> 80	1.3
Shigella spp.	2880	0.16	0.32	3.2	6.3	5.0	1.3
S. typhimurium	326	0.32	0.32	3.2	6.3	20.0	2.5
E. cloacae	2647[c]	0.16	0.32	12.5	12.5	20.0	1.3
E. cloacae	2646	0.63	0.63	> 100	>100	> 80	1.3
E. cloacae	2828	1.3	2.5	>100	>100	20.0	0.63
Enterobacter spp.	2903	0.63	1.3	>100	>100	5.0	1.3
Enterobacter spp.	2902	1.3	2.5	>100	>100	20.0	1.3
E. aerogenes	2906	2.5	5.0	100	100	5.0	1.3
K. pneumoniae	2921	0.63	0.63	6.3	12.5	> 80	1.3
K. pneumoniae	2922	0.63	0.63	6.3	100	> 80	> 20
Klebsiella spp.	2888	0.63	1.3	>100	>100	10.0	1.3
Klebsiella spp.	2890	1.3	1.3	>100	>100	10.0	1.3
Klebsiella. spp.	2889	2.5	5.0	>100	>100	10.0	1.3
Serratia spp.	2840	0.63	2.5	25.0	>100	10.0	2.5
Serratia spp.	2855	0.63	2.5	12.5	>100	> 80	1.3
P. mirabilis	3125	5.0	10.0	3.2	6.3	1.3	5.0
P. mirabilis	2831	2.5	5.0	25.0	50.0	2.5	10.0
P. mirabilis	2830	5.0	10.0	6.3	>100	> 80	2.5
P. morganii	2833	5.0	5.0	12.5	>100	> 80	2.5
P. morganii	2834	2.5	10.0	12.5	>100	1.3	0.32
Providencia spp.	2851	1.3	2.5	1.6	>100	1.3	0.63

a) Antibiotic Abbreviations: THM, thienamycin; CFX, cefoxitin, CEF, cephalothin, CAB, carbenicillin; GEN, gentamicin

b) Methicillin resistant

c) Beta-lactamase-negative mutant derived from parent strain 2646

TABLE 2

AGAR DILUTION SUSCEPTIBILITY OF PSEUDOMONAS ISOLATES
MIC (mcg/ml) of

STRAIN	(105CFU)	IMIPENEM	THM	CAB	GEN	AMK	PIP
40		1.6	3.1	5.0	50	6.3	3.1
2824		0.63	0.63	80	2.5		
2835		2.5	5	80	5.0		
3350b		10	20	> 80	> 20		
3286		2.5	10	80	5.0	6.3	6.3
3287c		2.5	10	>80	5.0		
3288d		20.0	40	80	5.0		
4293		6.3	25	100	12.5	25	6.3
4294		12.5	50	100	25	50	6.3

a) Antibiotic abbreviations: THM = thienamycin; CAB= carbenicillin; GEN = gentamicin; AMK = Amikacin; PIP = piperacillin.

b) Strain 3350 bears plasmid - mediated carbenicillin and gentamicin resistance.

c) Laboratory isolate from strain 3286, showing spontaneous resistance to carbenicillin.

d) Laboratory isolate from strain 3286, showing spontaneous resistance to thienamycin.

As shown in these tables, the potencies of the thienamycin antibiotics far exceed those of the other beta-lactam antibiotics against both gram-positive species, including enterococci, and gram-negative species, including Pseudomonas species. On the average, imipenem shows a two-fold advantage over thienamycin for the entire range of species. Isolates exhibiting beta-lactamase mediated resistance to one or more penicillins and cephalosporins are inhibited by the thienamycins at concentrations close to the MICs found for strains of the same species that are susceptible to beta-lactam antibiotics. An example of the absence of cross-resistance is seen by comparing Enterobacter #2646 with its beta-lactamase-negative isogenic derivative, Enterobacter #2647. Both strains have similar susceptibility to imipenem, showing the indifference of the antibiotic to - the beta-lactamase. All other beta-lactam agents tested, including the extended-spectrum cephalosporins, show much reduced activity on Enterobacter #2646. A single execption to the general absence of cross-resistance was obtained with a methicillin-resistant Staphylococcus isolate (#4428), whose intrinsic resistance to beta-lactam antibiotics is known to be unrealated to beta-lactamase activity. Cross-resistance did not occur between the thienamycins and carbenicillin for a P. aeruginosa isolate with heterotypic resistance to that antibiotic (#3287) nor was carbenicillin resistance found for thienamycin-resistant variant of P. aeruginosa (#3288). Both variants were isolated in in-vitro from the susceptible parental strain #3286.

A survey of 29 Bacteroides isolates showed that all have a very high susceptibility to imipenem (Table 3).

The median MIC for imipenem (0.25 mcg/ml) is comparable to clindamycin, 4-fold superior to thienamycin, and 64-fold superior to that of cefoxitin.

TABLE 3

Comparative Susceptibility Studies on 29
B. fragilis Strains to Imipenem and Three
Reference antibiotics
MIC (mcg/ml)

Compound	Range	For 50% of Strains	For 90% of Strains
Imipenem	0.13 to 1.0	0.25	1.0
Thienamycin	0.25 to 2.0	1.0	2.0
Clindamycin	> 0.06 to 4.0	0.13	2.0
Cefoxitin	8.0 to >32	16	32

Agar dilution susceptibility tests were conducted with 13 selected hospital isolates of Pseudomonas aeruginosa, of which 6/13 were judged resistant to carbenicillin (Table 4). Two inoculum levels, 10^5 and 10^7 CFU, were employed. Comparisons were made with two anti-pseudomonal cephalosporins, moxalactam and cefotaxime, and to gentamicin, amikacin, piperacillin, and carbenicillin. These isolates were uniformly susceptible to imipenem at both inoculum levels. Isolates resistant to carbenicillin were not significantly different in their susceptibility to the thienamycins. The median MICs for imipenem were superior both to thienamycins and to the reference antibiotics. At a higher inoculum level, the greater activity of imipenem is more pronounced.

TABLE 4

Effect of Inoculum Levels on Susceptibility
of 13 Clinical Pseudomonas aeruginosa Isolates
and Seven Reference Antibiotics
Agar Dilution MIC (mcg/ml)

Compound	10^5 CFU Inoculum Range	For % Strains 50	90	10^7 CFU Inoculum Range	For % Strains 50	90
Imipenem	0.8 - 12.5	3.1	6.3	3.1 - 25	6.3	12.5
Thienamycin	1.6 - 50	6.3	25	3.1 - 50	12.5	25
Moxalactam	12.5 -> 50	25	50	50 -> 50	> 50	> 50
Cefotaxime	12.5 -> 100	25	100	50 -> 100	> 100	> 100
Carbenicillin	50 - 400	100	400	100 -> 400	200	> 400
Piperacillin	3.1 -> 100	6.3	25	25 -> 100	100	> 100
Gentamicin	1.6 -> 50	6.3	50	6.3 -> 50	6.3	> 50
Amikacin	1.6 - 50	6.3	25	6.3 - 50	12.5	50

The effect of inoculum levels on both bacteriostatic and bactericidal activity of imipenem was compared with that of cephalothin, carbenicillin, cefotaxime, and moxalactam. A penicillin-sensitive Staphylococcus, beta-lactam resistant enteric species (E. coli, E. cloacae, K. pneumoniae, P. morganii, S. marcescens), and two carbenicillin-sensitive isolates of P. aeruginosa were used. At the low and intermediate inoculum levels (10^3 and 10^5CFU per microtiter well), imipenem is bactericidal at its MIC. At the high inoculum level(10^7CFU), MICs and MBCs were elevated, generally four-fold. This increase was less than that found for the reference agents which, in several instances, lost their bactericidal effect or were overgrown at the highest levels tested despite high potency apparent at the low inoculum levels.

Summary of Published In Vitro Microbiological Studies
of Imipenem by Independent (Non-Merck) Investigators

Samples of imipenem have been distributed to more than 500 university and hospital microbiological laboratories around the world. These laboratories have studied the drug in a large number of clinical isolates, and many of these studies have been submitted to scientific journals.
Tables 6-15 are compilations of comparative in-vitro susceptibility data described in 121 publications. A listing of the full spectrum of bacterial species measured for susceptibility to imipenem is presented in Tables 5-15.

COMPARATIVE IN VITRO ACTIVITY OF MK0787 WITH
BETA-LACTAM AND AMINOGLYCOSIDE ANTIBIOTICS

TABLE 5   GRAM POSITIVE ORGANISMS

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml 50%	90%
STAPH. AUREUS	MK0787	14	379	≤ 0.04	≤ 0.06
	CEFOTAXIME	9	150	2.1	3.7
	CEFOXITIN	2	35	3.3	8.9
	CEPHALOTHIN	6	199	0.34	0.7
	CEFTAZIDIME	3	37	19.2	30.0
	MOXALACTAM	8	160	9.2	12.5
	PIPERACILLIN	3	160	5.8	30.2
	TOBRAMYCIN	1	69	0.12	0.5
STAPHYLOCOCCUS EPIDERMIDIS	MK0787	8	163	≤ 0.06	0.44
	CEPHALOTHIN	5	105	≤ 0.16	1.2
	CEFTAZIDIME	1	12	8.0	32.0
	MOXALACTAM	3	40	16.6	≥ 45.0
	PENICILLIN G	6	117	0.69	5.8
	TOBRAMYCIN	1	18	0.25	> 32.0
STREPTOCOCCUS SPP.	MK0787	11	265	≤ 0.02	≤ 0.04
	CEPHALOTHIN	6	136	≤ 0.16	≤ 0.03
	MOXALACTAM	6	215	2.6	4.9
	OXACILLIN	3	32	0.13	0.21
	PENICILLIN G	9	170	≤ 0.02	≤ 0.05
	PIPERACILLIN	2	95	≤ 0.06	≤ 0.2
	TOBRAMYCIN	2	95	> 32.0	> 32.0
ENTEROCOCCUS	MK0787	9	307	1.17	2.1
	AMPICILLIN	3	94	1.15	1.4
	CARBENICILLIN	1	29	50.0	50.0
	CEFOPERAZONE	2	126	≥ 34.0	≥ 50.0
	PIPERACILLIN	3	110	5.4	20.5
	TICARCILLIN	1	29	100.0	200.00
	TOBRAMYCIN	1	26	> 32.0	> 32.0
	VANCOMYCIN	1	29	1.0	2.0

I = # OF INVESTIGATORS
N = # OF STRAINS EXAMINED

TABLE 5 (cont'd)   GRAM NEGATIVE ORGANISMS

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ul 50%	90%
ESCHERICHIA COLI	MK0787	9	446	0.16	0.35
	CEFOPERAZONE	2	80	0.13	1.5
	CEFOTAXIME	4	160	0.05	0.10
	CEFOXITIN	3	97	3.5	6.4
	CEFTAZIDIME	1	60	0.12	0.5
	MOXALACTAM	4	243	0.10	0.21
	PIPERACILLIN	3	206	1.82	45.0
	AMIKACIN	3	88	2.4	8.0
ENTEROBACTER SPP.	MK0787	16	518	0.36	1.04
	CEFOTAXIME	7	371	0.09	0.61
	CEFOXITIN	7	281	12.0	124.0
	CEFTAZIDIME	1	34	0.5	16.0
	MOXALACTAM	7	313	0.13	0.76
	CARBENICILLIN	4	106	5.7	47.0
	PIPERACILLIN	6	171	2.3	15.1
	TICARCILLIN	7	134	5.3	87.0
	AMIKACIN	6	51	2.0	4.0
	TOBRAMYCIN	2	27	0.5	0.73
KLEBSIELLA SPP.	MK0787	11	315	0.17	0.47
	CEFOTAXIME	4	139	0.02	0.09
	CEFOXITIN	4	48	2.7	4.8
	CEFTAZIDIME	1	57	0.25	1.0
	MOXALACTAM	5	141	0.10	0.03
	CARBENICILLIN	3	96	631.06	631.0
	PIPERACILLIN	4	174	6.3	22.0
	AMIKACIN	4	48	1.3	4.6
SERRATIA SPP.	MK0787	11	214	0.68	1.3
	CEFOTAXIME	4	102	0.26	2.0
	CEFOXITIN	4	47	20.0	55.0
	CEFTAZIDIME	1	30	0.25	0.25
	MOXALACTAM	6	77	0.76	2.1
	CARBENICILLIN	2	70	22.0	578.0
	GENTAMICIN	3	47	4.2	51.0

TABLE 5 (CONT'D)

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml 50%	90%
PROTEUS MIRABILIS	MKO787	7	210	1.4	3.0
	CEFOPERAZONE	2	74	0.61	2.0
	CEFOTAXIME	3	146	0.02	0.03
	CEFOXITIN	2	26	4.6	3.0
	CEFTAZIDIME	1	60	0.06	0.06
	MOXALACTAM	4	101	≤0.12	0.16
	CARBENICILLIN	1	33	0.78	0.78
	PIPERACILLIN	3	101	≤ 0.41	≤ 1.33
	TICARCILLIN	4	121	0.68	≥ 14.0
	TOBRAMYCIN	2	38	0.86	3.0
PROTEUS SPP. INDOLE (+)	MKO787	17	386	1.8	3.3
	CEFOPERAZONE	5	82	1.5	6.5
	CEFOTAXIME	11	318	≤ 0.04	0.4
	CEFOXITIN	6	215	4.3	> 15.0
	CEFTAZIDIME	4	60	0.12	0.21
	MOXALACTAM	10	265	0.11	0.20
	PIPERACILLIN	5	95	0.77	6.0
	TICARCILLIN	8	110	≥4.5	≥ 48.0
	AMIKACIN	4	38	2.3	5.8
PSEUDOMONAS AERUGINOSA	MKO787	12	590	1.5	4.9
	CEFOPERAZONE	5	254	3.9	22.4
	CEFOTAXIME	7	372	12.2	≥ 43.4
	CEFTAZIDIME	1	59	2.0	4.0
	CEFTIZOXIME	1	100	64.0	> 64.0
	MOXALACTAM	8	389	13.0	≥ 42.4
	CARBENICILLIN	4	198	75.0	563.0
	PIPERACILLIN	4	230	5.2	19.6
	GENTAMICIN	5	237	2.3	≥ 11.0
	TOBRAMYCIN	4	138	1.4	10.2
BACTEROIDES FRAGILIS	MKO787	5	345	0.15	0.4
	CEFOTAXIME	2	47	4.81	≥ 25.0
	CEFOXITIN	4	203	3.3	20.2
	MOXALACTAM	4	180	0.6	4.8
	CHLORAMPHENICOL	1	100	4.0	8.0
	CLINDAMYCIN	2	156	≤ 0.47	1.6
	METRONIDAZOLE	1	56	0.5	1.0

I = # OF INVESTIGATORS
N = # OF STRAINS EXAMINED

TABLE 6

MISCELLANEOUS SPECIES: SUSCEPTIBILITY TO MK0787

	N	GEOMETRIC MEAN MIC 90
AEROBES - GRAM-POSITIVE		
LISTERIA MONOCYTOGENES	11	0.125
MYCOBACTERIUM AVIUM - INTRACELLULARE	15	0.2(MIC 70)
NOCARDIA ASTEROIDES	8	1.56
AEROBES - GRAM-NEGATIVE		
ACINETOBACTER SPP	64	0.24
ALCALIGENES SPP	33	2.0
BRUCELLA MELITENSIS	98	2.0
HAEMOPHILUS INFLUENZAE	173	1.9
MORAXELLA SPP	28	0.125
NEISSERIA GONORRHOEAE	111	0.13
NEISSERIA MENINGITIDIS	93	0.04
SHIGELLA SPP	22	0.20
YERSINIA ENTEROCOLITICA	10	0.5
ANAEROBES - GRAM-POSITIVE		
CLOSTRIDIUM DIFFICILE	47	2.9
CLOSTRIDIUM PERFRINGENS	15	4.0
CLOSTRIDIUM SPP	100	0.25
EUBACTERIUM SPP	6	2.0
PEPTOCOCCUS SPP	49	0.07
PEPTOSTREPTOCOCCUS SPP	32	0.14
ANAEROBES - GRAM-NEGATIVE		
CAMPYLOBACTER FETUS SS. JEJUNI	36	0.03
CAMPYLOBACTER FETUS SS. INTESTINALIS	4	0.19
EIKENELLA CORRODENS	28	0.25
FUSOBACTERIUM SPP	57	0.5
VEILLONELLA SPP	23	0.25

SUSCEPTIBILITY DATA RECEIVED FROM NON-MERCK INVESTIGATORS. ON FILE AT MERCK SHARP & DOHME RESEARCH LABORATORIES, RAHWAY, NJ

TABLE 7

Susceptibility of MK0787 (N-Formimidoyl thienamycin) to
Wild Type (W.T.) and Multiply Resistant Clinical Isolates

	I	N	GEOMETRIC MEAN MIC90 mg/ml
Gram-Positive			
Staphyloccus aureus (W.T.)	22	1063	$\leq$ 0.06
Staphylococcus aureus (Pen-R)	5	110	0.08
Enterococci	20	795	1.58
Nocardia asteroides	3	45	2.66
Mycobacterium avium	2	22	0.48 (MIC$_{70}$)
Mycobacterium fortuitum	1	12	12.5
Gram Negative			
Pseudomonas aeruginosa (W.T.)	31	2278	3.54
Pseudomonas aeruginosa (A*-R)	9	317	3.80
Escherichia coli (W.T.)	22	1122	$\leq$ 0.26
Escherichia coli (Gen-R)	4	41	$\leq$ 0.70
Acinetobacter spp.	14	436	0.47
Campylobacter fetus	3	92	$\leq$ 0.07
Bacteroides fragilis	4	906	$\leq$ 0.33

I = Number of independent investigators
N = Number of clinical isolates tested
*A = Aminoglycosides, eg. Gentamicin, Amikacin, Tobramycin

TABLE 8

Comparative Activities Against Streptococcus faecalis Isolates
(n = 89)

Antibiotic	N	Geometric Mean MIC90, mg/ml
MK0787	89	0.9
Piperacillin	35	4.0
Cephalothin	54	32.0
Cefotaxime	89	> 128.0
Cefoperazone	89	34.3
Ceftazidime	54	> 128.0
Moxalactam	89	> 128.0
Cefsulodin	54	> 128.0
Ceftriaxone	54	> 128.0
Ceftizoxime	54	> 128.0
Cefuroxime	54	> 128.0
Gentamicin	35	15.0

TABLE 9

MK0787 Activity Against P. aeruginosa Isolates
Resistant to One or More Aminoglycosides or Penicillins

Antibiotic	No. of Isolates	MK0787 MIC90, mg/ml
Tobramycin (MIC ≥ 8)	15	8
Gentamicin (MIC ≥ 8)	65	4
Amikacin (MIC ≥ 32)	26	8
Azlocillin (MIC ≥ 128)	28	4
Ticarcillin (MIC ≥ 128)	29	8
	163	5.4 (Geom. Mean)

TABLE 10

Comparative Activities Against GEN-S and GEN-R P. aeruginosa Strains

Antibiotic	GEN-S, n = 29 MIC_{90}, mg/ml	GEN-R, n = 34 MIC_{90}, mg/ml
MK0787	2	8
Gentamicin	4	32
Amikacin	8	64
Tobramycin	2	8
Moxalactam	32	64
Cefoperazone	32	32
Cefotaxime	64	128
Piperacillin	16	32

TABLE 11   P

Carbenicillin-R. Pseudomonas aeruginosa Isolates

Cumulative Percentage (N = 20)
MIC, mg/ml

Antibiotic	3.13	6.25	12.5	25	50	100
MK0787	90	95	100			
Piperacillin			20	60	80	85
Cefotaxime					20	75
Moxalactam						5

TABLE 12

Comparative Activity Against Campylobacter fetus, supp. jejuni
n = 6

Antibiotic	MIC$_{90}$,mg/ml
MK0787	0.03
Ampicillin	4.0
Moxalactam	16.0
Cefotaxime	4.0
Erythromycin	0.5
Chloramphenicol	4.0
Rifampin	≥ 128.0
Cefoperazone	≥ 128.0
Vancomycin	≥ 128.0

TABLE 14

Comparative Activity Against Acinetobacter spp.
n = 14

Antibiotic	MIC$_{90}$,mg/ml
MK0787	0.25
Amoxicillin	32.0
Cefotaxime	16.0
Moxalactam	64.0
Ceftazidime	8.0
Ticarcillin	32.0

TABLE 14

Comparative Activity Against Bacteroides fragilis Isolates
n = 100

Antibiotic	MIC$_{90}$, mg/ml
MKC787	0.25
Moxalactam	4.0
Piperacillin	64.0
Mezlocillin	128.0
Carbenicillin	> 256.0
Ticarcillin	> 256.0
Azlocillin	> 256.0
Cefoxitin	16.0
Cefotaxime	256.0
Cefoperazone	256.0
Cefamandole	> 256.0
Clindamycin	1.0
Metronidazole	1.0
Chloramphenicol	4.0

TABLE 15

Susceptibility Reference List of MK0787 (N-Formimidoyl Thienamycin)

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC50	MIC90
Achromobacter Vd:				
Achromobacter Vd-1, Vd-2		10	2.0	2.0
Achromobacter xylosoxidans		7	2.0	4.0
Actinomyces spp.				
Actinomyces odontolyticus		5	0.06	0.13
Acinetobacter spp.	-	436	≤ 0.22	0.47
Acinetobacter calcoaceticus				
Acinetobacter calcoaceticus anitratus				
Acinetobacter calcoaceticus lwoffii				
Acinetobacter calcoaceticus haemolyticus				
Acinetobacter calcoaceticus alcaligenes				
Aeromonas hydrophilia	-	5	0.05	0.10
Alcaligenes spp.	-	86	≤ 0.97	2.04
Alcaligenes faecalis				
Bacteroides spp.	-	997	≤ 0.08	≤ 0.33
Bacteroides fragilis				
Bacteroides disiens				
Bacteroides distasonis				
Bacteroides melanin. melaninogenicus				
Bacteroides oralis				
Bacteroides ruminocola brevis				
Bacteroides thetaiotaomicron				
Bacteroides vulgatus				
Bacteroides ovatus				
Bacteroides uniformis				
Bordetella bronchicanis	-	13	4.0	4.0
Brucella melitensis	-	98	1.0	2.0
Campylobacter spp.	-	92	≤ 0.07	≤ 0.07
Campylobacter fetus jejuni				
Campylobacter fetus intestinalis				
Citrobacter/Salmonella	-	370	≤ 0.30	0.62
Citrobacter freundii				
Citrobacter diversus				
(Arizona hinshawii included)				
Clostridia spp.	+	292	≤ 0.31	≤ 1.14
Clostridium septicum				
Clostridium difficile				
Clostridium perfringens				
Clostridium bifermentans				
Clostridium botulinum				

TABLE 15 (CONT'D)

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC$_{50}$	MIC$_{90}$
Chlamidia trachomatis		7	Geom. Mean cidal level =	27.8
Corynebacterium sp.	+	4	> 32.0	> 32.0
E. coli	-	1122	≤ 0.14	≤ 0.26
Eikenella corrodens	-	56	0.15	0.22
Enterobacter spp.	-	1276	0.34	1.30
Enterobacter cloacae				
Enterobacter aerogenes				
Enterobacter agglomerans				
Erysipelothrix rhusiopathiae	+	2	≤ 0.02	≤ 0.02
Eubacterium sp.	+	6	≤ 0.06	2.0
Flavobacterium spp.	-	23	≤ 2.17	20.0
Flavobacterium IIb				
Fusobacterium sp.	-	57	0.03	0.50
Gardnerella vaginalis	-	25	-	0.50
Haemophilus influenzae		302	0.95	1.82
Hafnia spp.	-	14	≤ 0.28	≤ 0.46
Hafnia alvei				
Klebsiella spp.	-	952	0.18	0.41
Klebsiella pneumoniae				
Klebsiella oxytoca				
Listeria monocytogenes	+	36	≤ 0.08	0.11
Moraxella spp.	-	37	≤ 0.08	0.37
Moraxella osloensis				
Mycobacterium avium intracellulare	-	22		0.48 (MIC$_{70}$)
Mycobacterium fortuitum	+	12	3.12	12.50
Neisseria gonorrhoeae	-	387	≤ 0.10	≤ 0.30
Neisseria meningitidis	-	266	0.05	0.11
Nocardia spp.	+	45	≤ 1.15	2.66
Nocardia asteroides				
Pasteurella multocida	-	10	0.50	1.00
Peptococcus/Petostreptococcus	+	87	≤ 0.02	≤ 0.06
Peptococcus asaccharolyticus				
Peptococcus magnus				
Plesimonas shigelloides	-	15	≤ 0.13	0.25
Propionibacterium acnes	+	26	0.01	0.02
Proteus/Providencia spp.	-	1655	1.30	2.90
Proteus vulgaris				
Proteus mirabilis				
Proteus morganii				
Proteus rettgeri				
Prov. stuartii				
Staphylococcus aureus	+	1290	≤ 0.07	≤ 0.13
Staphylococcus epidermidis	+	509	≤ 0.09	≤ 1.33

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC50	MIC90
Pseudomonas spp.	-	2278	1.57	3.54
Pseudomonas aeruginosa				
Pseudomonas acidovorans				
Pseudomonas putrefaciens				
Pseudomonas stutzeri				
Pseudomonas fluorescens				
Pseudomonas cepacia		40	4.5	> 50.0
Pseudomonas maltophilia		118	> 64.0	> 128.0
Rhodococcus spp.	-	11	$\doteq$ 0.39	0.39
Serratia spp.	-	806	$\leq$ 0.76	1.93
Serratia marcescens				
Shigella sp.	-	33	0.17	0.27
Streptococcus spp. (Grps. A,B,C,G)	+	1293	$\leq$ 0.03	$\leq$ 0.05
Streptococcus agalactiae				
Streptococcus pneumoniae				
Streptococcus durans				
Streptococcus pyogenes				
Streptococcus bovis				
Viridans streptococci	+	51	$\leq$ 0.06	$\leq$ 0.11
Streptococcus faecalis (Grp. D)	+	795	0.93	1.58
Streptococcus faecium	+	30	20.0	78.0
Veillonella spp.	-	23	0.05	0.25
Veillonella parvula				
Yersinia spp.	-	234	$\leq$ 0.23	0.44
Yersinia enterocolitica				
Yersinia pseudotuberculosis				

Outstanding in-vitro potency is observed against gram-postive, gram-negative, aerobic and anerobic organisms. Worthy of particular note is the potent activity against P. aeruginosa, Serratia, Bacteroides, and enterococci organisms.

That imipenem is resistant to nearly all bacterial beta-lactamases has been confirmed in several of these studies. Thus, imipenem lacks cross-resistance with any other clinical or experimental antibiotic presently available. The only exceptions to the outstanding antimicrobical activity of imipenem are as follows: Pseudomonas maltophilia is the only organism which is fully resistant to imipenem. Although a large portion of methicillin-resistant S. aureus strains are susceptible to the antibiotic, these isolates do show a wide distribution of susceptibilities in contrast to wild-type strains which show a narrow distribution with low MICs (<0.1 mcg/ml). A portion of the methicillin-resistant S. aureus strains are considered resistant to imipenem (MIC>8 mcg/ml). Occasionally, strains of S. epidermidis have been found to have high MICs; again, the majority of isolates have an MIC of < 0.1 mcg/ml.

Combinations of imipenem and aminoglycosides have been reported to be synergistic against several bacterial species, such as multiply-resistant P. aeruginosa, S. faecalis, L. monocytogenes, and Serratia species. The degree of synergy achieved varies with the aminoglycoside used in combination. A lack of synergy against some organisms was in most instances attributable to the efficiency of killing by imipenem alone. Antagonism between combinations of imipenem and aminoglycosides has not been observed. Kallick and associates measured the interaction of imipenem with aminocyclital antibiotics against numerous strains of P. aeruginosa and S. aureus isolated from patients with endocarditis. Imipenem in combination with tobramycin was rapidly bactericidal (e.g., 1000 - fold reduction in 4h), a marked improvement over a carbenicillin plus tobramycin combination observed for all strains of P. aeruginosa tested. Similarly the killing rates for imipenem plus tobramycin against S. aureus were significantly enhanced compared to those of individual antibiotics. Gombert and associates reported on the synergistic interaction of imipenem with amikacin and gentamicin against Streptococcus faecalis. Sixty percent of the synergistic combinations were totally bactericidal (produced sterile cultures) at 24 h.

Efficacy Studies in Experimental Infections in Animals.

Drs. D. Durack and J. Perfect of Duke University demonstrated therapeutic levels of imipenem in the cerebrospinal fluid (CSF) of rabbits with inflamed and uninflamed meninges. They also demonstrated that excellent bactericidal and inhibitory titers in plasma and CSF of rabbits are achievable against both methicillin-sensitive and methicillin-resistant clinical isolates of Staphylococcus aureus. Dr. George McCracken, Jr., at the University of Texas Health Science Center in Dallas has confirmed this work.

In a 1982 publication, Drs. McCracken and Putamasucon report that imipenem penetrates the CSF of rabbits with inflamed meninges, experimentally infected with Escherichia coli.

Three studies to measure the effectiveness of imipenem in the treatment of polymicrobial intraperitoneal infections in the rat have been performed; one by Drs. T. Hau and Reid Nishikawa, the others by Dr. A. Onderdonk at Tufts University, and Drs. Nord and Lahnburg at the National Bacteriological Laboratory in Stockholm, Sweden.
The results of these studies indicate significant survival and cure rates, as well as substantial reductions in abscess formation as a result of imipenem treatment.

Dr. J. Pennington from the Peter Bent Brigham Hospital in Boston reported on the excellent survival rates (70-75%) observed in his experimental pneumonia model in guinea pigs. In this animal model, imipenem was the only beta-lactam antibiotic that matched the effectiveness of aminoglycosides against Pseudomonas aeruginosa. Further, Drs. D. Johnson nd S. Schimpf of the V.A. Medical Center and University of Maryland School   Medicine found that imipenem provided effective therapy of lethal Pset ionas infections in neutropenic rats.

Data, from Dr. L. Guze's laboratory at the Wadsworth (V.A.) Medical Center in Los Angeles, describing the therapeutic effectiveness of the imipenem/cilastatin combination in a hematogenous pyelonephritis model in rats demonstrated the excellent efficacy achieved with imipenem in this animal model against both methicillin-sensitive and methicillin-resistant clinical isolates.

Imipenem was also evaluated for its potential in the treatment of bacterial endocarditis in rat and rabbit models. Dr. M. Scheld of the University of Virginia reported that imipenem was significantly more rapid and potent in its bactericidal action than nafcillin against strains of S. aureus isolated from endocarditis patients. This investigator also observed excellent activity of imipenem against a clinical isolate of S. faecalis in the same endocarditis rabbit model. In this study, imipenem, as a single agent, was equivalent to penicillin plus gentamicin therapy.

The effectiveness of imipenem, as a single agent in the treatment of endocarditis due to S. faecalis isolates expressing tolerance to this antibiotic (MIC 1.56, MBC 128 mcg/ml) was explored by Drs. Auckerthaler and Wilson at the Mayo Clinic. In the rabbit model, designed to simulate streptococcal prosthetic valve infections in man, the activity of imipenem (administered at 20 mg/kg) was found to be equal to procaine penicillin (administered at 720 mg/kg) but less active than a combined dose of procaine penicillin plus gentamicin.

Dr. Anthony Chow and his associates at the Department of Ophthalmology, University of British Colombia, Canada, reported on the intrathecal penetration of imipenem when administered alone or in combination with cilastatin sodium in normal rabbits. Imipenem penetrated uninflamed meninges, and peak concentrations were significantly increased by coadministration of cilastatin sodium.

Overall, the results of these animal studies reflect the excellent spectrum of antibacterial activity of imipenem and confirm the in-vitro susceptibility data. The ability of this antibiotic to penetrate body tissues and the CSF has been established from the animal studies.

Lack of Antibacterial Activity of Cilastatin

The lack of antibacterial activity of cilastatin was demonstrated by use of the sensitivity disk method, as well as by measuring the minimal inhibitory concentration (MIC) using the broth dilution (Mueller-Hinton) Microtiter technique. Cilastatin was tested against nine bacterial strains made up of five different genera (S. aureus, E. coli, Enterobacter, K. pneumoniae, P. aeruginosa).
Cilastatin showed no antibacterial activity at 10 mcg/ml (the highest level tested) against any of the nine strains.
In addition, a combination of imipenem and cilastatin in a ratio of 1: 6.25 was tested. No sign of synergistic activity was observed. No significant antagonism occurred -- only an occasional tube upward shift of the MIC for imipenem was observed.

Lack of antibacterial activity of cilastatin and lack of interference with the activity of imipenem was also demonstrated in disk diffusion studies where the individual components, at concentration of 25 mcg/disk of imipenem and 50 mcg/disk of cilastatin, and a combination of the two agents in a ratio of 2:1 (cilastatin : imipenem), were measured for antibacterial potency against 41 bacterial strains selected from 10 species (S. aureus, enterococcus, E. coli, Shigella species, Salmonella species, Enterobacter species, Klebsiella species, Serratia species, Proteus species, Providencia species, and Pseudomonas species). Again, no synergistic activity or antagonism was observed when the agents were combined.

Metabolism of Imipenem

Thienamycin and its derviative imipenem undergo extensive, species-variable metabolism as measured by the low urinary recovery of antibiotic.
Measures of the systemic bioavailability of thienamycin and imipenem, such as half-life and AUC, compare favorably (in the mouse, rabbit, dog, and chimpanzee) with those of nonmetabolized antibiotics and to those that undergo only minor metabolism.

However, the renal clearance rats were unusually low. In the dog, the renal clearance of imipenem was 0.49 ml/min/kg which is far below the glomerular filtration rate for this animal (4.9 ml/min/kg). An analogous low rate of renal clearance of imipenem was observed in the chimpanzee, a species having a similar excretion pattern to man.

This low renal clearance rate suggests that the antibiotic is destroyed during the process of excretion.
The major role of the kidney in metabolism was confirmed by the finding of prolonged plasma levels of antibiotic following bilateral ligation of the renal arteries in the rat and the rabbit.

Subsequent biochemical studies demonstrated that the bulk of metabolic inactivation results from the hydrolysis of the beta-lactam ring in imipenem by a renal dipeptidase. This enzyme was originally described 40 years ago and given the name Dehydropeptidase-I (DHP-I).

The subcellular localization of Dehydropeptidase-I on the lumenal surface (the brush-border) of the proximal renal tubular epithelium accounts for its impact on the disposition of imipenem. It has access to the antibiotic both in the glomerular filtrate and in the transcellular flux mediated by the secretory process between the blood and the lumen of the nephron.
In both cases, the antibiotic has effectively been cleared from the plasma by processes preceding, and independent of, the metabolic events that occur while it is in transit to the urine. Thus, systemic persistence is insulated from the major site of metabolism, whereas urinary tract bioavailability of the antibiotic is greatly reduced.

Clinical pharmacology studies in normal volunteers have confirmed the presence of extensive metabolism of imipenem similar to laboratory animals and particularly to the chimpanzee. The experience with imipenem in man is, therefore, entirely analogous to that observed in most animal species tested; while systemic bioavailability is adequate, urinary tract bioavailability may be inadequate.

This deficit in urinary tract bioavailability of imipenem could in principle be compensated for by increasing the dose rate and frequency of administration. However, in view of the nephrotoxic potential of the antibiotic, this approach would decrease the available safety margin. An alternative strategy, as described below, was to coadminister a selective inhibitor of the enzyme responsible for metabolism of the antibiotc.

Development of Cilastatin

Several compounds, selected on the basis of their chemical homology with dehydropeptidase, were screened for inhibitory action against a purified preparation of porcine renal DHP-I.

The compound selected from the screen was benzoyl-NH_2-2- acrylate.
Systemic chemical modification resulted in homologs with inhibitory constants
(K_I) < 0.03 mcM, a 1000-fold increase over the lead compound. These
inhibitors also exhibited a comparable potency against DHP-I purified from
human kidney.
The mechanism of inhibition was found to be competitive and reversible. The
specificity of several inhibitors of DHP-I was demonstrated by their lack of
significant inhibitory activity against several other zinc metalloenzyme
peptidases (Carboxypeptidase-A, Carboxypeptidase-B, leucine - amino-peptidase
and Acylase-I).

Inhibitors at 1 to 4 mg/kg, coadministered with imipenem, dramatically
increased the urinary recovery of the antibiotic, particularly in larger
animal species. For example, in the chimpanzee urinary recovery increased
from an average of 13.5% to 65-76%.

Enhanced urinary recovery is a necessary, but not sufficient, criterion of
efficacy for the inhibitors of antibiotic metabolism. The ideal inhibitor
must remain in the circulation at effective levels during an appreciable
fraction of the period that will elapse before the next dose is administered.
The desired goal of prolonged action was initially met by increasing the
length of the C_3 substituent, good activity being found with the n-pentyl
analog.
This inhibitor, MK-0789, was the predecessor to MK-0791 (cilastatin sodium).

Although well tolerated by 15 volunteers who received it, MK-0789 was
subsequently found to produce unacceptable local irritation in laboratory
animals. This local irritation phenomenon was attributed to the lipophilic
substituents of this inhibitor.
Effort turned to the synthesis of analogues whose long duration of action
would not depend upon lipohilic substituents.

With MK-0791 (cilastatin sodium), prolonged action was achieved by
introduction of a zwitterionic substituent, L-cysteine, which decreases the
rate of plasma clearance resulting from renal secretion. The in-vitro potency
of this inhibitor (0.11 mcM) is somewhat less than that of MK-0789 (0.08 mcM);
however, this slightly lower potency is offset partially by the much reduced
plasma binding of this agent (42% vs 96% for MK-0789).
An additional advantage of cilastatin sodium is its relative metabolic
stability. Only 30% of cilastatin sodium is metabolized in the Rhesus monkey
and the chimpanzee. Further, the N-acetyl metabolite that is formed from
cilastatin sodium is somewhat more potent in-vitro than the parent compound.
The acetylated compound is found primarily in the urine suggesting that
acetylation occurs during excretion.

Coadministration of 2 or 4 mg/kg of cilastatin sodium with 5 mg/kg of imipenem
in the chimpanzee resulted in urinary recoveries for imipenem of 63 and 75%,
respectively (vs 13% in controls).

Cilastatin sodium was well tolerated both in acute and subacute toxicity studies. Importantly, no evidence of local irritation has been detected with its use.

Prevention of Nephrotoxicity of Imipenem by Coadministered Dehydropeptidase

Single large doses of imipenem induce proximal tubular necrosis in the rabbit at doses over 90 mg/kg and in the Rhesus monkey at doses of 180 mg/kg. Cephaloridine (a beta-lactam molecule resembling imipenem) produces a histomorphologically similar tubular lesion in the same two species. The mechanism of renal toxicity must be quite different for the two compounds. In the case of cephaloridine, nephrotoxicity has been correlated with high intracortical concentrations of intact antibiotic. They result from active anionic pumping of this agent into the proximal tubular epithelium followed by slow egress. With imipenem, however, the intact antibiotic does not accumulate to an appreciable extent within the tubular epithelium since the fraction transported into tubule from the plasma appears to be almost completely metabolized by DHP-I. Further, upon addition of low levels of dehydropeptidase inhibitors, transported fraction appears to be free to pass through the tublar epithelium and enter the lumen of the nephron. Therefore, imipenem is subject to conventional, net secretion and does not accumulate when protected from metabolism. On the premise that degradates resulting from hydrolysis of imipenem by DHP-I might be trapped in the epithelium and cause nephrotoxicity, inhibitors of DHP-I were coadministered with large nephrotoxic doses of imipenem. The result showed that nephrotoxicity was, in fact, prevented. Control studies revealed, however, that the prevention of nephrotoxicity results not from inhibition of DHP-I but from competitive exclusion of the antibiotic from the cell at the level of transport.

Imipenem Metabolites and Their Role in Nephrotoxicity

In experiments using radiolabeled imipenem, it was observed that good recovery of total radioactivity could be obtained in the rat and rabbit. The residual radioactivity remaining in kidneys of these animals was only a small fraction of the total recovered radioactivity. However, the difference between the residual label in the kidneys of the rat compared to the rabbit was striking. The rabbit, in which nerphrotoxicity can be induced by high levels of imipenem, had about ten-fold more residual label than did the kidneys of the rat, in which renal toxicity cannot be induced with imipenem. Analyses of the rabbit kidney cortex homogenates for intracellular degradates by liquid chromatography revealed four metabolites which retain the radioactiv+y from radiolabeled imipenem. Metabolite 1 was identified as the DHP-I hydrolysis products. Its accumulation was prevented by coadministration of DHP-I inhibitors with the radiolabeled imipenem.

Metabolite II, a minor component, arises during the the DHP-1 activity or
spontaneously from Degradate I.
Its identity remains unknown, but because of its very low concentration, it
probably has no role in nephrotoxicity.
The role of Metabolites III and IV may be more important.
They were identified as cysteine adducts that are generated independent of
DHP-I action and Degradate I. Degradate IV results from the conjugation of
imipenem with L-cysteine of glutathione; IV gives rise to Degradate III
spontaneously.
Upon intravenous injection, all four metabolites can gain entry into renal
cortical tissue, but they do not induce nephrotoxicity at levels where
imipenem causes renal damage. Thus, the metabolites per se are not
nephrotoxic.
Since imipenem is secreted when its metabolism is blocked by DHP-I inhibitors,
or is so rapidly metabolized in the tubular cell in the absence of inhibitor,
it per se cannot be the nephrotoxic agent.

The agent responsible for the nephrotoxicity of imipenem when administered
alone has yet to be identified.
What is clear at this point is that cilastatin sodium prevents the
nephrotoxcity of imipenem in animal models by excluding the antibiotic
competitively at the secretory site, thereby preventing its entry into the
tubular cells, the site of nephrotoxicity.

Physiological Disposition of Radiolabeled Imipenem

The disposition of intact drug and radioactivity was studied in the Rhesus
monkey, rabbit, rat, and man following intravenous dosing with radiolabeled
imipenem administered separately or in combination with an equal dose of
nonradioactive cilastatin sodium. Doses of 5, 10, 20, or 40 mg/kg of either
drug entity were given to animals; in humans, the dose was 500 mg of
radiolabeled imipenem alone or in combination with 500 mg of cilastatin sodium.

Renal excretion was the major mechanism for the elimination of drug-related
material following radiolabeled imipenem (^{35}S or ^{14}C) dosing. Except for
the rat, greater than 85% of the radioactive dose was recovered in the urine
within six hours in all species.
Cilastatin sodium coadministered did not alter the excretion profiles of
radioactivity. Negligible quantities of radioactivity were recovered in the
feces.
In man, the urinary recovery of intact imipenem was 20% of the dose when given
alone and increased to 70% when cilastatin sodium was coadministered.

The corresponding renal clearance estimates of imipenem were 74 and 182 ml/min.

High pressure liquid chromatographic analysis indicated that greater than 95%
of the human urinary radioactivity was associated with intact imipenem and
Metabolite I.

Combined radiometric and chromatographic analysis further established that greater than 80% of the human urinary radioactivity was Metabolite I when imipenem was given alone, while 70% of the dose was identified as intact imipenem when cilastatin sodium was coadministered.
In the case of the rat, rabbit, and Rhesus monkey, the majority of the urinary radioactivity chromatographed in the same region as imipenem and Metabolite I. Other minor radioactive fractions were observed at retention volumes corresponding to the cysteine adducts.

In all species, the plasma levels of radioactivity disappeared rapidly; in addition, AUCs of plasma radioactivity were similar for a given species when imipenem was given alone or in combination with cilastatin sodium. In man, it was shown that cilastatin sodium coadministration increased the plasma clearance of intact imipenem by 20%.

In tissue distribution studies with rats, radioactivity derived from imipenem was distributed primarily in the kidneys and the liver. The rapid disappearance profile of radioactivity from these tissues was analogous to the plasma concentration vs time profiles. Analysis of selected tissues for intact imipenem and Metabolite I demonstrated that cilastatin sodium drastically increased the levels of intact imipenem and decreased the Metabolite I levels in these tissues. In general, the disappearance of imipenem and Metabolite I from the tissues paralleled the disappearance of these compounds from the plasma.

Physiological Disposition of Radiolabeled Cilastatin Sodium

The disposition of cilastatin sodium and radioactivity was studied in the Rhesus monkey, rabbit, rat, dog, and man following intravenous dosing with radiolabeled cilastatin sodium administered separately or in combination with an equal dose of nonradioactive imipenem. Doses of 5, 10, or 40 mg/kg of either drug entity were given to animals; in humans, the dose was 250 mg of radiolabeled cilastatin sodium alone or in combination with 250 or 1000 mg of imipenem.

In the monkey, rabbit, and man, renal excretion was the sole mechanism for the elimination of cilastatin sodium drug-related materials; negligible levels of radioactivity were detected in the feces.
Feces excretion of radioactivity was significant in the rat (>40%) and somewhat less in the dog.
Biliary excretion was significant in the rat, and evidence was obtained for enterohepatic recycling.

Imipenem did not alter the excretion of intact cilastatin sodium. The amount excreted into the urine was 15% for the rabbit, 45% for the monkey, and 77% for man, whether or not imipenem was coadministered. For a given species, renal clearances of intact cilastatin sodium are similar between treatments;

the values for the rabbit, monkey, and man are estimated to be 10,30, 180 ml/min, respectively. In man, N-acetyl-cilastatin sodium accounted for 10% of the dose in the presence or absence of imipenem.

Plasma radioactivity levels decreased rapidly in all species; greater than a 100-fold reduction occurred within six hours with or without the coadministration of imipenem.

There was no accumulation of radiolabeled material by rat tissues. Liver, kidney, and small intestine gave the highest tissue-to-plasma ratios. Although the levels were high in the early time periods, the tissue concentrations of radioactivity decreased rapidly, concomitant with the decrease in plasma radioactivity.
Parallel studies conducted following coadministration of unlabeled imipenem resulted in no significant change in the disposition profile of radioactivity.

Imipenem did not alter the renal excretion or plasma clearance of intact cilastatin sodium in any of the species studied. In man, no change was noted in the extent of the N-acetyl conjugate that formed.

HUMAN PHARMACOKINETICS

Human clinical studies have been conducted in healthy volunteers to define the disposition of imipenem and cilastatin when administered separately and when administered as a mixture.

Imipenem - Single-Dose Kinetics: The single-dose pharmacokinetics of imipenem administered alone has been investigated at intravenous doses ranging from 100 mg to 1000 mg in healthy male volunteers. The drug was administered as bolus intravenous injection or as a 20 minute constant rate infusion. These studies also provided the opportunity to evaluate the variability of imipenem urinary excretion between subjects and within subjects on different occasions, as well as the effect of probenecid on imipenem disposition.

The urinary recovery of imipenem varied between individuals from 6% to 38% of the administered dose but remained constant with a subject receiving imipenem on separate occasions. The renal clearance of the drug showed similar variance, ranging from 12.7 to 96.5 ml/min, although for a given individual incremental renal clearance was comparable day-to-day. Plasma clearance, however, was similar to all dosage levels and between subjects averaging between 211 and 238 ml/min. Total area under the plasma concentration time curve (AUC) increased proportionately with dose. Individual plasma clearance and total AUC were also consistent on a day-to-day basis.

It was also noted that human volunteers could be evenly divided between those that excreted less than 16% of an imipenem dose in urine (low excretors) and those that excreted more than 16% of the dose (high excretors).

Based on individual imipenem plasma concentration and urinary excretion data
gathered in these studies, it was shown that the disposition of imipenem was
adequately described by a two compartment open model with elimination
occurring from the central compartment only. On the average the plasma
half-life of imipenem is 1 hour at all dose levels, and the volume of
distribution of the drug is 11 liters.

When an oral 1.0 g dose of probenecid was administered 10 hr and again 1 hr
before an intravenous 250 mg dose of imipenem, the urinary recovery of the
antibiotic decreased from 18.5% to 13.7% of the dose while renal clearance
dropped from 42.5 to 27.8 ml/min. Total AUC increased slightly as plasma
clearance decreased from 226 to 200 ml/min. The plasma half-life remained at
1 hour.

Imipenem - Multiple Dose Kinetics

The multiple dose pharmacokinetics of imipenem were assessed in healthy
volunteers who received 250 mg of imipenem every 8 hours, or 500 mg every 8
hours. All doses were administered as 20-minute constant rate intravenous
infusions.

As noted in the single dose studies, renal clearance varied by as much as a
factor of 3 between individuals but was constant from dose-to-dose for a given
individual. Also, the AUC did not change dose-to-dose for a given individual,
showed little variability between individuals given the same imipenem dose,
and was proportional to the imipenem dose. The plasma clearance of imipenem
was similar from dose-to-dose among individuals and was independent of dose
size. The plasma half-life averaged 1 hour.

In summary, when imipenem is administered alone intavenously at doses ranging
from 100 to 1000 mg to healthy volunteers, plasma concentrations of drug are
proportional to dose. The plasma clearance of imipenem is approximately 220
ml/min and its plasma half-life is 1 hour. The urinary excretion and renal
clearance of imipenem vary considerably between individuals ranging from 6% to
38% of the dose and from 13 to 97 ml/min, respectively. The disposition of
imipenem is adequately described by a two-compartment, open model with
elimination occurring from the central compartment only. Repeated
administration of imipenem every 8 hours does not alter the disposition of the
drug and no accumulation is observed.

Cilastatin Sodium

Single and multiple intravenous doses of cilastatin sodium have been
administered to parallel panels of healthy volunteers. One panel received 25,
100 and 500 mg single intravenous doses and then three 500 mg doses given at 8
hour intervals. The second panel received 50, 250 and 1000 mg single
intravenous doses and then three 100 mg doses given at 8 hour intervals.
Blood and urine samples were collected for 8 hours after the 50, 100 and 250
mg single dose treatment only. Blood samples were collected for 8 hours after
the first and third dose of repeated administration while urine was collected
for 8 hours following the first and second doses, and for 24 hours following
the third dose.

Results showed that, on the average, approximately 70% of the cilastatin dose was recovered in urine within 8 hours of administration be it after a single dose or after repeated administration. Plasma levels appear to increase in proportion to dose, and there was no drug accumulation upon 8 hour administration. The plasma half-life of cilastatin was determined to be approximately 45 minutes.

Primaxin - Single Dose Kinetics

Several studies have been conducted in healthy volunteers to determine the effect of imipenem or cilastatin on the disposition of each other following single intravenous dose administration.

In one study, ^{14}C-imipenem, 500 mg, was administered alone and with an equal dose of cilastatin sodium. In another, ^{14}C-cilastatin sodium 250 mg, was administered alone and with 250 mg and 1000 mg imipenem. All treatments were administered as 20-minute constant rate intravenous infusions. Study participants (4 subjects each) were evenly split amongst subjects who excrete less than 16% of an imipenem dose (low excretors) in urine when imipenem is administered alone and subjects who excrete more than 16% of an imipenem dose (high excretors) in urine.

As in previous studies, the intravenous administration of imipenem by itself resulted in low urinary recovery (a mean of 13% in low excretors and of 31% in high excretors) and variable urinary recovery (range of 12% to 42%). The individual renal clearance of the drug was also variable (range of 25 to 104 ml/min). Co-administration of an equal dose of cilastatin sodium brought urinary recovery of imipenem to a uniform 70-80% of the dose and renal clearance to approximately 160 ml/min. A slight increase in imipenem AUC, corresponding to about an 11% increase in plasma clearance, was also noted when cilastatin sodium was co-administered.

The disposition of imipenem when given intravenously with cilastatin sodium can also be adequately described by the same pharmacokinetic model previously described for imipenem administered alone.

Pharmacokinetic parameters for imipenem show no effect from the coadministration of cilastatin sodium except for the expected slight decrease in plasma clearance. The plasma half-life of the antibiotic remains 1 hour and the volume of distribution is 11 liters.

For cilastatin, coadministration of an equal or 4 times greater dose of imipenem had no effect on the disposition of cilastatin as observed after administration of cilastatin sodium alone. The urinary recovery of cilastatin averaged 77% of the dose while renal clearance average 148 ml/min. A two compartment open model also adequately describes cilastatin disposition following administration of cilastatin sodium alone or with imipenem. Regardless of the amount of imipenem coadministered, pharmacokinetic parameters for cilastatin remain unaffected. The plasma clearance of cilastatin was 195 ml/min, its plasma half-life was about 1 hour, and the volume of distribution was 9 liters. For all cilastatin parameters mentioned, little, if any, differences were noted between low and high imipenem excretors.

Two other studies have been conducted in healthy volunteers in which 250, 500 or 1000 mg doses of imipenem were administered alone or with various cilastatin doses ranging from 12.5 mg to 1000 mg. As noted in other studies, the urinary recovery of imipenem when administered alone was low averaging 13% of the dose in low imipenem excretors and 31% of the dose in high imipenem excretors. Variability in the renal clearance of the drug amongst subjects was also noted. However, once the imipenem/cilastatin dose ratio is 4:1 or less, the urinary recovery of imipenem stabilizes at approximately 70% of the dose for all subjects, and renal clearance of the drug is maintained at 130-140 ml/min. At imipenem/cilastatin dose ratios greater than 4:1, the urinary recovery and renal clearance of imipenem decrease, and the low and high excretor differences become apparent.

The plasma clearance of imipenem averaged approximately 220-240 ml/min when no cilastatin was coadministered and decreased slightly to approximately 190 ml/min at imipenem/cilastatin dose ratios of 4:1 or less. Total AUC for imipenem increased commensurately with this decrease in plasma clearance. The plasma half-life for imipenem was 1.0 hour regardless of the cilastatin dose.

At the higher cilastatin dose levels (250 mg and over), the plasma clearance of the inhibitor averaged 190-210 ml/min and appeared unaffected by coadministration of varying doses of imipenem. Total AUC increased in proportion to dose and the plasma half-life for cilastatin was generally about 1 hour. Varying the imipenem/cilastatin dose ratio from 4:1 to 1:4 had no effect on the disposition of cilastatin. The volume of distribution of cilastatin was 8-11 liters in all treatments.

In summary, the disposition of imipenem or cilastatin is independent of dose and is not affected by their coadministration. Cilastatin sodium inhibits the renal metabolism of the antibiotic. At the recommended ratio of 1:1, the plasma clearance of each drug is approximately 200 ml/min and the plasma half-life is nearly 1 hour. Renal clearance of imipenem is about 130 ml/min while that of cilastatin is about 150 ml/min.

Primaxin - Multiple Dose Kinetics

The multiple dose kinetics of imipenem and cilastatin have been studied in healthy volunteers following repeated administration of imipenem/cilastatin given every 6 hours.

At a dose of 1000 mg of each drug, the mean urinary recovery of imipenem was approximately 60% of the dose and renal clearance averaged 130 ml/min for 6 hours after the 1st, 17th, and 37th dose. The urinary excretion of cilastatin averaged 70% of the dose, and mean renal clearance was 143 ml/min after the 1st dose. Stabilized urine samples for cilastatin assay were not available after the 17th and 37th doses.

The plasma clearance of imipenem averaged approximately 210 ml/min in this study. The plasma half-life of imipenem throughout the study was approximately 1 hour. Little, if any, accumulation of imipenem was noted.

For cilastatin, plasma clearance averaged approximately 222 ml/min during all blood sampling periods. The plasma half-life of cilastatin was slightly less than 1 hour throughout the study. No accumulation of cilastatin was observed.

The results of two other studies, wherein 250/250 mg or 500/500 mg of imipenem/cilastatin was administered, confirmed the above findings.

In summary, repeated administration of 250/250 mg, 500/500 mg, or 1000/1000 mg of imipenem/cilastatin sodium every 6 hours does not affect the disposition of either drug. Little, if any, accumulation of either imipenem or cilastatin occurs, and pharmacokinetic parameters suggest that steady state is attained within the first day's dosing for either drug.

Special Studies

A. Effect of Probenecid: The effect of concomitant administration of probenecid on the plasma concentration and urinary excretion of imipenem and cilastatin was evaluated in healthy volunteers. Subjects received 500 mg imipenem alone (I.V. over 20 minutes), 500/500 mg imipenem/cilastatin (I.V. over 20 minutes), and 500/500 mg imipenem/cilastatin (I.V. over 20 minutes) preceded by two 1 gram oral doses of probenecid (1 gram 10 hours and 1 gram 1 hour prior to imipenem/cilastatin infusion). Inulin clearance was used to estimate the glomerular filtration rate (GFR).

The urinary excretion of imipenem averaged 12% and 32% of the dose in low and high imipenem excretors, respectively, when the antibiotic was administered alone. The renal clearance averaged 30 and 67 ml/min, respectively, in these two groups. The plasma clearance averaged approximately 230 ml/min, the volume of distribution averaged 10-11 liters, and the plasma half-life was 0.9 hour.

The coadministration of cilastatin increased the urinary recovery of imipenem to 66% of the dose and the renal clearance to 125 ml/min in all individuals. The plasma clearance decreased to 185 ml/min, and a concomitant increase in total AUC was observed. The volume of distribution and the plasma half-life of imipenem were not affected.

The concomitant administration of imipenem/cilastatin sodium and probenecid caused a decrease in the urinary recovery and renal clearance of imipenem to 55% of the dose and 88 ml/min, respectively. The plasma clearance of imipenem decreased to 159 ml/min resulting in a 16% increase in total AUC. The volume of distribution of imipenem remained 9 liters, and the plasma half-life was 1.1 hour.

The urinary recovery of cilastatin following I.V. administration of imipenem/cilastatin averaged 75% of the dose. Renal clearance was 173 ml/min. No difference was noted between low and high imipenem excretors. The plasma clearance averaged 218 ml/min, the volume of distribution was 9 liters, and the plasma half-life was 0.8 hour.

Addition of probenecid did not change the urinary recovery of cilastatin although the rate of excretion decreased as evidenced by a reduction in cilastatin renal clearance to 70 ml/min. Plasma clearance decreased to 89 ml/min resulting in a doubling of the total AUC and plasma half-life of cilastatin.

On the basis of individual determinations of GFR and that imipenem is 20% protein bound, it was shown that the net effect of renal tubular secretion and reabsorption of imipenem represents about 35% of imipenem renal clearance and that probenecid reduces this component to less than 10% of renal clearance.
Assuming that cilastatin completely inhibits the renal metabolism of imipenem, there still remains a non-renal component of imipenem elimination that represents 30-35% of imipenem plasma clearance. The contribution of this non-renal component increases to 45% of plasma clearance when probenecid is coadministered resulting in a decrease in the urinary recovery of imipenem. The effect of probenecid on the disposition of imipenem is minimal in comparison to the effect noted on other beta-lactam antibiotics.

The effect of probenecid on the disposition of cilastatin was more pronounced since renal clearance decreased from 173 to 70 ml/min, and plasma clearance decreased from 218 to 89 ml/min. As a result, the plasma AUC and the half-life of cilastatin doubled. Examination of the difference between plasma and renal clearance in both treatment situations revealed that the so-called "extra-renal" portion of cilastatin elimination decreased by a factor of 2.4 in the presence of probenecid. The parallel decrease in cilastatin plasma and renal clearance, as well as the 2.4 fold drop in the "extra renal" elimination of cilastatin indicate that not only is probenecid blocking the renal tubular secretion of cilastatin, but that this exclusion reduces the metabolic elimination of the drug. Hence, the "extra-renal" elimination of cilastatin appears to result from metabolism in the kidney and to be associated primarily with the secretory component of cilastatin excretion.

B.   Effect of Renal Insufficiency: The effect of renal insufficiency has been studied in patients with varying degrees of renal insufficiency. Subjects received imipenem or cilastatin sodium (250 mg) alone and imipenem/cilastatin (250/250 mg). Only the results from the imipenem/cilastatin treatment will be discussed since these are data representative of the clinical dosage form.

In patients with mild renal impairment (31 ml/min/1.73 m^2 < GFR ≤ 99 ml/min/1.73 m^2), the urinary recovery of imipenem averaged 44% of the dose and the mean renal clearance of the drug was 62 ml/min. The plasma clearance of imipenem dicreased to 147 ml/min, and the plasma half-life increased to 1.8 hours.

Mean urinary recovery decreased to 17% of the dose, and renal clearance of imipenem decreased to 15 ml/min in patients with moderate renal insufficiently (10 ml/min/1.73 $m^2 \leq$ GFR $\leq$ 30 ml/min/1.73 m^2). The plasma clearance of the drug dropped to 83 ml/min, while the plasma half-life increased to 2.7 hours.

For patients requiring hemodialysis who received imipenem/cilastatin between dialysis sessions, 2.9% of the imipenem dose was excreted in urine and the renal clearance of the drug was 1.6 ml/min. The plasma clearance averaged 62 ml/min and its plasma half-life increased to 3.4 hours.

In comparison to healthy volunteers, total AUC increased by a factor of 1.7 in patients with mild renal impairment, by a factor of 2.8 in patients with moderate impairment, and by a factor of 3.6 in patients requiring hemodialysis.

Hemodialysis removes imipenem from plasma bringing the plasma half-life of the drug back to 1-2 hours and plasma clearance to 184 ml/min.

The effect of renal impairment on the plasma levels and urinary excretion of cilastatin is more dramatic than that observed for imipenem. In patients with mild renal impairment, 65% of the cilastatin dose was recovered in urine, and renal clearance averaged 62 ml/min. The plasma clearance of cilastatin in these patients was slightly less than 100 ml/min, and the plasma half-life of the drug was 1.6 hours.

In patients with moderate renal impairment, mean urinary recovery of cilastatin decreased to 48% of the dose, and renal clearance decreased to 18 ml/min. The plasma clearance of the drug decreased to 36 ml/min, while the plasma half-life increased to approximately 4 hours.

For patients requiring hemodialysis who received imipenem/cilastatin between dialysis sessions, the urinary recovery of cilastatin averaged 18% of the dose, and its renal clearance was 2 ml/min. The plasma clearance of cilastatin was low in these patients, averaging 13 ml/min, and the plasma half-life increased to 12 hours.

In comparison to healthy volunteers, total AUC increased by a factor of approximately 2 in patients with mild renal impairment, by a factor of 6.5 in patients with moderate renal impairment, and by a factor of 15-16 in patients requiring hemodialysis.

The 15-fold decrease in cilastatin plasma clearance and resultant similar increase in total AUC between healthy volunteers and patients requiring hemodialysis strongly suggests that the extra-renal elimination of cilastatin results from kidney metabolism. This portion of cilastatin total elimination decreases as kidney function declines.

Cilastatin is cleared from blood by hemodialysis producing an increase in plasma clearance to 75 ml/min and reducing the plasma half-life of the drug to 2-3 hours.

The results of these studies show that the elimination of imipenem and
cilastatin decreases as the degree of renal impairment advances.
Cilastatin is affected to a greater extent in this respect than is
imipenem. The increased plasma levels of either entity noted in patients
requiring hemodialysis would certainly be tempered by their undergoing
periodic hemodialysis.

Based on the information derived from these studies, it is recommended
that the daily dosage of Primaxin be cut in half either by reducing the
dose of the drug given every 6 hours or by administering the drug every 12
hours. Monitoring of imipenem and cilastatin plasma levels is indicated
to establish the proper regimen.

Conclusions:
1.   Whether administered separately or together in man, imipenem and
     cilastatin are excreted exclusively in the urine.
2.   When administered alone to man, imipenem urinary recovery and renal
     clearance are low and variable between subjects because of metabolism
     of the drug within the kidney primarily to the opened lactam.
3.   At the recommended dosage ratio of 1:1, cilastatin inhibits the renal
     metabolism and alleviates the nephrotoxic potential of imipenem. The
     renal clearance of the antibiotic is 70% of the plasma clearance (195
     ml/min).
4.   Cilastatin is apparently metabolized by the kidneys, the principal
     metabolite being N-acetyl cilastatin. Seventy percent of an I.V.
     dose is recovered unchanged in urine. Imipenem has no effect on
     cilastatin disposition.
5.   The disposition of either imipenem or cilastatin is not dose
     dependent. The plasma half-life of each drug is approximately 1 hour.
6.   Probenecid coadministered with Primaxin has minimal effect on the
     disposition of imipenem.
7.   Little, if any, accumulation of either drug is observed for Primaxin
     regimens given every 6 to 8 hours to patients with normal and mildly
     impaired renal function.
8.   Decreasing renal function slows the elimination of imipenem and
     cilastatin. The effect is more notable for cilastatin. Primaxin
     dosage adjustment is indicated when creatinine clearance is $\leq$ 30
     ml/min. Hemodialysis is relatively efficient in removing both
     imipenem and cilastatin from blood.

Imipenem Levels in Human Body Fluids and Tissues

Imipenem Levels in Aqueous Humor After 1 GM Dose

Investigator: Dr. Azelrod

No. of Patients: 13

Time after Dose	Serum	Aqueous Humor (mcg/ml)
25 minutes	95.2	3.60
30 minutes	73.5	1.44
30 minutes	73.2	4.00
30 minutes	68.3	1.83
1 hour	39.2	1.80
1.5 hours	36.0	5.88
2 hours	56.5	2.40
2 hours	13.5	3.90
2 hours 15 minutes	17.1	2.40
3 hours 45 minutes	20.8	1.92
4 hours	6.1	1.14
5 hours 30 minutes	9.6	2.92
6 hours 30 minutes	12.2	0.5

Tissue and Fluid Levels from Randomly Selected Patients
(Dr. McGregor's Phase III study)

Tissue or Fluid	No. of Patients	Dose	Time After Dose	Levels (mcg/ml)
Saliva	6	1 g	15 minutes	0.3
		500 mg	15 minutes	0.3
		1 g	15 minutes	0.6
		500 mg	20 minutes	0.3
		500 mg	1 hour	0.3
		1 g	20 minutes	$<$ 0.3*
Sputum	5 (10 samples)	1 g	30 minutes	2.5
			60 minutes	2.1
			2 hours	0.88
			4 hours	0.96
			-	4.3
			-	2.6
			-	6.0
			-	3.4
			-	4.2
			-	10.4
Bile	1	1 g	30 minutes	2.5
Pleural Fluid	1	1 g	1 hour	22.0
Ileal Fluid	2	500 mg	6 hr collection	$<$ 0.3*
Nasal Gastric Aspirate	3	1 g	30 minutes	$\leq$ 0.3*
			15 minutes	$<$ 0.3
			30 minutes	$<$ 0.3
Gastric Aspirate	1 (2 samples)	500 mg	15 minutes	0.6
			1.5 hours	1.7
Abdominal Drain	1	500 mg	2 hours	9.8
Peritoneal Fluid	1	1 g	30 minutes	3.9
				(mcg/g)
Bone	6 (9 samples)	1 g 6 h	-	0.52
		1 g 6 h	-	4.05
		1 g 6 h	-	1.5
		1 g	10 minutes	0.42
		1 g	1.5 hours	2.5
		1 g	25 minutes	5.4
		1 g	20 minutes	3.9
		1 g	-	1.6
		1 g	-	1.3

*Undetectable

Imipenem Tissue Levels in Female Reproductive Organs

Investigator: Rudolph Galask, M.D.

This investigation is in progress.
Results obtained in three patients who completed the study were as follows:

Dose	Time after Dose	Tissue Level (mcg/g)	
500 mg	5 hours, 15 minutes	Ovary	- 5.1
		Fallopian tube	- 0.3
		Myometrium	- 0.2
		Endometrium	- 0.2
500 mg	3 hours, 45 minutes	Ovary	- 0.7
		Fallopian tube	- 0.9
		Myometrium	= 0.3
		Endometrium	- 0.9
1.0 g	2 hours, 30 minutes	Ovary	- 3.8
		Fallopian tube	- 5.1
		Myometrium	- 4.2
		Endometrium	- 4.2

Penetration of Primaxin (imipenen and cilastatin) Into Human Cerebrospinal Fluid

Investigator: P. J. Duma, M.D., Medical College of Virginia and McGuire Veteran Administration Hospital, Richmond, Virginia.

Cerebrospinal fluid penetration of Primaxin was studied in 33 adult patients;
22 had normal CSF, and 11 had inflamed meninges. Patients received a single
intravenous infusion of 1 g over 30 minutes. Serum and CSF levels of imipenem
and cilastatin were measured both by bioassay and by high pressure liquid
chromatography. Data obtained at 1, 2, 4, 6, and 8 hours were pooled for
analysis.

Results were as follows:

Part A: Underlined meninges (22 patients)

Mean Time After Dose (Hours)	Mean Serum Concentration (mcg/ml)		Mean CSF Concentration (mcg/ml)	
	Imipinem	Cilastatin	Imipinem	Cilastatin
1.2	28.7	28.2	0.62	< 0.25
2.2	23.7	25.7	0.73	0.32
4.2	4.8	3.7	0.90	0.37
6.2	2.0	< 2.0	0.88	1.70
8.1	2.7	2.4	0.78	0.59

Part B: Inflamed meninges (11 patients)

1.3	26.5	25.0	1.60	0.42
1.8	14.0	12.4	2.30	1.30
4.3	3.2	3.7	1.39	0.61
6.6	1.6	< 2.0	1.10	0.83

In patients with uninflamed meninges, levels of imipenem in CSF peaked at 4 to 6 hours and appeared to plateau for at least 8 hours (despite 8 hour concentrations more than twice those of CSF, suggesting saturation kinetics). Calculated percent penetration by areas under the curve over 4 hours was 2.2. CSF levels of imipenim were higher in patients with inflamed meninges than in those with uninflamed meninges. In serum, cilastatin levels usually equaled imipenem levels, but in CSF cilastatin levels usually were lower than imipenem levels.

Penetration of Primaxin Into Interstitial Fluid
Investigator: Dr. Tan
No of Patients: 12
Dose: 1 g I.V. over 30 minutes

Hour	Serum	Skin Window Fluid (intermittent)	Skin Window Fluid (Continuous)
0.5	64.0	6.8	1.3*
1.0	37.8	16.1	7.1*
1.5	19.2	9.7	12.0
2.0	10.6	5.8	13.3
3.0	6.2	5.1	10.8
4.0	2.8	2.5	8.6
5.0	-	1.2	5.8
6.0	0.8	0.6	3.7
AUC	79.05	29.8	48

*Dr. Tan could not explain the discrepancy between continuous and intermittent during the 0.5 and 1 hour samples.

Imipenem Levels in CSF in Compassionate Treatment of Meningitis Cases (Assayed by MSDRL)

Patient	Treatment Day	Time of Dose Dose	Sample Time	Imipenem (mcg/ml) CSF	Serum	Cilastin (mcg/ml) CSF	Serum
1	3	3:45 p.m.	3:15 p.m.	0.6	0.3	0.10	0.24
		500 mg q 8 h	4:30 p.m.	0.3	15.4	-	17.24
			5:30 p.m.	2.2	5.2	0.74	4.25
			6:30 p.m.	2.0	1.1	0.80	0.43
	5	10.00 a.m.	9:30 a.m.	0.9	0.3	0.80	0.34
		500 mg q 8 h	11.15 a.m.	0.8	26.6	0.92	27.3
			12.15 p.m.	0.6	7.5	0.53	7.43
			1.15 p.m.	0.6	3.4	-	2.54
	8 (day 1 of higher dose)	1 g q 8 h	trough	-	0.3	-	0.43
			1 hr post dose	2.6	21.7	0.22	32.31
			2 hr post dose	4.1	7.0	0.45	8.16
			3 hr post dose	-	2.4	-	1.37
	10	1 g q 8 h	trough	0.5	0.4		0.43
			1 hr post dose	1.0	16.7	1.04	27.03
			2 hr post dose	-	-	-	7.32
			3 hr post dose	-	14.6		15.53
	12	1 g q 8 h	trough	0.5	-	0.91	0.27
			1 hr post dose	1.2	25.4	0.98	-
			2 hr post dose	-	5.4	-	2.89
			3 hr post dose	-	3.1	0.35	1.14
	17	1 g q 8 h	trough	0.4	0.4	0.56	0.24
			1 hr post dose	3.3	28.8	1.14	35.54
			2 hr post dose	-	-	-	-
			3 hr post dose	1.8	1.9	1.12	0.91
2	7	- 1 g q 6 h	trough	-	0.8	-	0.93
			15 min p-dose	-	33.2	-	69.91
			5 h p-dose	3.7	16.9	3.57	21.53
	14	1 g q 8 h	trough	-	0.3	-	0.22
			15 min p-dose	-	31.8	-	47.08
			2 h p-dose	2.6	5.5	2.26	25.41
3	-	1 g q 6 h	trough	-	0.9	-	0.51
			peak	-	27.8	-	29.11
			5 h p-dose	3.7	-	4.02	-

Clinical Studies (Domestic)

I. Controlled (3 studies)

1. Protocol No. 001

Title: "A Multicenter Study of the Comparative Efficacvy, Safety and Tolerance of Primaxin (imipenem/cilastatin sodium) and of Cefazolin in the Parenteral Therapy of Infections in Hospitalized Patients Caused by Susceptible Pathogenic Bacteria."

Study Design: This was an open, randomized, controlled trial conducted in 11 medical centers across the United States. Hospitalized patients were considered for admission into the study if they exhibited strong presumptive evidence of bacterial infection. If the patient agreed to enter the study, an informed consent form was signed by the patient or by the patient's representative.

Procedure: The study was conducted in the following manner: Each patient was assigned to the Primaxin or cefazolin treatment group based on a randomized schedule prepared by MSDRL. Each patient in the Primaxin group received 250 mg intravenously every 6 hours, infused over a 5 to 15 minute period. Each patient in the cefazolin group received 1 g intravenously every 6 hours, infused over a 5 to 15 minute period.

The patients were to be treated from 5 to 14 days based on the progress of their infection. Cultures from the site of the infection were collected from each patient pre, during, and post therapy to determine the efficacy of the treatment. Disk and MIC determinations were done for all isolated pathogens. Patients were carefully observed for any local or systemic adverse experiences.

Laboratory tests including hematology, blood chemistries, and urinalysis were obtained prior to, during, and after the study drug therapy.

At the conclusion of drug therapy, and after all clinical and laboratory data had been obtained, judgement was made by the investigator of the safety, tolerability, and clinical and bacteriologic efficacy of the study drug therapy for each patient.

Response to treatment was assessed by both clinical and bacteriological outcomes. Favorable clinical outcomes included:

-Cure (Investigators judgment that the signs and symptoms of the infection were resolved).
-Improvement (Investigators judgment that the infection was brought under control, and the need for further intravenous therapy was not indicated).

Unfavorable clinical outcome included:

  -No improvement
  -Patients died of infection primarily (with or without a
  contributing background disease).

Favorable bacteriological outcome:

  -Eradication of the etiologic pathogen(s)

Unfavorable bacteriological outcome:

  -Suppression of the etiologic pathogen(s)
  -Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse
reactions. When an abnormal laboratory result or clinical event was
noted, the investigator was required to render a judgment as to the
intensity and seriousness of the occurrence and its relationship to
the drug. They were also required to indicate the outcome and the
type of action taken with regard to the adverse effect.

The following 11 investigators treated patients under Protocol No. 001:

Investigators	Number of Patients	
	Primaxin	Cefazolin
Richard E. Bryant, M.D.	3	2
University of Oregon Health Science Center		
Gordon M. Dickinson, M.D.	28	27
University of Miami School of Medicine		
Charles D. Ericsson, M.D.	8	8
University of Texas Medical School		
Robert J. Fass, M.D.	14	16
Ohio State University Hospitals		
Robert Fekety, M.D.	1	-
University of Michigan Hospitals		
Earl H. Freimer, M.D.	12	12
Medical College of Ohio		
John Leedom, M.D.	15	14
University of Southern California School of Medicine		
Robert L. Marier, M.D.	43	42
L.S.U. Medical School		
Richard V. McCloskey, M.D.	23	23
Albert Einstein Medical Center Daroff Division		

(Continued)

Investigators	Number of Patients	
	Primaxin	Cefazolin
John Mills, M.D. San Francisco General Hospital	7	8
Emmanuel Wolinsky, M.D. Cleveland Metropolitan General Hospital	7	6
TOTAL 11 STUDIES	161	158

Overall Summary of Studies Conducted Under Protocol No. 001

	Primaxin	Cefazolin
Total No. of Patients	161	158
Age Range (yrs)	17 - 83	16 - 84

Sex

Male	99	90
Female	62	68

Evaluation

Efficacy

	Primaxin	Cefazolin
No. of Cases Evaluable	104	98
No. of Sites of Infection Evaluable	115	101
No. of Cases Unevaluable	57	60

Reasons Cases Unevaluable		
No pre-treatment pathogen	30	25
Effective concomitant antibiotic	0	5
Treatment course too short	17	16
Inadequate cultures	9	11
Patient lost to follow-up	1	0
Organism resistant to study drug	0	3

	Primaxin	Cefazolin
DOSE (Evaluable Cases)	250 mg q 6 h (1 pt. received 2g/day)	1 g q 6 h

DURATION OF TREATMENT (days)
(Evaluable Cases)

	Primaxin	Cefazolin
5 - 14	93 patients	94 patients
> 14	11 patients	4 patients

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CEFAZOLIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, cellulitis, carbuncle/furuncle pyoderma, infected ulcers)	68	48(71%)	17(25%)	3(4%)	70	48(68%)	20(28%)	2(3%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5	2(40%)	3(60%)		4	2(50%)	2(50%)	
LOWER RESPIRATORY (Pneumonia, lung abscess, bronchiolitis)	14	9(64%)	4(29%)	1(7%)	15	11(73%)	4(27%)	
GYNECOLOGIC (Pelvic cellulitis)	1		1 (100%)		-			
SEPTICEMIA	16	14(88%)	2(12%)		5	4(80%)	1(20%)	
ENDOCARDITIS	1	1(100%)			-			
UTI (Uncomplicated) (Pyelonephritis)	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated)	3	2(67%)		1(33%)	2	2(100%)		

INFECTION SKIN AND SKIN STRUCTURE	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	CEFAZOLIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERA
S. aureus (S)*	6	4(67%)	1(17%)	1(17%)	3	3(100%)		
S. aureus ( )**	34	31(91%)	1(3%)	2(6%)	39	34(87%)	3(8%)	2(5%)
S. epidermidis	7	6(86%)	1(14%)		2	2(100%)		
Beta-hem-Strep (Group A)	20	18(90%)	2(8%)		29	29(100%)		
Alpha-hem-Strep	3	3(100%)			1	1(100%)		
Other strepto- coccus species	10	8 (80%)		2 (20%)	11	11 (100%)		
Group B Strep.	5	4(80%)		1(20%)				
Group D Strep (enterococcus)	7	7(100%)			3	3(100%)		
Aeromonas hydrophilia	1	1(100%)			1	1(100%)		
Alcaligenes spp.	1	1(100%)			-			
C. freundii	2	2(100%)			1	1(100%)		
Eikenella corrodens	1	1(100%)			1	1(100%)		
E. aerogenes	1	1(100%)			-			
E. cloacae	2	2(100%)			1	1(100%)		
E. coli	6	5(83%)		1(17%)	3	2(67%)	1(33%)	
K. pneumoniae	2	2(100%)			1		1(100%)	
K. oxytoca	3	3(100%)			2	1(50%)		1(50%)
M. morganii	2	1(50%)		1(50%)	-			
P. multocida	1	1(100%)			-			
P. mirabilis	4	4(100%)			2	1(50%)	1(50%)	
P. rettgeri	2	2(100%)			-			
Providencia stuartii	1	1(100%)			-			
P. aeruginosa	2	2(100%)			-			
S. marcescens	1	1(100%)			-			
Vibrio parahemolyticus	1	1(100%)			1	1(100%)		
Lactobacillus spp	1	1(100%)			-			
B. fragilis	5	5(100%)			1	1(100%)		
B. melaninogenicus	3	3(100%)			3	3(100%)		
B. bivius	1	1(100%)			-			
Peptococcus spp	1	1(100%)			5	5(100%)		
Peptostreptococcus spp	1	1(100%)			-			
Fusobacterium spp	1	1(100%)			2	2(100%)		
A. eriksonii	1	1(100%)			-			
Clostridium spp	-				3	3(100%)		
Bacteroides spp	-				6	6(100%)		

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	CEFAZOLIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERAD
BONE/JOINT								
S. aureus (R)	2	2(100%)			2	2(100%)		
Beta-hem-Strep (Group A)	2	2(100%)			1	1(100%)		
Streptococcus spp	1	1(100%)			1	1(100%)		
E. coli	1	1(100%)			-			
P. aeruginosa	1			1(100%)	-			
S. marcescens	1			1(100%)	-			
B. melaninogenicus					1	1(100%)		
Enterobacter cloacae	-				1	1(100%)		
P. mirabilis	-				1	1(100%)		
LOWER RESPIRATORY								
S. aureus (S)	1	1(100%)			-			
S. pneumoniae	8	8(100%)			11	11(100%)		
H. influenzae	4	3(75%)		1(25%)	6	5(83%)		1(17%)
H. parainfluenzae	1	1(100%)			-			
E. cloacae	1	1(100%)			-			
P. aeruginosa	1			1(100%)	-			
Klebsiella ozaenae	-				1		1 (100%)	
GYNECOLOGIC								
Streptococcus spp	1	1(100%)			-			
E. coli	1	1(100%)			-			
Peptostreptococcus spp	1	1(100%)			-			
Bacteroides spp	1	1(100%)			-			
SEPTICEMIA								
S. aureus (R)	3	3(100%)			-			
S. aureus (S)	1	1(100%)			-			
Streptococcus spp	1	1(100%)			-			
S. epidermidis	3	3(100%)			1	1(100%)		
S. pneumoniae	4	4(100%)			3	3(100%)		
Beta-hem-Strep (Group A)	1	1(100%)			-			
Group D Strep (enterococcus)	1	1(100%)			-			
Micrococcus	1	1(100%)			-			
C. diversus	1	1(100%)			-			
Bacillus subtilis	1	1(100%)			-			
E. coli	-				1	1(100%)		
ENDOCARDITIS								
S. aureus (R)	1	1(100%)			-			

(Continued)

		PRIMAXIN BACTERIOLOGICAL RESPONSE				CEFAZOLIN BACTERIOLOGICAL RESPONSE		
INFECTION	NO.	ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	ERAD[1]	SUPP[2]	NOT ERAD[3]
UTI (Uncomplicated) E. coli	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated) E. coli	2	2(100%)			2	2(100%)		
C. diversus	1			1(100%)	-			

*(S) = Sensitive to penicillin
**(R) = Resistant to penicillin
1 = Eradicated
2 = Suppressed
3 = Not eradicated

In the Primaxin treatment group, one patient with pneumonia developed a superinfection with a resistant P. aeruginosa. In the cefazolin treatment group, 2 patients with pneumonia and 2 with urinary tract infection developed superinfections.

SAFETY

	Primaxin	Cefazolin
Total No. of Patients	161	158
No. of Patients with Systemic Side Effects	9(6%)	8(5%)
No. of Patients with Local Side Effects	10(6%)	5(3%)

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	PRIMAXIN POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Pain at I.V. site	1(0.6%)		1(0.6%)		
Vein infection	1(0.6%)	1(0.6%)			
Phlebitis/thrombo- phlebitis	8(5.0%)	2(1.2%)	5(3.1%)	1(0.6%)	

			CEFAZOLIN		
Pain at I.V. site	1(0.6%)	1(0.6%)			
Vein infection	1(0.6%)		1(0.6%)		
Phlebitis/thrombo- phlebitis	3(1.9%)	1(0.6%)	2(1.3%)		

(Continued)

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
SYSTEMIC SIDE EFFECTS			PRIMAXIN		
Vomiting	2(1.2%)		1(0.6%)		1(0.6%)
Diarrhea	1(0.6%)	1(0.6%)			
Pruritus	1(0.6%)			1(0.6%)	
Rash	1(0.6%)	1(0.6%)			
Dizziness	1(0.6%)				1(0.6%)
Apnea	1(0.6%)	1(0.6%)			
Chest pain/cough	1(0.6%)	1(0.6%)			
Hyperventilation	1(0.6%)				1(0.6%)
Paresthesia	1(0.6%)				1(0.6%)
Weakness	1(0.6%)				1(0.6%)
Thoracic spine pain	1(0.6%)				1(0.6%)
			CEFAZOLIN		
Diarrhea	1(0.6%)	1(0.6%)			
Pruritus	1(0.6%)				1(0.6%)
Rash	1(0.6%)		1(0.6%)		
Fever	1(0.6%)		1(0.6%)		
Asthenia	1(0.6%)		1(0.6%)		
Megacolon	1(0.6%)		1(0.6%)		
Vaginal candidiasis	2(1.3%)			2(1.3%)	

Deaths: There were two deaths in each treatment group. None was considered to be related to the study drug.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFAZOLIN	
Hemoglobin	(D) 7	(D) 7	
Hematocrit	(D) 5	(D) 7	
WBC	(D) 3	(D) 2	
Neutrophils	(D) 4	(D) 2	
Eosinophils	(I) 2	(I) 4	
Monocytes	(I) 3	0	
Lymphocytes	(I) 2	(I) 1	
Platelets	(I) 2	(D) 1	(I) 3
Positive Coombs' Test	1	1	
Glucose	(I) 2	(I) 1	
BUN	(I) 3	(I) 1	
Creatinine	(I) 3	(I) 1	
Uric acid	0	(I) 1	
SGOT (AST)	(I) 13	(I) 4	
SGPT (ALT)	(I) 14	(I) 3	

(Continued)

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFAZOLIN
Bilirubin	(I) 3	(I) 2
Alk. phosphatase	(I) 9	(I) 1
LDH	(I) 5	(I) 1
Serum potassium	0	(I) 1
Urine protein	0	(I) 1
Urine uric acid	0	(I) 1
Urine WBC	(I) 1	(I) 2
Urine RBC	(I) 1	(I) 1
Urine epithelial cells	(I) 1	0

    (D) = Decreased
    (I) = Increased

Summary and Conclusions: This was an open, randomized, controlled multicenter study comparing Primaxin and cefazolin in the treatment of infections caused by susceptible bacterial. A total of 161 patients, 99 males and 62 females, ranging in age from 17 to 83 years were enrolled in the Primaxin group. A total of 158 patients, 90 males and 68 females, ranging in age from 16 to 84 years were enrolled in the cefazolin group. Demographic characteristics of patients in each treatment group were similar. One hundred and four patients with 115 sites of infection in the Primaxin treated group and 98 patients with 101 sites of infection in the cefazolin treated group were acceptable for evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure of improvement occurred in 109/115 (95%) infections in the patients in the Primaxin group and in 99/101 (98%) infections in the patients in the cefazolin group.

A favorable bacteriological outcome (eradication) was achieved in 172 (90%) of 191 organisms isolated in the Primaxin group and in 146 (93%) of the 157 organisms isolated in the cefazolin group.

Systemic side effects were reported in 6% of the patients in the Primaxin group and in 5% of the patients in the cefazolin group. Local side effects were reported in 6% of the patients in the Primaxin group and in 3% of the patients in the cefazolin group.

Laboratory test abnormalities were similar in each treatment group, except for a higher incidence of abnormal SGOT and SGPT values in the Primaxin group.

The two deaths that occurred in each treatment group were not considered by the investigators to be related to study drug.

This study demonstrates that Primaxin is as safe and effective as cefazolin in the treatment of patients with serious infections caused by susceptible bacteria.

2. Protocol No. 003
    Title: "A Multiclinic Study of the Comparative Efficacy, Safety, and
    Tolerability of Primaxin (imipenem/cilastatin sodium) and of
    Moxalactam in the Parenteral Therapy of Infections in Hospitalized
    Patients Caused by Susceptible Pathogenic Bacteria."

    Study Design: This was an open, randomized, controlled trial
    conducted in 19 medical centers across the United States.
    Hospitalized patients were considered for admission into the study if
    they exhibited strong presumptive evidence of bacterial infection.
    If the patient agreed to enter the study, an informed consent form
    was signed by the patient or the patient's representative.

    Procedure: The study was conducted in the following manner:
    Each patient was assigned to the Primaxin or moxalactam treatment
    group based on a randomized schedule prepared by MSDRL. Neither the
    investigator nor the patient knew in advance which of the two
    treatments the patient would receive.

    Patients receiving Primaxin were treated with 2 g/day (500 mg every 6
    hours). Patients receiving moxalactam were treated with up to 6
    g/day. Both drugs were given by intravenous infusion. The patients
    were to be treated from 5-14 days based on the progress of their
    infections. The clinical and bacteriological courses of each
    patient's treatment were followed and documented. Culture from the
    site of infection and blood and urine samples were collected from
    each patient pre, during, and post therapy to determine the efficacy
    and safety of the treatment. Disk and/or MIC determinations were
    done for all isolated pathogens and compared to the patients'
    clinical outcome. Daily observations of the tolerability of
    intravenous therapy were made, and patients were carefully observed
    for any adverse clinical or laboratory experiences. At the
    conclusion of drug therapy, and after all clinical and laboratory
    data had been obtained, judgement was made by the investigator of the
    safety, tolerability, and clinical and bacteriologic efficacy of the
    study drug therapy for each patient.

    Response to treatment was assessed by both clinical and
    bacteriological outcomes.

    Favorable clinical outcome included:
        -Cure (Investigator's judgment that the signs and symptoms of
        the infection were resolved).
        -Improvement (Investigator's judgment that the infection was
        under control and that the need for further treatment was not
        indicated).

    Unfavorable clinical outcome included:
        -No improvement
        -Patient died of infection primarily

Favorable bacteriologic outcome:
    -Eradication of the etiologic pathogen(s)

Unfavorable bacteriologic outcome:
    -Suppression of the etiologic pathogen(s)
    -Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse reactions.

When an abnormal laboratory result or clinical event was noted, the investigators were required to render a judgment as to the intensity and seriousness of the occurrence and its relationship to the study drug. They were also required to indicate the outcome and the type of action taken with regard to the adverse effect.

The following 19 investigators treated patients under Protocol 003:

Investigators	Number of Patients	
	Primaxin	Moxalactam
Alan S. Berkeley, M.D. Cornell Medical Center	18	16
Steven Berman, M.D. Internal Medicine & Infectious Diseases Honolulu, HI	20	20
Arnold W. Cohen, M.D. Albert Einstein Medical Center	5	4
Robert E. Condon, M.D. Medical College of Wisconsin	11	11
Lawrence J. Eron, M.D., F.A.C.P. Infectious Diseases Physicians, Inc. Fairfax, VA	20	20
David A. Eschenbach, M.D. University of Washington Seattle, WA	7	8
Robert J. Fass, M.D. Ohio State University Hospital	22	25
F. Robert Fekety, M.D. University of Michigan Hospital	2	2
Earl H. Freimer, M.D. Medical College of Ohio	11	10

(Continued)

Investigators	Number of Patients	
	Primaxin	Moxalactam
Charles A. Kallick, M.D. Cook County Hospital	4	6
Captain Walter W. Karney, MC, USN National Naval Medical Center	8	10
Richard D. Meyer, M.D. Cedars-Sinai Medical Center	15	16
Burt R. Meyers, M.D. The Mount Sinai Medical Center	3	3
James J. Rahal, Jr., M.D. V.A. Hospital New York, New York	13	12
William M. Rambo, M.D. Charleston Memorial Hospital Charleston, S.C.	21	19
Charles L. Rice, M.D. Michael Reese Hospital and Medical Center Chicago, IL	3	1
Gary L. Simon, M.D. George Washington University	12	13
Larry J. Strausbaugh, M.D. University of Missouri - Columbia Columbia, MO	5	6
Francis P. Tally, M.D. New England Medical Center Hospital Boston, MA	18	21
TOTAL	218	223

Three investigators, Berman, Eron and Freimer, decided to treat additional patients with Primaxin after meeting the requirements of their segment of the comparative trial. A total of 21 patients were entered into a noncomparative Primaxin arm. These patients have been excluded from the analysis of efficacy and safety of comparative patients and will be evaluated separately.

OVERALL SUMMARY OF STUDIES CONDUCTED UNDER PROTOCOL NO. 003

	Primaxin	Moxalactam
Total No. of Patients	218	223
Age Range (yrs)	14 - 91	14 - 96
Mean Age	43.9	48.4
Sex		
Male	109	99
Female	109	124

EVALUATION

EFFICACY

	Primaxin	Moxalactam
No. of Cases Evaluable	145	148
No. of Sites of Infection Evaluable	161	156
No. of Cases Unevaluable	73	75

REASONS CASES UNEVALUABLE

	Primaxin	Moxalactam
No pre-treatment pathogen	45	42
Organism resistant to study drug	1	4
Clinical diagnosis not clear	2	1
Inadequate bacteriological cultures	11	10
Treatment course too short	11	11
Effective concomitant treatment	3	4
Infection not included in claims	0	3

	Primaxin	Moxalactam
DOSE (Evaluable Cases)	500 mg q 6 h (2 g/day)	1-2 g q 8 h (3-6 g/day)

DURATION OF TREATMENT (days)
(Evaluable Cases)

	Primaxin	Moxalactam
4 - 14	117 patients	138 patients
15 - 21	18 patients	7 patients
≥21*	10 patients	3 patients

*Four patients were treated for 41 days.

RESULTS

| INFECTION | NO. | PRIMAXIN CLINICAL RESPONSE | | | NO. | MOXALACTAM CLINICAL RESPONSE | | |
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess cellulitis, carbuncle/ furuncle, ulcers)	44	27(61%)	16(36%)	1(2%)	48	23(48%)	17(35%)	8(17%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5		5(100%)		1		1(100%)	
LOWER RESPIRATORY (Pneumonia, empyema)	28	20(71%)	7(25%)	1(4%)	28	17(61%)	7(25%)	4(14%)
GYNECOLOGIC (Endometritis, pelvic cellulitis, PID, tuboovarian abscess)	27	23(85%)	3(11%)	1(4%)	27	21(78%)	5(18%)	1(4%)
SEPTICEMIA	22	17(77%)	3(14%)	2(9%)	12	10(83%)	1(8%)	1(8%)
OTITIS MEDIA	1	1(100%)						
ENDOCARDITIS	1	1(100%)						
UTI (Uncomplicated) (Pyelonephritis)	6	6(100%)			13	11(85%)	2(15%)	
UTI (Complicated) (Pyelonephritis, renal abscess, cystitis)	5	2(40%)	1(20%)	2(40%)	6	4(67%)	1(16%)	1(16%)
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, liver abscess)	22	14(64%)	6(27%)	2(9%)	20	13(65%)	3(15%)	4(20%)
INFECTED VASCULAR GRAFT	—				1		1(100%)	

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE ERAD	SUPP	NOT ERAD	NO.	MOXALACTAM BACTERIOLOGICAL RESPONSE ERAD	SUPP	NOT ERAD
SKIN AND SKIN STRUCTURE								
Bacillus spp.	–				1	1(100%)		
S. aureus(S)	2	1(50%)		1(50%)	5	5(100%)		
S. aureus(R)	17	13(76%)	1(6%)	3(18%)	16	15(94%)		1(6%)
S. epidermidis	3	3(100%)			3	3(100%)		
Strep. (Group A)	5	5(100%)			4	4(100%)		
Strep. (Group B)	2	1(50%)	1(50%)		2	2(100%)		
Streptococcus spp.	8	7(88%)	1(12%)		4	4(100%)		
S. faecalis	7	7(100%)			2	1(50%)		1(50%)
Acinetobacter spp.	–				2	2(100%)		
Citrobacter spp.	2	2(100%)			1	1(100%)		
C. freundii	–				1	1(100%)		
E. aerogenes	2	2(100%)			–			
E. cloacae	2	2(100%)			3	3(100%)		
E. coli	5	4(80%)		1(20%)	8	6(75%)	1(12.5%)	1(12.5%)
Klebsiella spp	1	1(100%)			1	1(100%)		
K. oxytoca	1	1(100%)			5	5(100%)		
K. pneumoniae	3	3(100%)			2	2(100%)		
M. morganii	2	2(100%)			1	1(100%)		
P. mirabilis	5	1(20%)	1(20%)	3(60%)	12	11(92%)		1(8%)
P. vulgaris	2	2(100%)			2	1(50%)		1(50%)
P. stuartii	2	2(100%)			–			
Pseudomonas spp	–				1	1(100%)		
P. aeruginosa	11	6(55%)	1(9%)	4(36%)	8	5(62.5%)		3(37.5%)
Serratia spp.	1	1(100%)			2	2(100%)		
S. marcescens	2	2(100%)			2	1(50%)	1(50%)	
Eubacterium spp.	–				1	1(100%)		
Gaffkya anaerobia	–				1	1(100%)		
Peptococcus spp.	2	2(100%)			4	4(100%)		
Bacteroides spp.	7	7(100%)			4	4(100%)		
B. fragilis	1	1(100%)			1	1(100%)		
F. russii	1	1(100%)			1	1(100%)		
V. parvula	1	1(100%)			1	1(100%)		
BONE/JOINT								
S. aureus(R)	2	2(100%)			1	1(100%)		
S. faecalis	2	2(100%)			–			
E. coli	–				1	1(100%)		
P. mirabilis	2	2(100%)			1	1(100%)		
P. aeruginosa	1		1(100%)		–			
S. marcescens	1			1(100%)	–			
Bacteroides spp.	1	1(100%)			–			
B. fragilis	1	1(100%)			–			

(Continued)

		PRIMAXIN BACTERIOLOGICAL RESPONSE				MOXALACTAM BACTERIOLOGICAL RESPONSE		
INFECTION	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
LOWER RESPIRATORY								
S. aureus (S)	1	1(100%)			1	1(100%)		
S. intermedius	-				1	1(100%)		
S. pneumoniae	8	8(100%)			7	7(100%)		
Strep. (Group A)	1	1(100%)			-			
Strep. (Group B)	-				1	1(100%)		
S. viridans	1	1(100%)			1	1(100%)		
Beta-hem Strep.	2	2(100%)			-			
Acinetobacter spp	2	2(100%)			-			
A. hydrophilia	1	1(100%)						
Alcaligenes spp	1	1(100%)			-			
Citrobacter spp	1	1(100%)			-			
E. aerogenes	1			1(100%)				
E. cloacae	1	1(100%)			2	2(100%)		
E. coli	1	1(100%)			1	1(100%)		
H. influenzae	6	5(83%)	1(17%)		2	2(100%)		
H. parainfluenzae	1	1(100%)			1	1(100%)		
K. oxytoca	1	1(100%)			2	2(100%)		
K. pneumoniae	2	2(100%)			4	3(75%)		1(25%)
M. morganii	-				2	2(100%)		
P. mirabilis	1			1(100%)	4	2(50%)	1(25%)	1(25%)
Pseudomonas spp	1	1(100%)						
P. aeruginosa	3	3(100%)			5	1(20%)	2(40%)	2(40%)
S. marcescens	-				2	2(100%)		
B. catarrhalis	-				1	1(100%)		
Peptostreptococcus spp.	1	1(100%)						
Bacteroides spp.	3	3(100%)						
GYNECOLOGIC								
Corynebacterium spp	-				1	1(100%)		
S. aureus (R)	4	3(75%)	1(25%)		4	3(75%)		1(25%)
S. intermedius	-				1	1(100%)		
Strep. (Group A)	-				1	1(100%)		
Strep. (Group B)	7	7(100%)			7	7(100%)		
S. viridans	2	2(100%)			2	2(100%)		
Strep (non-hemolytic)	2	2(100%)			1	1(100%)		
S. faecalis	8	7(88%)	1(12%)		2			2(100)
A. calcoaceticus	-				1			1(100)
Enterobacter spp.	-				1	1(100%)		
E. cloacae	1	1(100%)			1	1(100%)		
E. coli	8	6(75%)	1(12.5%)	1(12.5%)	9	9(100%)		
Klebsiella spp.	1	1(100%)			1	1(100%)		
P. mirabilis	2	2(100%)			1	1(100%)		
P. aeruginosa	-				1			1(100)
N. gonorrheae (-)*	2	2(100%)			-			
N. gonorrheae (+)**	-				1	1(100%)		

(Continued)

GYNECOLOGIC	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Bifidobacterium spp	1	1(100%)			-			
Propionibacterium spp	1	1(100%)			-			
Peptococcus spp	3	3(100%)			9	9(100%)		
Peptostreptococcus spp	1	1(100%)			-			
Bacteroides spp	5	5(100%)			4	4(100%)		
B. fragilis	1	1(100%)			-			
Fusobacterium spp	-				1	1(100%)		
G. vaginalis	4	4(100%)			2	2(100%)		
M. hominis	1	1(100%)			-			
Ureaplasma urealyticum	2	2(100%)			-			
Veillonella parvula	1	1(100%)			6	6(100%)		

    (-)* = penicillinase negative
    (+)** = penicillinase positive

SEPTICEMIA	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
S. aureus (S)	-				1	1(100%)		
S. aureus (R)	-				1	1(100%)		
S. pneumoniae	1	1(100%)			1	1(100%)		
Strep. (Group A)	1	1(100%)			1	1(100%)		
S. viridar	-				1	1(100%)		
e. sanguis	1	1(100)						
S. faecalis	1	1(100%)			-			
Acinetobacter spp	1	1(100%)			-			
E. cloacae	1	1(100%)			-			
E. coli	6	6(100%)			2	2(100%)		
K. pneumoniae	1	1(100%)			3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. stuartii	1	1(100%)			-			
P. aeruginosa	1	1(100%)			-			
S. marcescens	2	1(50%)		1(50%)	-			
Y. enterocolitica	1	1(100%)			-			
Clostridium spp.	1			1(100%)				
Peptostreptococcus spp	2	2(100%)			-			
Bacteroides spp	2	2(100%)			-			
Fusobacterium spp	2	2(100%)			-			
B. fragilis	-				1			1(100%)

OTITIS MEDIA	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
S. pneumoniae	1	1(100%)			-			

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE			NO.	MOXALACTAM BACTERIOLOGICAL RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
OTITIS MEDIA								
S. pneumoniae	1	1(100%)			-			
ENDOCARDITIS								
S. sanguis	1	1(100%)			-			
INFECTED VASCULAR GRAFT								
S. aureus(R)	-				1	1(100%)		
UNCOMPLICATED UTI								
E. coli	3	3(100%)			8	7(87.5%)		1(12.5%)
E. cloacae	-				1	1(100%)		
P. mirabilis	1	1(100%)			2	2(100%)		
S. marcescens	-				1	1(100%)		
P. aeruginosa	-				1	1(100%)		
Klebsiella spp.	-				1	1(100%)		
K. pneumoniae	2	2(100%)			1	1(100%)		
COMPLICATED UTI								
E. coli	2	1(50%)		1(50%)	3	3(100%)		
P. mirabilis	-				1	1(100%)		
E. aerogenes	1	1(100%)			-			
K. pneumoniae	-				1	1(100%)		
P. aeruginosa	1			1(100%)	1			1(100%)
S. marcescens	1			1(100%)	-			
INTRA-ABDOMINAL								
S. aureus(R)	-				1			1(100%)
S. epidermidis	1	1(100%)			1			1(100%)
S. intermedius	4	4(100%)			1	1(100%)		
S. mitis	1	1(100%)			2	2(100%)		
S. morbillorum	2	2(100%)			-			
Strep. (Group A)	-				2	2(100%)		
Strep. (Group B)	-				1	1(100%)		
S. viridans	3	2(67%)		1(33%)	-			
S. faecalis	-				3	1(33%)		2(67%)
S. faecium	1	1(100%)			1	1(100%)		
S. bovis	1	1(100%)			-			
S. sanguis	1	1(100%)			-			
S. salivarus	-				-			
A. hydrophilia	-				1	1(100%)		
E. aerogenes	1	1(100%)			2	2(100%)		
E. cloacae	-				1	1(100%)		
E. coli	14	11(79%)		3(21%)	12	9(75%)		3(25%)

(Continued)

INTRAABDOMINAL	PRIMAXIN BACTERIOLOGICAL RESPONSE				MOXALACTAM BACTERIOLOGICAL RESPONSE		
	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Klebsiella spp.	1	1(100%)		1		1(100%)	
K. pneumoniae	4	4(100%)		4		4(100%)	
P. multocida	1	1(100%)		-			
M. morganii	-			2		2(100%)	
P. mirabilis	1	1(100%)		3		2(67%)	1(33%)
P. vulgaris	1	1(100%)					
P. aeruginosa	2	2(100%)		4		2(50%)	2(50%)
Bifidobacterium spp.	-			1		1(100%)	
Clostridium spp	9	9(100%)					
C. perfringens	2	2(100%)		3		3(100%)	
Eubacterium spp	2	2(100%)		3		2(67%)	1(33%)
Peptococcus spp	1	1(100%)					
Peptostreptococcus spp	4	4(100%)		3		3(100%)	
Bacteroides spp.	5	5(100%)		7		7(100%)	
B. fragilis	12	12(100%)		13		12(92%)	1(8%)
Fusobacterium spp.	5	5(100%)		4		4(100%)	
V. parvula	1	1(100%)					

Bacterial superinfection occurred in 5 patients in the Primaxin group and in 8 patients in the Moxalactam group. However, none of the 5 patients in the Primaxin group who developed superinfections had resistant pathogens, whereas, 6 of the 8 patients who developed superinfections in the Moxalactam group had resistant pathogens.

Three patients in each treatment group developed candida superinfections.

SAFETY

	Primaxin	Moxalactam
Total No. of Patients	218	210
No. of Patients with Systemic Side Effects	24(11%)	19(9%)
No. of Patients with Local Side Effects	5(2%)	2(1%)

SYSTEMIC SIDE EFFECTS

	NO.	PRIMAXIN PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Diarrhea	6(2.8%)	2(0.9%)	3(1.4%)	1(0.5%)	
Nausea	1(0.5%)		1(0.5%)		
Vomiting	6(2.8%)	2(0.9%)	3(1.4%)	1(0.5%)	
Pruritus	1(0.5%)	1(0.5%)			

(Continued)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	PRIMAXIN POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Rash	3(1.4%)		1(0.5%)	1(0.5%)	1(0.5%)
Urticaria	1(0.5%)			1(0.5%)	
Fever	2(1.0%)	1(0.5%)	1(0.5%)		
Transient hearing loss	1(0.5%)		1(0.5%)		
Palpitation	1(0.5%)		1(0.5%)		
Tachycardia	1(0.5%)		1(0.5%)		
Respiratory distress syn.	1(0.5%)	1(0.5%)			
Pharyngeal pain	1(0.5%)			1(0.5%)	
Menorrhagia	1(0.5%)	1(0.5%)			
Hemorrhagic colitis	1(0.5%)			1(0.5%)	
Asthenia	1(0.5%)		1(0.5%)		
Hyperhydrosis	1(0.5%)		1(0.5%)		

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	MOXALACTAM POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Diarrhea	9(4.3%)	4(1.9%)	4(1.9%)	1(0.5%)	
Nausea	1(0.5%)		1(0.5%)		
Vomiting	2(1.0%)		2(1.0%)		
Serum Sickness	1(0.5%)				1(0.5%)
Epistaxis	1(0.5%)		1(0.5%)		
Hemoperitoneum	1(0.5%)			1(0.5%)	
GI hemorrhage	1(0.5%)			1(0.5%)	
Dysuria	1(0.5%)	1(0.5%)			
Urinary frequency	1(0.5%)	1(0.5%)			
Abdominal pain	1(0.5%)	1(0.5%)			
Respiratory insufficiency	1(0.5%)	1(0.5%)			
Headache	1(0.5%)	1(0.5%)			
Convulsive disorder	1(0.5%)	1(0.5%)			
Alcohol intolerance	1(0.5%)		1(0.5%)		
Somnolence	1(0.5%)		1(0.5%)		
Vaginal discharge	1(0.5%)			1(0.5%)	
Myocardial infarction	1(0.5%)	1(0.5%)			

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	PRIMAXIN POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Phlebitis/ Thrombophlebitis	12(5.5%)		12(5.5%)		
Infused vein pain	1(0.5%)			1(0.5%)	
Infused vein infection	1(0.5%)		1(0.5%)		

	NO.	PROBABLY NOT RELATED	MOXALACTAM POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
I.V. site hemorrhage	1(0.5%)	1(0.5%)			
Infused vein pain	1(0.5%)			1(0.5%)	
Phlebitis/ Thrombophlebitis	4(1.9%)		4(1.9%)		

Deaths: There were eight deaths in the Primaxin treated group and eleven deaths in the Moxalactam treated group. None of these deaths was considered by the investigators to be related to the test drug.

Abnormal Laboratory Tests

TEST	PRIMAXIN	MOXALACTAM
Hemoglobin	(D) 1	(D) 8
Hematocrit	(D) 2	(D) 6
WBC	(D) 3	(D) 4
Neutrophils	(D) 1	(D) 1
Eosinophils	(I)17	(I)13
Platelets	(I) 2	(I) 2
	(D) 4	(D) 3
Positive Coombs' Test	7	5
Prothrombin time	(I) 9	(I) 9
Glucose	0	(I) 1
Creatinine	(I) 2	(I) 6
SGOT (AST)	(I) 7	(I)12
SGPT (ALT)	(I)10	(I)14
Bilirubin	(I) 2	(I) 1
Alk. phosphatase	(I) 6	(I) 6
Serum sodium	0	(D) 1
Serum potassium	0	(D) 1
Serum chloride	(I) 1	(D) 1
Urine protein	(I) 3	(I) 2
Urine WBCs	(I) 4	(I) 2
Urine RBCs	(I) 3	(I) 3
Urine casts	(I) 2	(I) 1
C. difficile Toxin assay (stool)	2	0

Summary of 21 Patients Entered into the Non-Comparative Primaxin Arm Under
Protocol 003

	PRIMAXIN
TOTAL NO. OF PATIENTS	21
Age Range (years)	21 - 78

Sex
    Male   13
    Female   8

EVALUATION

EFFICACY

No. of Cases Evaluable	19
No. of Sites of Infection Evaluable	19
No. of Cases Unevaluable	2

REASONS CASES UNEVALUABLE
No pretreatment pathogen   2

DOSE - 500 mg q 6 h (2g/day)
        (One patient received 3g/day)

DURATION (days) - 5 - 14 days (13 patients)
                 15 - 21 days (3 patients)
                 34 - 37 days (3 patients)

RESULTS

		PRIMAXIN CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMP	FAIL
SKIN & SKIN STRUCTURE	9	2(22%)	6(67%)	1(11%)
BONE/JOINT	1		1(100%)	
LOWER RESPIRATORY	2	1(50%)		1(50%)
UTI (Uncomplicated)	1		1(100%)	
INTRA-ABDOMINAL	6		5(83%)	1(17%)

		BACTERIOLOGIC RESPONSE		
ORGANISM	NO.	ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE				
S. aureus(R)	1	1(100%)		
Strep (Group A)	1	1(100%)		
Strep (Group B)	1	1(100%)		
S. faecalis	5	3(60%)	1(20%)	1(20%)
E. coli	3	2(67%)	1(33%)	

(Continued)

ORGANISM	NO.	BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE				
P. mirabilis	3	1(33%)		2(67%)
A. calcoaceticus	1	1(100%)		
P. aeruginosa	3	1(33%)		2(67%)
K. pneumoniae	1		1(100%)	
Peptostreptococcus spp	1	1(100%)		
Bacteroides spp	3	3(100%)		
B. fragilis	1	1(100%)		
BONE/JOINT				
S. faecalis	1	1(100%)		
P. mirabilis	1			1(100%)
P. stuartii	1			1(100%)
P. aeruginosa	1			1(100%)
LOWER RESPIRATORY				
K. pneumoniae	1	1(100%)		
E. hafniae	1			1(100%)
P. aeruginosa	1			1(100%)
UTI (Uncomplicated)				
E. coli	1			1(100%)
INTRA-ABDOMINAL				
S. faecalis	1	1(100%)		
E. coli	3	2(67%)		1(33%)
P. mirabilis	1			1(100%)
K. pneumoniae	2	1(50%)		1(50%)
P. aeruginosa	1	1(100%)		

The overall response rate for these non-randomized patients was significantly lower than in those in the comparative trial.

These patients were in general more severly ill and in almost all of the patients with unfavorable response there were medical reasons to explain the clinical failure or bacteriologic persistance.

Four patients had fungal superinfections. There were no bacterial superinfections.

SAFETY

	PRIMAXIN
Total No. of Patients	21
No. of Patients with Systemic Side Effects	2(9.5%)
No. of Patients with Local Side Effects	0

SYSTEMIC SIDE EFFECTS

	NO.	DEFINITELY RELATED
Candidiasis	1(4.8%)	1
Diarrhea*	1(4.8%)	1

*This patient's diarrhea was associated with a positive C. difficile toxin assay.

Two patients who had non drug-related adverse effects had drug discontinued. One had severe diarrhea that was probably related to previous piperacillin therapy. Another patient who had a brain tumor and seizures developed a grand mal seizure during therapy, and his primary physician decided not to continue the trial. The investigator called the seizure probably not related to study drug therapy.

Deaths: Two patients died of non-drug related causes.

Abnormal Laboratory Tests

Test	Abnormality	No
Platelets	I	2
Urine RBCs	I	1
BUN	I	1
SGOT	I	4
SGPT	I	3
Alk. phosphatase	I	4
Bilirubin	I	1

Summary and Conclusions (Comparative Arm of Protocol No. 003)
This was an open, randomized, controlled multicenter study comparing Primaxin and moxalactam in the treatment of infections caused by susceptible bacteria. A total of 218 patients, 109 males and 109 females, ranging in age from 14 to 91 years were enrolled in the Primaxin group. A total of 223 patients, 99 males and 124 females, ranging in age from 14 to 96 years were enrolled in the moxalactam group.
Demographic characteristics of patients in each treatment group were similar. One hundred and forty-five patients with 161 sites of infection in the Primaxin group and 148 patients with 156 sites of infection were acceptable for evaluation of drug efficacy. Safety was assessed in 218 patients in the Primaxin group and in 210 patients in the moxalactam group.

Clinical cure or improvement occurred in 152/161 (94%) infections in the Primaxin treated patients and in 137/156 (88%) infections in the moxalactam treated patients.

A favorable bacteriological outcome (eradication) was achieved in 288 (89%) of 323 organisms isolated in the Primaxin group and in 271 (88%) of 308 organisms isolated in the moxalactam group.

Systemic side effects were reported in 11% of the patients in the Primaxin group and in 9% of the patients in the moxalactam group. Local side effects were reported in 2% of the patients in the Primaxin group and in 1% of the patients in the moxalactam group.

Laboratory test abnormalities were similar in both treatment groups.

None of the deaths reported in each treatment group was considered by the investigator to be related to the study drug.

This study demonstrates that Primaxin and moxalactam are safe and effective in the treatment of patients with infections caused by susceptible bacteria.

3.   Protocol No. 11
      Title: "A Multicenter Randomized Study of the Comparative Efficacy, Safety and Tolerance of Primaxin Versus Clindamycin/Gentamicin in the Parenteral Therapy of Infections in Hospitalized Patients Caused by Susceptible Pathogenic Bacteria."

      Study Design: This was an open, controlled, randomized, multicenter study.

      Procedure: Patients with acute bacterial infections caused by organisms presumed or proven to be susceptible to both antibiotic regimens (Primaxin and clindamycin/gentamicin) were entered in the study according to a computer-generated randomized schedule. Evaluations were made concerning the bacteriologic and clinical efficacy, as well as the safety and tolerance of the two antimicrobial regimens. Laboratory data to assess safety were obtained before, during, and after therapy.
      Each patient in the Primaxin group received a total daily dose of 2.0 g administered in four equally divided doses every 6 hours by intravenous infusion.
      Each patient in the clindamycin/gentamicin group received 300-600 mg clindamycin every 6 to 8 hours and 1.0 to 1.7 mg/kg of gentamicin every 8 hours (gentamicin dosage was adjusted according to serum concentration assays).

      Two investigators enrolled patients under this protocol. Joseph S. Solomkin, M.D., University of Cincinnati Medical Center, Cincinnati, Ohio. Toni Hau, M.D., Case Western Reserve University, Cleveland, Ohio.

Overall Summary of Studies Conducted Under Protocol No. 11

	Primaxin	Clindamycin/Gentamicin
Total No. of Patients	13	13
Age Range (yrs)	24 - 95	26 - 73
Mean Age	50.5	49.0
Sex		
Male	9	10
Female	4	3

EVALUATION

EFFICACY

	Primaxin	Clindamycin/Gentamicin
No. of Cases Evaluable	8	5
No. of Sites of Infection Evaluable	8	5
No. of Cases Unevaluable	5	8

REASONS CASES UNEVALUABLE

No pre-treatment pathogen	3	4
Treatment course too short	1	2
Organism resistant to study drug	-	1
Inadequate bacteriological cultures	1	-
Concomitant effective antibiotic	-	1

	Primaxin	Clindamycin	Gentamicin
DOSE	500 mg q 6 h	300-600 mg q 6 h	1.0-1.7 mg/kg q 8 h

DURATION OF TREATMENT (days)

5 - 14	8 patients	5 patients	5 patients

RESULTS

		PRIMAXIN CLINICAL RESPONSE			CLINDAMYCIN/GENTAMICIN CLINICAL RESPONSE			
INFECTION	NO.	CURE	IMP.	FAIL	NO.	CURE	IMP.	FA
SKIN & SKIN STRUCTURE (Wound infection, abscess)	2	2(100%)			-			
LOWER RESPIRATORY (Pneumonia, bronchopneumonia)	2	1(50%)	1(50%)		2		1(50%)	1(5(

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CLINDAMYCIN/GENTAMICIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	F/
UTI (Complicated) (Pyelonephritis)	1			1(100%)	-			
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE		NO.	CLINDAMYCIN/GENTAMICIN BACTERIOLOGIC RESPONSE	
		ERAD	NOT ERAD		ERAD	NOT ER/
SKIN & SKIN STRUCTURE						
S. viridans group	1	1(100%)				
Streptococcus spp	1	1(100%)				
S. faecalis	1	1(100%)				
E. coli	1	1(100%)				
Peptococcus spp	1	1(100%)				
Bacteroides spp	2	2(100%)				
LOWER RESPIRATORY						
H. influenzae	1		1(100%)	-		
E. coli	1	1(100%)		1	1(100%)	
Enterobacter spp	-			1	1(100%)	
P. aeruginosa	-			1		1(100%
INTRA-ABDOMINAL						
S. aureus(S)	-			1	1(100%)	
Strep (Group A)	1	1(100%)		-		
Strep (Group D enterococci)	1	1(100%)		-		
S. viridans group	1	1(100%)		-		
Beta-hemolytic Strep	1	1(100%)		-		
E. coli	2	2(100%)		1	1(100%)	
E. cloacae	1	1(100%)		-		
K. pneumoniae	1	1(100%)		-		
P. aeruginosa	1	1(100%)		-		
Peptococcus spp.	1	1(100%)		-		
Peptostreptococcus spp	1	1(100%)		-		
B. fragilis	-			2	2(100%)	
Bacteroides spp.	4	4(100%)		1	1(100%)	
Fusobacterium spp.	2	2(100%)		-		
UTI (Complicated)						
Providencia spp.	1		1(100%)	-		

SAFETY

SIDE EFFECTS
There were no local or systemic side effects reported in these studies.

Deaths: Two patients in the Primaxin-treated group and one patient in the clindamycin/gentamicin-treated group died during or shortly after discontinuation of treatment. These deaths were considered by the investigators definitely not drug related.

Abnormal Laboratory Tests
The only abnormality reported was an increase in serum creatinine in 2 patients in the clindamycin/gentamicin group.

Summary and Conclusions: This was an open, randomized, controlled study comparing Primaxin and clindamycin plus gentamicin in the treatment of infections caused by susceptible bacteria.

A total of 13 patients, 9 males and 4 females, ranging in age from 24 to 95 years were enrolled in the Primaxin group. A total of 13 patients, 10 males and 3 females, ranging in age from 20 to 73 years were enrolled in the clindamycin/gentamicin group.

Eight patients in the Primaxin group and 5 patients in the clindamycin/gentamicin group were acceptable for evaluation of drug efficacy. Safety was assessed in all 13 patients in each treatment group.

Clinical cure or improvement occurred in 7/8 (87.5%) patients in the Primaxin group and in 4/5 (80.0%) of the patients in the clindamycin/gentamicin group.

A favorable bacteriological outcome (eradication) was achieved in 25 (93%) of 27 organisms isolated in the Primaxin group and in 7 (87.5%) of 8 organisms isolated in the clindamycin/gentamicin group.

No systemic or local side effects were reported in this study. The only laboratory test abnormality reported was an increase in serum creatinine in 2 patients in the clindamycin/gentamicin group.

Although the number of patients in this study was rather small, results tend to indicate that Primaxin compares favorably with clindamycin plus gentamicin in the treatment of patients with infections caused by susceptible bacteria.

CLINICAL STUDIES (Domestic)
II. Uncontrolled

1.   Protocol No. 016
     Title: "A Multicenter Open Study of the Efficacy, Safety, and Tolerance of Primaxin (imipenem/cliastatin) in the Parenteral Therapy of Infections Caused by Pathogenic Bacteria in Hospitalized Patients."

Study Design: This was an open, dose ranging, bacteriologically controlled study of the efficacy, safety, and tolerance of Primaxin in hospitalized patients with presumed or proven bacterial infection.

Procedure: Patients accepted for entry into the study were required to provide a signed written informed consent form. A clinical history was obtained, and a complete physical examination was performed.
Once the clinical diagnosis was established and the proper bacteriologic cultures and susceptibility studies, and laboratory tests were obtained, treatment was started with Primaxin at a dose ranging from 1.0 to 4.0 g/day depending on the type and severity of the infection. Each dose was administered by intravenous infusion over a period of 15 to 30 minutes.
During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded. A daily infusion tolerance record was also kept.

Any abnormal physical sign or symptom which occurred during the course of drug treatment was recorded in the case report form. Patients were observed with particular attention to any evidence of allergic phenomenon including rashes, itching, or anaphylactic manifestations.

Follow-up cultures were obtained during and after completion of therapy, except in the obvious cases in which cultures were impossible to obtain by virtue of a healed site such as in cases of cellulitis, abscesses, etc.

Laboratory tests of hematologic, renal, and hepatic function were repeated at various times during therapy and following completion of therapy.

At the conclusion of drug therapy and after all clinical and laboratory data had been obtained. Judgment was made by the investigator of the safety, tolerability, and clinical and bacteriological efficacy of the study drug for each patient.

Response to treatment was assessed by both clinical and bacteriological outcomes
Favorable clinical outcomes included:
     -Cure (Investigators judgment that the signs and symptoms of the infection were resolved).
     -Improvement (Investigators judgment that the infection was brought under control, and the need for further intravenous therapy was not indicated).

Unfavorable clinical outcome included:
     -No improvement
     -Patient died of infection primarily (with or without a contributing background disease).

Favorable bacteriologic outcome:
-Eradication of the etiologic pathogen(s)

Unfavorable bacteriologic outcome:
-Suppression of the etiologic pathogen(s)
-Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse
reactions. When an abnormal laboratory result or clinical event was
noted, the investigator was required to render a judgment as to the
intensity and seriousness of the occurrence and its relationship to
the drug. They were also required to indicate the outcome and the
type of action taken with regard to the adverse effect.

Investigators: Fifty-two well-qualified investigators in the USA
participated in this multiclinic study.

Overall Summary of Studies Conducted Under Protocol No. 016

Total No. of Patients: 717
Age Range (years): 12-101
Mean Age (years): 50.7
Sex
    Male: 437
    Female: 280

EVALUATION

EFFICACY
No. of Cases Evaluable: 506
No. of Sites of Infection Evaluable: 573
No. of Cases Unevaluable: 211

REASONS CASES UNEVALUABLE
No pretreatment pathogen: 97
Organism resistant to study drug: 3
Clinical diagnosis not clear: 5
Inadequate bacteriologic culture: 30
Treatment course too short: 35
Effective therapy prestudy: 1
Effective concomitant therapy: 14
No post-treatment culture: 20
No follow-up: 6

DURATION OF TREATMENT
(Evaluable Cases)

Days	No. Patients
4-14	366
15-29	98
30-49	41
61	1

RESULTS

INFECTION	NO.	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/furuncle decubitus and other skin ulcers)	129	67(51.9%)	56(43.4%)	6(4.7%)
BONE/JOINT (Osteomyelitis, pyogenic arthritis)	53	27(50.9%)	21(39.6%)	5(9.4%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess, bronchitis)	108	45(41.7%)	48(44.4%)	15(13.9%)
UPPER RESPIRATORY (Peritonsillar abscess, tracheitis)	2		1(50%)	1(50%)
OTITIS	3	1(33.3%)	1(33.3%)	1(33.3%)
GYNECOLOGIC (PID, endometritis, tubo-ovarian abscess, pelvic abscess)	49	36(73.5%)	10(20.4%)	3(6.1%)
INTRA-ABDOMINAL (Peritonitis, abscess, liver abscess, cholangitis, cholecystitis)	44	30(68.2%)	12(27.3%)	2(4.5%)
UTI (Uncomplicated) (Cystitis, pyelonephritis)	12	11(91.7%)	1(8.3%)	
UTI (Complicated) (Cystitis, pyelonephritis, renal abscess)	73	55(75.3%)	16(21.9%)	2(2.7%)

BACTERIAL SEPTICEMIA	66	50(75.8%)	14(21.2%)	2(3.0%)
BACTEREMIA	24	15(62.5%)	8(33.3%)	1(4.2%)
ENDOCARDITIS	9	9(100%)		
BRAIN ABSCESS	1	1(100%)		

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
SKIN & SKIN STRUCTURE		
Corynebacterium spp.	4	4(100%)
S. aureus(S)	9	8(88.9%)
S. aureus(R)	43	36(83.7%)
S. epidermidis	7	4(57.1%)
Alpha-hemolytic streptococci	7	7(100%)
Beta-hemolytic streptococci	1	1(100%)
Group A Streptococci	15	14(93.3%)
Group B Streptococci	5	5(100%)
Group D Streptococci (enterococci)	16	12(75%)
S. faecalis	6	6(100%)
Other Streptococcus species	17	17(100%)
Acinetobacter spp.	1	1(100%)
Acinetobacter calcoaceticus	4	4(100%)
Aeromonas hydrophilia	3	2(66.7%)
Citrobacter diversus	2	2(100%)
Citrobacter freundii	2	2(100%)

(Continued)

	No.	Eradicated
Enterobacter spp.	1	1(100%)
Enterobacter aerogenes	4	4(100%)
Enterobacter cloacae	9	9(100%)
Escherichia coli	17	17(100%)
Klebsiella oxytoca	7	7(100%)
Klebsiella pneumoniae	4	3(75%)
Morganella morganii	7	7(100%)
Proteus spp.	1	1(100%)
Proteus rettgeri	1	1(100%)
Proteus vulgaris	4	3(75%)
Proteus mirabilis	20	12(60%)
Pseudomonas aeruginosa	37	26(70.3%)
Serratia spp.	1	1(100%)
Serratia marcescens	5	4(80%)
Eikenella spp.	1	1(100%)
Eubacterium spp.	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus spp.	13	13(100%)
Peptostreptococcus spp.	5	5(100%)
Bacteroides spp.	19	19(100%)
Bacteroides fragilis	12	12(100%)
Fusobacterium spp.	3	3(100%)
Veillonella parvula	1	1(100%)

BONE/JOINT

	No.	Eradicated
S. aureus(S)	8	8(100%)
S. aureus(R)	16	15(93.8%)
S. epidermidis	5	5(100%)
Streptococcus spp.	10	10(100%)
Group D Streptococci (enterococci)	5	5(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
S. faecalis	2	2(100%)
Acetinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	1	1(100%)
Enterobacter aerogenes	3	3(100%)
Enterobacter cloacae	6	6(100%)
Escherichia coli	2	1(50%)
Morganella morganii	2	2(100%)
Proteus species	1	0
Proteus vulgaris	2	1(50%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	21	19(90.5%)
Serratia marcescens	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus species	3	3(100%)
Peptostreptococcus spp.	1	1(100%)
Bacteroides species	2	1(50%)
Bacteroides fragilis	3	2(66.7%)
Fusobacterium spp.	1	1(100%)
LOWER RESPIRATORY		
S. aureus(S)	2	2(100%)
S. aureus(R)	6	6(100%)
S. epidermidis	1	0
S. pneumoniae	20	20(100%)
Group A Streptococci	1	1(100%)
Group D Streptococci (enterococci)	4	2(50%)
Other Streptococcus species	8	8(100%)
Acinetobacter calcoaceticus	4	4(100%)
Citrobacter freundii	1	0
Enterobacter aerogenes	2	2(100%)
Enterobacter agglomerans	1	1(100%)
Enterobacter cloacae	8	7(87.5%)
Escherichia coli	8	7(87.5%)
H. influenzae	24	22(91.7%)
H. parainfluenzae	2	2(100%)
Klebsiella pneumoniae	17	14(82.3%)
Proteus mirabilis	12	4(33.3%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	38	9(23.7%)
Serratia marcescens	5	3(60%)
Branhamella catarrhalis	1	1(100%)
Eikenella corrodens	1	1(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
UPPER RESPIRATORY		
S. aureus^(R)	1	0
Streptococcus spp.	1	1(100%)
Enterobacter aerogenes	1	1(100%)
Klebsiella pneumoniae	1	1(100%)
Peptostreptococcus spp.	1	1(100%)
Bacter es (not fragilis)	1	1(100%)
Fusobacterium spp.	1	1(100%)
GYNECOLOGIC		
S. aureus^(S)	3	3(100%)
S. aureus^(R)	4	4(100%)
S. epidermidis	16	16(100%)
Alpha-hemolytic Streptococci	3	3(100%)
Group B Streptococci	13	13(100%)
Group D Streptococci		
(Enterococci)	13	11(84.6%)
S. faecalis	3	3(100%)
Other Streptococcus species	6	6(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	2	2(100%)
Citrobacter freundii	1	1(100%)
Enterobacter aerogenes	2	2(100%)
Escherichia coli	16	15(93.8%)
Klebsiella pneumoniae	5	5(100%)
Morganella morganii	1	1(100%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	1	0
Bifidobacterium spp	2	2(100%)
Clostridium perfringens	1	1(100%)
ffkya anaerobia	1	1(100%)
tococcus spp	1	1(100%)
Pe streptococcus spp	6	6(100%)
Bacteroides spp	22	20(90.9%)
Bacteroides fragilis	7	6(85.7%)
Gardnerella vaginalis	3	3(100%)
Veillonella parvula	1	1(100%)
INTRA-ABDOMINAL		
S. aureus^(R)	1	1(100%)
Group D Streptococci		
(Enterococci)	7	5(71.4%)
S. faecalis	1	0
Streptococcus viridans group	6	6(100%)
Other Streptococcus species	8	8(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter species	2	2(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
Citrobacter freundii	1	1(100%)
Enterobacter aerogenes	2	2(100%)
Enterobacter cloacae	3	1(33.3%)
Escherichia coli	25	20(80%)
Klebsiella oxytoca	3	3(100%)
Klebsiella pneumoniae	6	6(100%)
Morganella morganii	2	2(100%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	5	4(80%)
Pseudomonas alcaligenes	1	1(100%)
Bifidobacterium adolescentis	1	1(100%)
Clostridium spp	12	12(100%)
Propionibacterium acnes	3	3(100%)
Peptococcus spp	2	2(100%)
Peptostreptococcus spp	2	1(50%)
Bacteroides spp	4	4(100%)
Bacteroides fragilis	19	18(94.7%)
Fusobacterium spp	2	2(100%)

UNCOMPLICATED UTI

Escherichia coli	8	8(100%)
Proteus mirabilis	2	2(100%)
Proteus vulgaris	1	1(100%)
Enterobacter cloacae	1	1(100%)
Pseudomonas aeruginosa	1	1(100%)

COMPLICATED UTI

S. aureus(R)	1	0
Group D Streptococcus (Enterococci)	4	3(75%)
Escherichia coli	15	11(73.3%)
Proteus mirabilis	6	4(66.7%)
Morganella morganii	3	3(100%)
Providencia stuartii	3	1(33.3%)
Proteus rettgeri	3	2(66.7%)
Enterobacter cloacae	7	6(85.7%)
Klebsiella pneumoniae	5	5(100%)
Klebsiella oxytoca	1	1(100%)
Pseudomonas aeruginosa	35	31(88.6%)
Serratia species	1	1(100%)
Serratia marcescens	1	1(100%)
Bifidobacterium spp	1	1(100%)
Peptococcus spp	1	1(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
BACTERIAL SEPTICEMIA		
S. aureus(S)	2	2(100%)
S. aureus(R)	9	8(88.9%)
S. epidermidis	1	1(100%)
S. pneumoniae	7	7(100%)
Group D Streptococci (enterococci)	2	2(100%)
S. faecalis	1	1(100%)
Other Streptococcus species	9	9(100%)
H. influenzae	1	1(100%)
Escherichia coli	17	17(100%)
Proteus mirabilis	1	1(100%)
Klebsiella pneumoniae	3	3(100%)
Klebsiella oxytoca	1	1(100%)
Citrobacter freundii	1	1(100%)
Acinetobacter calcoaceticus	1	1(100%)
Pseudomonas aeruginosa	1	1(100%)
Serratia marcescens	4	4(100%)
Flavobacterium spp	1	1(100%)
Salmonella (Group D)	1	1(100%)
N. gonorrhoeae	1	1(100%)
Corynebacterium acnes	1	1(100%)
Clostridium bifermentans	1	1(100%)
Bacteroides fragilis	3	2(66.7%)
BACTEREMIA		
S. aureus(S)	1	1(100%)
S. aureus(R)	2	2(100%)
S. epidermidis	1	1(100%)
S. pneumoniae	1	1(100%)
Group D Streptococci (Enterococci)	1	1(100%)
H. influenzae	1	1(100%)
Escherichia coli	7	7(100%)
Enterobacter cloacae	3	3(100%)
Citrobacter diversus	1	1(100%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	4	4(100%)
Bacteroides bivius	1	1(100%)
ENDOCARDITIS		
S. aureus(S)	1	1(100%)
S. aureus(R)	5	5(100%)
Streptococcus spp	1	1(100%)
S. pneumoniae	1	1(100%)
Streptococcus viridans group	1	1(100%)
BRAIN ABSCESS		
S. aureus(R)	1	1(100%)

The incidence of superinfections due to bacteria was approximately 2%, and that due to yeast or fungi was approximately 1%.
The bacteria most frequently involved in superinfections were resistant strains of P. aeruginosa, P. maltophilia, and S. epidermidis.

Resistance to Primaxin developed in 27 of 143 (19%) Pseudomonas aeruginosa isolates. Many of these were isolated from sputum or endotracheal tubes or from chronic wounds. One strain each of Proteus mirabilis and enterococcus also developed resistance to Primaxin.

SAFETY

Total No. of Patients: 717
No. of Patients with Systemic Side Effects: 81(11.3%)
No. of Patients with Local Side Effects: 18(2.5%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Nausea	16(2.2%)	2(0.3%)	6(0.8%)	7(0.9%)	1(0.1%)
Vomiting	12(1.8%)	4(0.6%)	4(0.6%)	2(0.3%)	2(0.3%)
Diarrhea	16(2.2%)	5(0.7%)	8(1.7%)	1(0.1%)	2(0.3%)
Pseudomembranous colitis*	3(0.4%)			3(0.4%)	
Heartburn	1(0.1%)		1(0.1%)		
Pruritus	2(0.3%)		1(0.1%)	1(0.1%)	
Facial edema	1(0.1%)			1(0.1%)	
Rash	7(0.9%)		3(0.4%)	3(0.4%)	1(0.1%)
Urticaria	2(0.3%)			1(0.1%)	1(0.1%)
Erythema multiforme	1(0.1%)				1(0.1%)
Pruritus vulvae	1(0.1%)		1(0.1%)		
Fever	4(0.5%)		3(0.4%)		1(0.1%)
Septic shock	2(0.3%)	2(0.3%)			
Tinnitus	1(0.1%)		1(0.1%)		
Vertigo	2(0.3%)		2(0.3%)		
Headache	3(0.4%)	1(0.1%)	2(0.3%)		
Confusion	3(0.4%)	2(0.3%)		1(0.1%)	
Dizziness	2(0.3%)	1(0.1%)	1(0.1%)		
Encephalopathy	1(0.1%)			1(0.1%)	
Seizures	9(1.3%)	3(0.4%)	3(0.4%)	3(0.4%)	
Myoclonus	2(0.3%)			2(0.3%)	
Palpitations	1(0.1%)		1(0.1%)		
Hypotension	7(0.9%)	4(0.5%)	3(0.4%)		
Chest pain	2(0.3%	1(0.1%)	1(0.1%)		
Dyspnea	1(0.1%)	1(01.%)			

(Continued)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Syncope	1(0.1%)	1(0.1%)			
Cyanosis	1(0.1%)		1(0.1%)		
Polyarthropathy	1(0.1%)		1(0.1%)		

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Phlebitis/thrombo-phlebitis	16(2.2%)		2(0.3%)	12(1.7%)	2(0.3%)
Infused vein pain	2(0.3%)			1(0.1%)	1(0.1%)

*Five other patients had abnormal intestinal mucosa on colonoscopy or sigmoidoscopy or had C. difficile toxin in their stools.

A brief description of the events surrounding the development of seizures in nine patients follows·

Patients with seizures considered 'probably not drug related' by the investigator

A 44 year-old male with osteomyelitis developed a single episode of tonic-clonic seizure activity on day 26 of Primaxin therapy. No cause for his seizure could be found with the possible exception that he was also being treated with hyperbaric oxygen. The patient was medicated with phenytoin, and Primaxin therapy was continued for a total of 6 weeks without further seizures.

A 63 year-old male with a history of COPD, CHF, alcoholism, liver disease, esophogeal varices, and a left lung mass developed respiratory distress after aspiration. He was intubated and started on Primaxin therapy. The patient became hypotensive and developed renal failure and acidosis. On the fifth day of Primaxin treatment he developed status epilepticus as an agonal event.
At autopsy he was found to have carcinomatous pneumonia with metastases to lymph nodes, adrenal glands, liver, brain, and bones.

A 30 year-old female with history of multiple sclerosis and seizure disorder developed a septicemia and was placed on Primaxin therapy. After 14 days of treatment she had one seizure without obvious cause except for her underlying seizure disorder. An extensive work-up, including LP, EEG, CT scan, was unrewarding. Phenytoin treatment was started, and she was treated with Primaxin for 6 more days without any more seizures.

Patients with seizures considered 'possibly drug related' by the investigator

A 69 year-old female with a history of seizure disorder (on Dilantin maintenance) was started on Primaxin treatment, but Dilantin was not administered. On the 3rd day of treatment she started having multiple seizures. Primaxin was discontinued on the 6th day partly because no organism was cultured and partly because of the seizures. After reinstitution of Dilantin and institution of phenobarbital her seizures were controlled.
During her hospitalization this patient had received metoclopramide which is contraindicated in patients with history of seizures, because it can increase the frequency and severity of seizures.

A 71 year-old female with a history of COPD, respiratory insufficiency (respiratoi-dependent), and arrythmias developed quadriparesis possibly due to a brainstem infarct. One day after Primaxin was started for the treatment of pneumonia, she developed supra-ventricular tachycardia with marked hypotension. On the 3rd and 4th days of Primaxin therapy she had brief (1-2 min) tonic/clonic seizures, and the Primaxin dose was lowered. From the 6th to the 9th day of therapy she had intermittent seizures (treated with Dilantin and phenobarbital) and episodes of bradycardia and marked hypotension. Because a resistant Pseudomonas was isolated from the sputum, Primaxin was discontinued, and clindamycin and amikacin were started. She continued to have seizures while on these antibiotics, along with severe episodes of hypotension. She finally died six days after therapy had been discontinued.

A 68 year-old male had a past history of ASCVD, poorly-controlled insulin dependent diabetes, chronic renal insufficiency, and organic CNS disease (chronic organic brain syndrome secondary to multiple cerebrovascular accidents). Two weeks following amputation of a gangrenous foot, a new episode of CVA occurred. The patient's impaired level of consciousness continued to deteriorate, and he developed CHF and acute respiratory failure probably secondary to aspiration. He had to be intubated and required mechanical ventilation and subsequently developed a gram-negative pneumonia. Treatment with cefamandole was instituted, but when the patient failed to improve and cefamandole-resistant organisms were isolated, Primaxin therapy was initiated. On the 5th day of treatment, 10 minutes after he had both jugular and subclavian catheters removed, he experienced a 30-60 second grand mal seizure. Laboratory evaluation at that time revealed a blood sugar greater than 300 and a serum calcium of 3.6. An additional decreased dose of Primaxin was given and tolerated without incident. The patient subsequently recovered.

NDA 50-587

Patients with seizures considered 'probably drug related' by the investigator

A 90 year-old female was treated with Primaxin for a bacterial septicemia. On the 14th day of treatment she developed a grand mal seizure which lasted approximately 2 minutes. Laboratory values at that time were normal. A CT head scan with contrast showed diffuse cortical atrophy.

A 70 year-old female with a past history of grand mal seizures (3 occurrences over a 48 hour interval) was treated with Primaxin for an osteomyelitis. On the 4th day of treatment the patient experienced myoclonic activity, and on the 6th day she had a grand mal seizure. This event and the ensuing post-ictal state lasted for approximately 24 hours during which time neurologic evaluation demonstrated a normal CT scan of the head, EEG, and LP (except for an increased CSF protein). Primaxin therapy was discontinued, and the patient was started on Dilantin and recovered without any focal neurological deficit.

A 77 year-old female with endocarditis was placed on Primaxin treatment. On the 6th day of therapy she developed grand mal seizures. A CAT scan showed possible cerebral emboli. She was started on Dilantin therapy and had seizures again on day 15 and 16 of therapy. Primaxin was discontinued on day 18, and she had no further seizures.

Deaths: Forty-five deaths were reported in this study. None was considered by the investigator to be related to Primaxin therapy.

Abnormal Laboratory Tests

Test	
Hemoglobin	(D) 4
Hematocrit	(D) 4
WBC	(D)11
Neutrophils	(D) 3
Monocytes	(I) 2
Eosinophils	(I)27
Platelets	(I)12
	(D) 6
Positive Coombs' test	16
Prothrombin time	(I) 2
BUN	(I) 2
Creatinine	(I) 1
Bilirubin	(I) 3
SGOT (AST)	(I)26

(Continued)

Abnormal Laboratory Tests

Test
SGPT (ALT)   (I)25
Alkaline phosphatase   (I)23
Serum chloride   (I) 3
Urine protein   (I) 1
WBCs in urine   (I) 1
Urine bilirubin   (I) 3
Urine urobilinogen   (I) 4

Summary and Conclusions

This was an open, multiclinic, non-comparative study of the efficacy and
safety of Primaxin in the treatment of patients with serious infections caused
by susceptible pathogenic bacteria.
A total of 717 patients, 437 males and 280 females, ranging in age from 12 to
101 years were enrolled in this protocol.
Five hundred and six patients with 573 sites of infection were acceptable for
evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure or improvement occurred in 123/129 (95%) skin and skin structure
infections, in 48/53 (91%) bone and/or joint infections, in 93/108 (86%) lower
respiratory tract infections, in 46/49 (94%) gynecologic infections, in 42/44
(95%) intra-abdominal infections, in 12/12 (100%) uncomplicated urinary tract
infections, in 71/73 (97%) complicated urinary tract infections, in 64/66
(97%) bacterial septicemia, and in 9/9 (100%) patients with endocarditis.

As shown in the table depicting the bacteriologic response to Primaxin
treatment, the eradication rate for most infections was, in general, very good
considering the nature of the infections treated. Regarding the low
eradication rate of P. aeruginosa in lower respiratory tract infections, it
should be noted that many of these patients had severe infections superimposed
on some chronic lung disease (COPD, cystic fibrosis, bronchiectasis) where
complete eradication of the infecting organism is hardly ever achieved. In
addition, many of these patients had previously failed treatment with other
antibiotic regimens to which the organism had developed resistance.

Systemic side effects were reported in 11.3% of the patients. The most common
side effects were nausea, vomiting, diarrhea, and allergic skin rashes.
Seizures and/or myoclonus occurred in 1.5% of the patients.

Local side effects were reported in 2.5% of the patients.

The most commonly reported abnormal laboratory values were eosinophilia and
abnormal liver function tests.

2.   Protocol No. 009
     Title: "An Open, Multiple-Dose Clinical Pharmacology and Therapeutic
     Study of the Safety, Tolerance, and Efficacy of Primaxin
     (imipenem/cilastatin) in the Parenteral Therapy of Bacterial
     Infections in Hospitalized Patients."

     Study Design and Procedure: This was an open multiple-dose stud
     conducted in 20 hospitalized patients with proven or suspected
     bacterial infections caused by pathogens presumed or known to be
     susceptible to Primaxin.

     Upon admission to the hospital each patient had a complete history
     and physical examination, and all abnormal signs and symptoms
     relating to both the acute infection and to background diseases were
     noted and recorded.
     Following appropriate diagnostic studies, patients were treated with
     Primaxin, 500 mg every 6 hours, by constant intravenous infusion of
     approximately 20 minutes duration.
     During the study period, daily measurements of temperature, pulse,
     blood pressure, and respiratory rate were recorded.

     The clinical and bacteriological course of the patient was followed
     and documented with serial observations including safety studies of
     blood and urine obtained before, during, and after therapy.
     Patients were observed with particular attention to any evidence of
     allergic reactions including rash, itching, or anaphylactic
     manifestations. Daily observations of the tolerance of intravenous
     therapy were made.

     Multiple blood samples for drug assay were obtained following the
     first dose and again following a dose given within the last 3 days of
     drug therapy. The total urine voided during the 6 hour dosing
     interval on each of these occasions was collected at 0-1, 1-2, 2-4,
     and 4-6 hours.

     At the conclusion of drug therapy, and after all clinical and
     laboratory data were obtained, judgment was made on the clinical and
     bacteriological efficacy of study drug therapy, its safety and
     tolerability.

Summary of Study Conducted Under Protocol No. 009

Investigator: W. Lance George, M.D., V.A. Wadsworth Medical Center, Los
Angeles, California

TOTAL NO. OF PATIENTS: 20

AGE RANGE (Years): 39-76

MEAN AGE (Years): 56.1

SEX:
   Male: 20

EVALUATION

EFFICACY
NO. OF CASES EVALUABLE: 15
NO. OF SITES OF INFECTION EVALUABLE: 16
NO. OF CASES UNEVALUABLE: 5

REASONS CASES UNEVALUABLE
No pre-treatment pathogen: 2
Inadequate bacteriologic culture: 2
No post-treatment follow-up: 1

DURATION OF TREATMENT
  (Evaluable Cases)

DAYS	NO. OF PATIENTS
4-14	7
15-29	3
30-41	5

RESULTS

INFECTION	NO.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE (cellulitis)	1	1(100%)		
BONE/JOINT (Osteomyelitis, pyogenic arthritis)	6	1(16.7%)	5(83.3%)	
LOWER RESPIRATORY (Pneumonia, bronchitis)	2	1(50%)	1(50%)	
UTI (Uncomplicated) (Cystitis)	1	1(100%)		
UTI (Complicated) (Cystitis)	6	3(50%)	3(50%)	

ORGANISM	NO.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
SKIN & SKIN STRUCTURE			
Corynebacterium spp	1	1(100%)	
S. aureus(R)	1	1(100%)	
E. coli	1	1(100%)	
BONE/JOINT			
S. aureus(R)	2	2(100%)	
Streptococcus spp	1	1(100%)	
E. coli	2	2(100%)	
M. morganii	1	1(100%)	
P. mirabilis	2	1(50%)	1(50%)
P. aeruginosa	4	3(75%)	1(25%)
B. fragilis	1	1(100%)	
B. vulgatus	1	1(100%)	
LOWER RESPIRATORY			
E. coli	1	1(100%)	
P. mirabilis	1		1(100%)
P. aeruginosa	2	1(50%)	1*(50%)
S. marcescens	1	1(100%)	
UTI (Uncomplicated)			
E. coli	1	1(100%)	
UTI (Complicated)			
Strep. (Group B)	2	2(100%)	
Strep. (Group D enterococci)	1	1(100%)	
E. coli	4	2(50%)	2(50%)
C. diversus	1		1(100%)
Citrobacter spp	1	1(100%)	

*P. aeruginosa persisted in one patient with pneumonia and underlying bronchiectasis. Organisms are usually difficult to eradicate in this chronic condition.

SAFETY

TOTAL NO. OF PATIENTS: 20
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 2(10%)
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 1(5%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Fever	1(5%)	1(5%)			
Abdominal pain	1(5%)	1(5%)			
Diarrhea	1(5%)		1(5%)		

(Continued)

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL					
Phlebitis	1(5%)		1(5%)		

Abnormal Laboratory Tests

Hemoglobin	(D)1
Hematocrit	(D)1
WBC	(D)1
Eosinophils	(I)1
Platelets	(D)1
SGPT	(I)1
Positive Coombs' test	1

PHARMACOKINETICS

Based on creatinine clearance (GFR) information, the majority of the patient population enrolled in this study could be divided into two groups: those with apparently normal renal function and those with mild renal impairment. In patients with GFR > 100 ml/min, the urinary recovery of imipenem during each dose interval averaged 50-57% of the dose, and mean renal clearance was between 105 and 128 ml/min.

In patients with GFR < 100 ml/min, the urinary recovery of imipenem averaged 37-46% of the dose, and mean renal clearance was 69-88 ml/min. In the same comparison, the urinary excretion of cilastatin was 52% to 68% of the dose, and renal clearance averaged between 101 and 123 ml/min (GFR >100) while in patients with mild renal impairment, urinary excretion of cilastatin averaged 41-45% of the dose, and mean renal clearance was between 50 and 72 ml/min.

In this study the urinary excretion of either imipenem or cilastatin in patients with apparent normal renal function was somewhat lower than expected. The reason for this occurrence is not obvious, although most subjects were noted as having neurologic disorders leading to a neurogenic bladder, difficulty in voiding, and/or urine reduction.

The plasma clearance of imipenem averaged 201-223 ml/min during each dosing interval studied in patients with GFR >100 ml/min and 167-176 ml/min in patients with GFR <100 ml/min.

The mean area-under-the serum curve (AUC) was 25% greater in patients with mild renal impairment, but the AUC did not change from the first to the 9th dose for either group. Similarly, cilastatin plasma clearance averaged 215-223 ml/min in patients with GFR > 100 ml/min during each dosing interval and 142-159 ml/min in patients with GFR <100 ml/min. The AUC was 50% greater in patients with mild renal impairment but did not change between dosing intervals for either group.

The plasma half-life of imipenem and cilastatin did not change throughout the study for either group but was slightly longer in patients with mild renal impairment.

These results indicate that repeated administration of 500 mg each of imipenem/cilastatin every 6 hours does not alter the disposition of either drug in patients with normal renal function or patients with mild renal impairment from that observed after a single dose. Little if any accumulation of either drug occurs in either patient group indicating that steady state conditions prevail by the end of the first day's dosing.

3. Compassionate Protocol No. 002
    Early in the Primaxin program a special protocol was designed which would allow the entry of patients who would need the antibiotic on a compassionate basis.
    As a rule, most patients treated under this protocol were seriously ill and had already been treated with several courses of other antibiotics. With rare exceptions, Primaxin was not made available unless it was the only antibiotic (or at least the only beta-lactam) to which the primary pathogen(s) was (were) susceptible. In addition, because early in these studies the rate of development of resistance to Primaxin was unknown, Merck insisted upon the adjunctive use of a second antibiotic, usually an aminoglycoside. However, although virtually every patient received two antibiotics, many had organisms susceptible only to Primaxin; therefore, these cases were eligible for evaluation of drug efficacy.

    Forty patients were tr ted with Primaxin under the compassionte protocol. They ranged in age from 16 to 81 years with a mean age of 43.9 years. There were 17 females and 23 males. Primaxin was administered at the following daily doses:

        1G - 2 patients
        2G - 13 patients
        3G - 10 patients
        4G - 15 patients

    Duration of treatment was as follows:

3 - 5 days	6 patients
6 - 10	7 patients
11 - 15	11 patients
$\geq$ 16	16 patients

The results obtained in 13 patients considered eligible for efficacy evaluation were as follows:

INFECTION	NO.	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
LOWER RESPIRATORY	8	1(12.5%)	5(62.5%)	2(25.0%)
INTRA-ABDOMINAL	2		2(100%)	
BACTERIAL SEPTICEMIA	1		1(100%)	
SKIN & SKIN STRUCTURE	2		1(50%)	1(50%)

ORGANISM	NO.	BACTERIOLOGIC RESPONSE	
		ERADICATED	NOT ERADICATED
LOWER RESPIRATORY			
Acinetobacter calcoaceticus	3	2(66.7%)	1(33.3%)
P. aeruginosa	6		6(100%)
P. maltophilia	1		1(100%)
S. marcescens	1		1(100%)
INTRA-ABDOMINAL			
P. aeruginosa	2	2(100%)	
P. fluorescens	1		1(100%)
BACTERIAL SEPTICEMIA			
P. aeruginosa	1	1(100%)	
SKIN & SKIN STRUCTURE			
Strep (Group D enterococci)	2	1(50%)	1(50%)
Enterobacter cloacae	1		1(100%)
P. aeruginosa	2		2(100%)

SAFETY

NO. OF PATIENTS: 40
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 2(5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 8(20%)

SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL					
Erythema I.V. site	1(2.5%)	1(2.5%)			
Phlebitis/thrombo- phlebitis	1(2.5%)			1(2.5%)	

(Continued)

SIDE EFFECTS

SYSTEMIC	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Chills	1(2.5%)	1(2.5%)			
Nausea	2(5%)	1(2.5%)	1(2.5%)		
Dysuria	1(2.5%)	1(2.5%)			
Nystagmus	1(2.5%)	1(2.5%)			
Hyperhydrosis	1(2.5%)	1(2.5%)			
Confusion	1(2.5%)	1(2.5%)			
Hearing loss	2(5%)	2(5%)			
Apnea	1(2.5%)	1(2.5%)			
Intracerebral hemorrhage	1(2.5%)	1(2.5%)			
Oliguria and anuric	1(2.5%)	1(2.5%)			
Convulsive disorder	2(5%)	1(2.5%)		1(2.5%)	

Both patients who developed hearing loss were also receiving an aminoglycoside antibiotic which could have contributed to this adverse effect.

Of the two patients who developed convulsions, one had recurrent seizures while on tobramycin and cefoperazone, 2 weeks after Primaxin therapy had been discontinued. The other patient was found to have a cerebellar abscess at autopsy.

Deaths: Twelve patients died during or shortly after Primaxin treatment. All were considered by the investigators "definitely not drug related".

Abnormal Laboratory Tests

Leukopenia	2 cases
Neutropenia	2 cases
Eosinophilia	3 cases
Increased SGOT	1 case
Increased alkaline phosphatase	2 cases
Increased serum creatinine	1 case

CLINICAL STUDIES (Foreign)

I. Controlled (3 Studies)

1. Protocol No. 514
    Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety and Tolerance of I.V. Administered Primaxin and Cephalothin in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

Study Design: This was an open, controlled, randomized, multiclinic study to compare the efficacy, safety and tolerability of Primaxin versus cephalothin in the treatment of hospitalized patients with infections caused by susceptible bacteria.

Procedure: Patients were assigned to receive either Primaxin or cephalothin according with a computer-generated, randomized allocation schedule.
Each patient in the Primaxin group received 250 mg every 6 hours, and those in the cephalothin group received 2 grams every 6 hours. Both antibiotics were administered by intravenous infusion over 15 to 30 minutes.
Patients were to be treated for a minimum of 5 days.

After signing an informed consent form, all patients provided a complete clinical history and underwent a physical examination. During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded.
A daily infusion tolerance record of the study drug was kept.
Tolerance was evaluated on the basis of pain, erythema, induration of the vein, and ulceration of the infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function were carried out in all patients before study drug therapy, four to seven days after initiation of therapy, and one to three days after termination of therapy. Additional diagnostic test (e.g., X-ray, sonography) were performed as indicated.

Blood cultures and cultures of other suspected sites were obtained prior to, during, and after study drug therapy. Gram stains and standard bacteriologic susceptibility tests were performed on all cultures. Standard susceptibility tests were performed by either disc or broth dilution method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

The five investigators who conducted studies under this protocol and their affiliations are listed below:

Y. Benard, Centre Hospitalier Universitaire Co'te de Nacre, Caen, France.
M. Des Roseaux, Centre Hospitalier Universitaire, Co'te de Nacre, Caen, France.
J. Modai, Hopital Claude Bernard, Paris, France.
F. Vachon, Hopital Claude Bernard, Paris, France.
D. L. Tyrell, University of Alberta, Edmonton, Alberta, Canada.

Summary of Studies Conducted Under Protocol No. 514

	PRIMAXIN	CEPHALOTHIN
TOTAL NO. OF PATIENTS	47	38
AGE RANGE (Years)	19-68	20-75
MEAN AGE (Years)	50.9	52.5
SEX		
Male	28	20
Female	19	18

EVALUATION

EFFICACY

	PRIMAXIN	CEPHALOTHIN
NO. OF CASES EVALUABLE	15	11
NO. OF SITES OF INFECTION EVALUABLE	16	11
NO. OF CASES UNEVALUABLE	32	27

REASONS CASES UNEVALUABLE

No pre-treatment pathogen	17	15
Clinical diagnosis not clear	2	1
Effective concomitant antibiotic	1	0
Treatment course too short	3	2
Inadequate cultures	9	9

	PRIMAXIN	CEPHALOTHIN
DOSE (Evaluable Cases)	250 mg q 6 h	2g q 6 h
DURATION OF TREATMENT (Days) (Evaluable Cases)	6-15	5-14

RESULTS

		PRIMAXIN CLINICAL RESPONSE				CEPHALOTHIN CLINICAL RESPONSE	
INFECTION	NO.	CURE	IMP.	FAIL	NO.	CURE	IMP.
SKIN & SKIN STRUCTURE (Abscess)	1	1(100%)			-		
LOWER RESPIRATORY (Bronchitis, pneumonia, empyema)	7	5(71%)		2(29%)	5	4(80%)	1(20%)
SEPTICEMIA	3	3(100%)			4	3(75%)	1(25%)
UTI (Uncomp) (cystitis, pyelonephritis)	4	4(100%)			1	1(100%)	
UTI (Complicated) (pyelonephritis)	1	1(100%)			1	1(100%)	

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEPHALOTHIN BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
SKIN & SKIN STRUCTURE								
S. aureus(S)*	1	1(100%)			-			
LOWER RESPIRATORY								
K. pneumoniae	-				1	1(100%)		
P. multocida	1	1(100%)			-			
K. ozaenae	1	1(100%)			-			
E. coli	1	1(100%)			-			
S. pneumoniae	2	2(100%)			1	1(100%)		
P. aeruginosa	1	1(100%)			-			
H. influenzae	2	2(100%)			3	3(100%)		
SEPTICEMIA								
E. coli	1	1(100%)			2	2(100%)		
B. fragilis	1	1(100%)			-			
S. pneumoniae	1	1(100%)			1	1(100%)		
P. mirabilis	-				1	1(100%)		
UTI (Uncomp.)								
E. coli	4	4(100%)			1	1(100%)		
UTI (Complicated)								
K. pneumoniae	1	1(100%)			-			
E. coli	-				1	1(100%)		

*(S) = Sensitive

In the Primaxin treated group, 1 patient with an empyema developed a reinfection with a resistant P. aeruginosa strain. In the Cephalothin treated group, 1 patient with urinary tract infection developed a reinfection.

SAFETY

	PRIMAXIN	CEPHALOTHIN
TOTAL NO. OF PATIENTS	47	38
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	2(4%)	4(10.5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	1(2%)	1(3%)

LOCAL SIDE EFFECTS

	PRIMAXIN	
	NO.	PROBABLY RELATED
Pain on infusion	1(2.1%)	1(2.1%)
Phlebitis/thrombo-phlebitis	1(2.1%)	1(2.1%)

	NO.	CEPHALOTHIN PROBABLY RELATED
Pain on infusion	1(2.6%)	1(2.6%)
Phlebitis/thrombo- phlebitis	1(2.6%)	1(2.6%)
Venous intolerance	1(2.6%)	1(2.6%)
Erythema, IV Site	1(2.6%)	1(2.6%)

SYSTEMIC SIDE EFFECTS

		PRIMAXIN	DEFINITELY RELATED
Pruritus	1		1(2.1%)

		CEPHALOTHIN
STEVENS-JOHNSON SYNDROME	1	1(2.6%)

Deaths

Two patients in the cephalothin group died during treatment. They were judged by the investigators to be definitely not drug-related.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEPHALOTHIN
Eosinophils	1/6	1/1
SGOT (AST)	1/4	1/1
SGPT (ALT)	1/1	0
Bilirubin	1/1	
Alk. phosphatase	1/1	1/1
LDH	1/1	0

Summary and Conclusions

This was an open, randomized, controlled multicenter study comparing Primaxin and cephalothin in the treatment of infections caused by susceptible bacteria.

A total of 47 patients, 28 males and 29 females, ranging in age from 19 to 68 years were enrolled in the Primaxin group. A total of 38 patients, 20 males and 18 females, ranging in age from 20 to 75 years were enrolled in the cephalothin group. Demographic characteristics of patients in each treatment group were similar.

Fifteen patients with 16 sites of infection in the Primaxin group and 11 patients in the cephalothin group were acceptable for evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure or improvement occurred in 14/16 (87.5%) infections in the Primaxin treated patients and in 11/11 (100%) in the cephalothin treated patients.

One of the treatment failures in the Primaxin group occurred in a patient with empyema who developed a reinfection with a Pseudomonas strain resistant to Primaxin.

A favorable bacteriological outcome (eradication) was achieved in 17 (100%) of 17 organisms isolated in the Primaxin group and in 11 (100%) of 11 organisms isolated in the cephalothin group.

Systemic side effects were reported in 2% of the patients in the Primaxin group and in 3% of the patients in the cephalothin group. Local side effects were reported in 4% of the patients in the Primaxin group and in 10.5% of the patients in the cephalothin group.

The laboratory test abnormalities reported in the Primaxin group were eosinophilia (6 patients), increased SGOT values (4 patients), and an instance each of elevated SGPT, bilirubin, alkaline phosphatase, and LDH values. In the cephalothin group, one instance each of eosinophilia, and elevated SGOT and alkaline phosphatase values.

No deaths occurred in the Primaxin group, and two occurred in the cephalothin group. They were judged by the investigators as "definitely not drug related".

Results of this study demonstrate Primaxin and cephalothin are relatively safe and effective in the treatment of patients with serious infections caused by susceptible bacteria.

2. Protocol No. 513
   Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety, and Tolerance of Intravenously Administered Primaxin and Cefotaxime in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

   Study Design: This was an open, active, drug-controlled, randomized, multiclinic study to compare the efficacy, safety, and tolerance of Primaxin and Cefotaxime in the intravenous treatment of hospitalized patients with infections caused by bacteria presumed susceptible to both agents.

   Procedure: Treatment group assignment was made using a computer-generated randomization allocation schedule. Having completed the informed consent procedure and screening for study eligibility, patients were allocated either to the Primaxin or the Cefotaxime group.
   Each patient in the Primaxin group received a total daily dose of 1.5 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.
   Patients in the Cefotaxime group received a total daily dose of 6 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.

Before entry into the study, all patients provided a complete
clinical history and underwent a physical examination. During the
study drug period, daily measurements of temperature, pulse, blood
pressure, and respiratory rate were recorded. A daily infusion
tolerance record of the study drug was kept. Tolerance was evaluated
on the basis of pain, erythema, induration of the vein, and
ulceration of the infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function
were carried out in all patients before, during, and after
termination of therapy. Additional diagnostic tests (e.g., x-ray,
sonography) were performed as indicated.

Blood cultures and cultures of other suspected sites were obtained
prior to, during, and after study drug therapy. Gram stains and
standard bacteriologic susceptibility tests (by either disc or broth
dilution method) were performed in all cultures.

Response to treatment was assessed by both clinical and
bacteriological outcomes.

Thirteen investigators conducted studies under Protocol No. 513.
Their names and affiliations are listed below:

Achong, M., St. Joseph's Hospital, Hamilton, Ontario
Bowie, W., Vancouver General Hospital, Shaughnessy Hospital,
   Vancouver, Canada
Daikas, G., "King Paul" Hospital, University of Athens Medical
   School, Athens, Greece
Glauser, M., Clinique Medicale Universitaire, Lausanne,
   Switzerland
Hell, K., Chirurgische Abteiluy, Liestal, Switzerland
Opperkuch, W., Ruhr-University of Bochum, Bochum, West Germany
Ronald, A., Basic Sciences Center, St. Boniface General Hosptial
   Winnipeg, Canada
Stamboulian, D., British Hospital of Buenos Aires, Buenos Aires,
   Argentina
Stille, W., Klinixum A. J. W. Goethe-Universitaet, Frankfurt,
   West Germany
Ten Napel, C., Hospital 'Ziekenzorg', Enschede, Holland
Veriava, Y., Coronation Hospital, Johannesburg, South Africa
Wittmann, D., Allgemeines Krankenhaus Altona, Hamburg, West
   Germany
Yourassowsky, E., Hospital Brugmann, Brussels, Belgium

Overall Summary of Studies Conducted Under Protocol 513

	PRIMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS	123	111
AGE RANGE (Years)	16-80	18-81
MEAN AGE (Years)	52.6	54.9
SEX		
Male	78	65
Female	45	46

EVALUATION

EFFICACY

	PRIMAXIN	CEFOTAXIME
NO. OF CASES EVALUABLE	69	69
NO. OF SITES OF INFECTION EVALUABLE	68	84
NO. OF CASES UNEVALUABLE	54	42

REASONS CASES UNEVALUABLE

No pretreatment pathogen	24	19
Organism resistant to study drug	1	0
Clinical diagnosis not clear	2	1
Inadequate bacteriologic cultures	8	13
Effective concomitant antibiotic	4	2
Treatment course too short	15	6
Infection not included in claims	-	1

DOSE

	PRIMAXIN	CEFOTAXIME
	500 mg q 6 h	2 g q 8 h

DURATION OF TREATMENT (Days)
(Evaluable Cases)

5-14	65 patients	63 patients
15-17	4 patients	5 patients
33		1 patient

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL.	NO.	CEFOTAXIME CLINICAL RESPONSE CURE	IMP.	FAIL.
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, erysipelas)	16	13(81%)	2(13%)	1(6%)	15	10(67%)	3(20%)	2(13%)
LOWER RESPIRATORY (Bronchitis, pneumonia, bronchopneumonia, empyema, lung abscess)	19	11(58%)	3(16%)	5(26%)	24	18(75%)	3(12.5%)	3(12.5%)

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CEFOTAXIME CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
MEDIASTINITIS	1	1(100%)			1	1(100%)		
SEPTICEMIA	28	26(93%)		2(7%)	27	23(85%)	2(7.4%)	2(7.4%)
UTI (Complicated) (cystitis, pyelonephritis)	7	3(43%)	3(43%)	1(14%)	4	3(75%)	1(25%)	
UTI (Uncomplicated) (cystitis, pyelonephritis, perinephric abscess)	2	2(100%)			2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, cholecystitis)	15	6(40%)	5(33%)	4(27%)	11	10(91%)	1(9%)	

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	CEFOTAXIME BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERA
SKIN & SKIN STRUCTURE								
S. aureus(S)	1	1(100%)			1	1(100%)		
S. aureus(R)	6	5(83%)		1(17%)	4	4(100%)		
Strep (Group A)	2	2(100%)			2	2(100%)		
Strep (Group D)	1	1(100%)						
Alpha-hem strep	1	1(100%)						
S. intermedius	1	1(100%)						
S. faecalis	-				1			1(100
E. cloacae	-				3	3(100%)		
A. calcoaceticus	1	1(100%)						
A. odorans	1	1(100%)						
E. coli	6	6(100%)			2			2(100
K. pneumoniae	1	1(100%)			1	1(100%)		
M. morganii	2	1(50%)		1(50%)	1	1(100%)		
P. mirabilis	1			1(100%)				
P. vulgaris	-				1			1(100
P. aeruginosa	1	1(100%)			1	1(100%)		
S. marcescens	1	1(100%)			2	2(100%)		
Peptococcus sp.	2	3(100%)			1	1(100%)		
Peptostrep sp.	3	3(100%)						
B. fragilis	4	4(100%)			1			1(10

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEFOTAXIME BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
LOWER RESPIRATORY								
S. aureus(R)	–				1	1(100%)		
S. bovis	1	1(100%)			–			
S. pneumoniae	4	4(100%)			9	9(100%)		
Beta-hem-strep	–				1	1(100%)		
Non-hem-strep	–				1	1(100%)		
E. cloacae	–				1	1(100%)		
E. coli	3	3(100%)			4	2(50%)		2(50%)
H. influenzae	5	4(80%)		1(20%)	6	6(100%)		
H. parainfluenzae	1	1(100%)			1	1(100%)		
K. pneumoniae	1	1(100%)			2	2(100%)		
P. mirabilis	3	1(33%)		2(67%)	1	1(100%)		
P. aeruginosa	2			2(100%)				
MEDIASTINITIS								
S. aureus(R)	1	1(100%)						
S. marcescens	–				1			1(100%)
SEPTICEMIA								
S. aureus(S)	–							
S. aureus(R)	5	4(80%)		1(20%)	4	1(100%)		
S. pneumoniae	3	3(100%)			1	1(100%)		
E. cloacae	2	2(100%)			–			
A. calcoaceticus	–				1	1(100%)		
C. diversus	–				1	1(100%)		
E. coli	11	10(91%)		1(9%)	15	13(87%)		2(13%)
H. influenzae	1	1(100%)						
K. pneumoniae	3	3(100%)			1	1(100%)		
K. oxytoca	–				1	1(100%)		
M. morganii	1	1(100%)			3	3(100%)		
P. mirabilis	–				1	1(100%)		
P. vulgaris	–				2	2(100%)		
S. marcescens	–				2	2(100%)		
Serratia spp.	1	1(100%)						
Meningococcus (Group B)	1	1(100%)						
B. fragilis	1	1(100%)						
UTI (Uncomp.)								
E. coli	1	1(100%)			2	2(100%)		
S. faecalis	1	1(100%)			–			
E. cloacae	1	1(100%)			–			

(Continued)

ORGANISM	PRIMAXIN NO.	BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERAD	CEFOTAXIME NO.	BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERA
UTI (Complicated)								
S. aureus(R)	-				1	1(100%)		
E. coli	4	2(50%)		2(50%)	3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. vulgaris	1			1(100%)	-			
S. faecalis	1	1(100%)			-			
K. pneumoniae	1	1(100%)			-			
C. freundii	1			1(100%)	-			
C. diversus	-				1	1(100%)		
P. aeruginosa	3	2(67%)		1(33%)	1			1(100%)
INTRA-ABDOMINAL								
S. epidermidis	1	1(100%)			-			
S. mitis	-				1	1(100%)		
Strep (Group D)	2	2(100%)			-			
S. faecalis	7	5(71%)		2(29%)	2	2(100%)		
E. cloacae	1	1(100%)			1			1(100%)
E. coli	8	5(62.5%)		3(37.5%)	7	7(100%)		
K. pneumoniae	3	2(67%)		1(33%)	1	1(100%)		
M. morganii	-				4	3(75%)		1(25%)
P. mirabilis	2	1(50%)		1(50%)	2	2(100%)		
P. aeruginosa	6	2(33%)		4(67%)	1			1(100%)
Bifidobacterium	1	1(100%)			-			
Lactobacillus	1	1(100%)			-			
Peptostreptococcus	-				1	1(100%)		
B. fragilis	-				3	3(100%)		
B. melaninogenicus	1	1(100%)			-			
B. ruminicola	1	1(100%)			-			
Veillonella	1	1(100%)			-			

In the Primaxin group, one patient with a chronic pyelonephritis due to P. aeruginosa, E. coli and S. faecalis improved, and all organisms were eradicated. However, 14 days post-treatment the same E. coli and S. faecalis were isolated from the urine together with a M. morganii (designated as a reinfection).
Another patient with acute pyelonephritis due to E. coli developed a reinfection with a different E. coli strain.

Three patients in the cefotaxime group, one with an infected ulcer due to M. morganii, and two with complicated urinary tract infections due to E. coli relapsed during the follow-up period.

Superinfection developed in 3 patients in the Primaxin group and in 4 patients in the cefotaxime group.

SAFETY

	PRIMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS	123	111
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	8(6.5%)	3(3%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	13(10.5%)	9(8%)

LOCAL SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Infused vein infection	1(0.8%)	1(0.8%)			
Infused vein pain	3(2.4%)	1(0.8%)		1(0.8%)	1(0.8%)
Phlebitis/thrombo-phlebitis	6(4.8%)			3(2.4%)	3(2.4%)

CEFOTAXIME

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Phlebitis/thrombo-phlebitis	3(2.7%)		1(0.9%)	1(0.9%)	1(0.9%)

SYSTEMIC SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	2(1.6%)			1(0.8%)	1(0.8%)
Vomiting	2(1.6%)				2(1.6%)
Glossitis	1(0.8%)				1(0.8%)
Fever	2(1.6%)			1(0.8%)	1(0.8%)
Flushing	1(0.8%)				1(0.8%)
Rash	1(0.8%)		1(0.8%)		
Somnolence	3(2.4%)		1(0.8%)	2(1.6%)	
Headache	1(0.8%)	1(0.8%)			
Hypotension	1(0.8%)			1(0.8%)	
Oliguria/anuria	1(0.8%)			1(0.8%)	
Polyuria	1(0.8%)			1(0.8%)	
Meningitis	1(0.8%)		1(0.8%)		
Fullness in ears	1(0.8%)	1(0.8%)			

CEFOTAXIME

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Vomiting	1(0.9%)			1(0.9%)	
Diarrhea	3(2.7%)		2(1.8%)		1(0.9%)
Mucous in feces (C. difficile positive)	1(0.9%)		1(0.9%)		
Constipation	1(0.9%)				1(0.9%)
Fever	2(1.8%)		1(0.9%)	1(0.9%)	
Pruritus	1(0.9%)		1(0.9%)		
Rash	1(0.9%)		1(0.9%)		
Septic shock	1(0.9%)			1(0.9%)	

Deaths

Ten patients in the Primaxin group died during the study or within two weeks
after therapy was discontinued. Six of these deaths were considered by the
investigator as definitely not drug related, three as probably not drug
related, and one as probably drug related. This patient died of septic shock
with blood cultures positive for Primaxin resistant Pseudomonas which emerged
during therapy. Although this was not a toxic effect of the drug, the
investigator rated this adverse experience probably drug related (failure of
therapy).

Seven patients in the cefotaxime group died during or shortly after therapy
was discontinued. Six of these were considered by the investigator as
definitely not drug related and one as possibly drug related. This patient
received cefotaxime for six days for complicated cystitis with bacteremia and
died of septic shock.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFOTAXIME
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
RBC	–	(D) 1
WBC	–	(D) 2
Eosinophils	(I) 5	(I) 3
Platelets	(I) 5	(I) 1
	(D) 1	
Blood Urea	(I) 3	(I) 2
BUN	(I) 3	(I) 2
Creatinine	(I) 1	(I) 1
SGOT (AST)	(I) 6	(I) 4
SGPT (ALT)	(I) 6	(I) 5
Bilirubin	(I) 2	(I) 1
Alk. phosphatase	(I) 5	(I) 6
Serum potassium	–	(D) 1
Positive Coombs' test	4	–
Urine protein	(I) 2	(I) 1
Urine casts	–	(D) 1
Prothrombin time	–	(I) 1

Summary and Conclusions

This was an open, randomized, controlled multicenter study comparing Primaxin
and cefotaxime in the treatment of infections caused by susceptible bacteria.
A total of 123 patients, 78 males and 45 females, ranging in age from 16 to 80
years were enrolled in the Primaxin group. A total 111 patients, 65 males and
46 females, ranging in age from 18 to 81 years were enrolled in the cefotaxime
group. Demographic characteristics of patients in each treatment group were
similar.

Sixty nine patients with 88 sites of infection in the Primaxin group and 69
patients with 84 sites of infection in the cefotaxime group were acceptable
for evaluation for drug efficacy. All patients were considered in assessing
safety.

Clinical cure or improvement occurred in 75/88 (85%) infections in the Primaxin treated patients and in 77/84 (92%) infections in the cefotaxime treated patients.

A favorable bacteriological outcome (eradication) was achieved in 109 (81%) of 135 organisms isolated in the Primaxin group and in 100 (85%) of 114 organisms isolated in the cefotaxime treated group.
The main reason for the difference in cure rate between the two antibiotics was the unusually high failure rate of Primaxin in infections caused by P. mirabilis.

Systemic side effects were reported in 10.5% of the patients in the Primaxin group and in 8% of the patients in the cefotaxime group. Local side effects were reported in 6.5% of the patients in the Primaxin group and in 3% of the patients in the cefotaxime group.

The laboratory test abnormalities reported were similar in both treatment groups, except for Coombs' test which was positive in 4 patients in the Primaxin group. None was reported in the cefotaxime group.

There were 10 deaths in the Primaxin group. One of these was considered by the investigator "probably drug related" not because of a toxic effect but because of failure of therapy. Seven patients died in the cefotaxime group. One of these was considered "possibly drug related" because of treatment failure.

Results of this study demonstrate that both Primaxin and cefotaxime are relatively safe and effective in the treatment of patients with serious infections caused by susceptible bacteria. A difference, however, was evident in infections caused by P. mirabilis where Primaxin was not quite as effective as cefotaxime.

3.   Protocol No. 5004
     Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety and Tolerance of Intravenously Administered Primaxin and Gentamicin/Clindamycin in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

     Study Design: This was an open, controlled, randomized, multiclinic study.

     Procedure: Treatment group assignment was made using a computer-generated, randomized allocation schedule. Having completed the informed consent procedure, patients were allocated either to the Primaxin or the Gentamicin/Clindamycin group.
     Each patient in the Primaxin group received a total daily dose of 2.0 g administered in four equally divided doses every 6 hours as an intravenous infusion over 15 to 30 minutes. Each patient in the Gentamicin/Clindamycin group received 600 mg clindamycin every 6 hours and gentamicin (1.5 ug/kg/dose t.i.d.) adjusted according to serum concentration assays.

Before entry into the study, all patients provided a complete
clinical history and underwent a physical exam. During the study
period, daily measurements of temperature, pulse, blood pressure, and
respiratory rate were recorded. A daily infusion tolerance record of
the study drug was kept. Tolerance was evaluated on the basis of
pain, erythema, induration of the vein, and ulceration of the
infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function
were carried out before, during and after completion of therapy. In
addition to the serum creatinine analyses that were part of the
routine blood chemistry studies, renal function in terms of
creatinine clearance was also estimated. Additional diagnostic test
(e.g., x-ray, sonography) were performed as indicated.
Serum concentrations of gentamicin were determined at least twice
weekly for adjustment in gentamicin dosage.
Blood cultures and cultures of other suspected sites were obtained
prior to, during, and after study drug therapy. Gram stains and
standard bacteriologic susceptibility tests were performed by either
disc or broth dilution method.

Response to treatment was assessed by both clinical and
bacteriological outcomes.

Eight investigators conducted studies under this protocol. Their
names and affiliations are listed below:

      Alestig, K., Ostra Hospital, Goteborg, Sweden
      Cronberg, S., Malmo General Hospital, Malmo, Sweden
      Kager, L., Huddinge Hospital, Huddinge, Sweden
      Philipson, A.E.L., Danderyd Hospital, Danderyd, Sweden
      Schreiner, A., Haukeland Hospital, Bergen, Norway
      Trollfore, B., Umea Regional Hospital, Umea, Sweden
      Welch, D.J.V., University of the Orange Tree State,
         Bloemfontein, South Africa
      Guerra, J., Instituto de Enfermedades Tropicales Alexander Von
      Humbolt, Lima, Peru

Overall Summary of Studies Conducted Under Protocol 5004

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
TOTAL NO. OF PATIENTS	102	112
AGE RANGE (Years)	15-79	16-84
MEAN AGE (Years)	48.9	50.4
SEX		
Male	64	57
Female	38	55

EVALUATION

EFFICACY

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
NO. OF CASES EVALUABLE	70	80
NO. OF SITES OF INFECTION EVALUABLE	77	85
NO. OF CASES UNEVALUABLE	32	32

REASONS CASES UNEVALUABLE
No pretreatment pathogen	19	24
Treatment course too short	10	4
Organism resistant to study drug	1	1
Inadequate bacteriologic cultures	2	3

	PRIMAXIN	GENTAMICIN	CLINDAMYCIN
DOSE	500 mg q 6 h	1.5 mg/kg q 8 h	600 mg q 6 h

DURATION OF TREATMENT (days) (Evaluable Cases)	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
4-14	65 patients	77 patients
15-20	5 patients	3 patients

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	GENTAMICIN/CLINDAMYCIN CLINICAL RESPONSE CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/ furuncle, ulcers)	14	9(64.3%)	5(37.7%)		17	11(64.7%)	4(23.5%)	2(11.8%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess)	12	11(91.7%)	1(8.3%)		21	16(76.2%)	4(19.0%)	1(4.8%)
SEPTICEMIA	10	10(100%)			11	8(72.7%)	1(9.1%)	2(18.2%)
UTI (Uncomplicated) (Cystitis, pyelo- nephritis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	
UTI (Complicated) (Cystitis, pyelonephritis)	8	5(62.5%)	3(37.5%)		2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, cholecystitis)	20	16(80%)	2(10%)	2(10%)	24	14(58.3%)	8(33.3%)	2(8.3%)

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
GYNECOLOGIC (Endometritis, PID, tubo-ovarian abscess)	8	6(75%)	2(25%)		5	5(100%)		
BONE/JOINT (Infectious arthritis, osteomyelitis)	1	1(100%)			1			1(100%)
ENTERITIS	1	1(100%)			1	1(100%)		

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE								
S. aureus(S)	1	1(100%)			2	2(100%)		
S. aureus(R)	5	3(60%)		2(40%)	10	9(90%)		1(10%)
S. epidermidis	2	2(100%)			-			
Strep (Group A)	2	1(50%)		1(50%)	5	5(100%)		
S. pyogenes	-				1	1(100%)		
Beta-hem-strep	-				1	1(100%)		
S. faecalis	1			1(100%)	4	2(50%)		2(50%)
E. coli	1	1(100%)			2	1(50%)		1(50%)
P. mirabilis	1	1(100%)			2	1(50%)		1(50%)
Klebsiella spp.	1	1(100%)			-			
E. agglomerans	1	1(100%)			-			
Pseudomonas spp.	1	1(100%)			-			
P. aeruginosa	1			1(100%)	1			1(100%)
Bacteroides spp.	1	1(100%)			-			
B. fragilis	1	1(100%)			1	1(100%)		
Peptostreptococcus	1	1(100%)			-			
Anaerobes, mixed	2	2(100%)			-			
LOWER RESPIRATORY								
S. aureus(R)	-				1	1(100%)		
S. pneumoniae	5	5(100%)			11	10(90.9%)		1(9.1%)
Alpha-hem-strep	-				2	2(100%)		
Streptococcus spp	-				1	1(100%)		
H. influenzae	6	6(100%)			6	4(66.7%)	1(16.6%)	1(16.6%)
H. parainfluenzae	-				1	1(100%)		
E. coli	-				1			1(100%)
Gram-neg-rods	1	1(100%)			-			
P. mirabilis	-				1	1(100%)		
Enterobacter spp.	-				1	1(100%)		

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Klebsiella spp.	1	1(100%)			-			
B. catarrhalis	1	1(100%)			-			
S. marcescens	-				1	1(100%)		
M. meningitidis	1	1(100%)			1	1(100%)		
B. fragilis	-				1	1(100%)		
Fusobacterium	-				1	1(100%)		

SEPTICEMIA

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
S. aureus(S)	1	1(100%)			1	1(100%)		
S. aureus(R)	2	2(100%)			-			
S. epidermidis	-				1	1(100%)		
Alpha-hem-strep	1	1(100%)			1	1(100%)		
S. pneumoniae	1	1(100%)			1	1(100%)		
S. bovis	1	1(100%)			-			
E. coli	4	4(100%)			6	4(66.7%)		2(33.3%)
Klebsiella spp	-				1	1(100%)		
P. mirabilis	-				1	1(100%)		
Salmonella (Group B)	1	1(100%)			-			
Bacteroides spp	1	1(100%)			1	1(100%)		
B. fragilis	1	1(100%)			-			
B. melaninogenicus	1	1(100%)			-			
B. corrodens	1	1(100%)			-			

UTI (Uncomp.)

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
E. coli	3	2(66.7%)		1(33.3%)	3	2(66.7%)		1(33.3%)

UTI (Complicated)

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
E. coli	3	2(66.7%)		1(33.3%)	2	2(100%)		
P. mirabilis	1			1(100%)	-			
P. stuartii	1			1(100%)	-			
Pseudomonas spp	2	2(100%)			-			
P. aeruginosa	1	1(100%)			-			

INTRA-ABDOMINAL

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
S. aureus(S)	-				1	1(100%)		
S. aureus(R)	2	1(50%)		1(50%)	2	2(100%)		
S. epidermidis	-				4	2(50%)		2(50%)
Streptococcus spp	-				1	1(100%)		
Alpha-hem-Strep	1	1(100%)			-			
Beta-hem-Strep	1	1(100%)			1		1(100%)	
S. faecalis	-				4	3(75%)		1(25%)
A. calcoaceticus	1	1(100%)			-			
K. pneumoniae	2	2(100%)			2	1(50%)		1(50%)

(Continued)

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERAD	NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERAD
Haemophilus spp	1	1(100%)			-			
Citrobacter spp	1	1(100%)			-			
C. diversus	1	1(100%)			-			
Gram-neg-rods	-				1	1(100%)		
E. cloacae	-				1			1(100%)
E. agglomerans	2	2(100%)			2	1(50%)		1(50%)
E. hafniae	1	1(100%)			1	1(100%)		
E. coli	10	10(100%)			14	12(85.7%)		2(14.3%)
P. mirabilis	-				1			1(100%)
P. rettgeri	-				1	1(100%)		
M. morganii	-				1			1(100%)
Pseudomonas spp	-				1			1(100%)
P. aeruginosa	1	1(100%)			1			1(100%)
Serratia spp	-				1	1(100%)		
C. perfringens	1	1(100%)			1	1(100%)		
C. butyricum	-				1	1(100%)		
C. histolyticum	-				1	1(100%)		
S. typhi	1	1(100%)			-			
S. choleraesuis	1	1(100%)			-			
Peptococcus spp	2	2(100%)			1	1(100%)		
Peptostreptococcus spp	1	1(100%)			-			
P. granulosum	-				1	1(100%)		
E. lentum	1	1(100%)			-			
Lactobacillus	1	1(100%)			-			
Bacteroides spp	2	2(100%)			2	2(100%)		
B. fragilis	3	3(100%)			7	4(57.1%)	1(14.3%)	2(28.6%)
B. bivius	1	1(100%)			-			
B. melaninogenicus	-				1	1(100%)		
B. ruminicola	-				1	1(100%)		
GYNECOLOGIC								
S. aureus(R)	-				1			1(100%)
S. epidermidis	1	1(100%)			-			
Strep (non-hem)	1	1(100%)			-			
Alpha-hem-strep	-				1	1(100%)		
Beta-hem-strep	-				1	1(100%)		
E. coli	1	1(100%)			1			1(100%)
E. agglomerans	1	1(100%)			-			
H. influenzae	1	1(100%)			-			
K. pneumoniae	1	1(100%)			-			
P. mirabilis	1	1(100%)			-			
P. aeruginosa	-				1	1(100%)		
N. gonorrhoeae	-				1	1(100%)		
E. lentum	-				1	1(100%)		

(Continued)

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
P. granulosum	1	1(100%)			-			
Peptococcus spp	1	1(100%)			1	1(100%)		
Peptostreptococcus spp	-				1	1(100%)		
Bacteroides spp	1	1(100%)			-			
B. fragilis	1	1(100%)			1	1(100%)		
BONE/JOINT								
S. pyogenes	1	1(100%)			-			
B. fragilis	-				1			1(100%)
ENTERITIS								
Campylobacter	1	1(100%)			1	1(100%)		
Salmonella Type B	1			1(100%)				

Two patients in the Primaxin group and seven in the Gentamicin/Clindamycin
group developed superinfections.

Reinfections occurred in eight patients in the Primaxin group (seven with
urinary tract infections and one with a severe intraabdominal infection) and
in one patient with urinary tract infection in the Gentamicin/Clindamycin
group.

SAFETY

	PRIMAXIN	CLINDAMYCIN/GENTAMICIN
TOTAL NO. OF PATIENTS	102	112
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	6(5.9%)	5(4.5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	17(16.7%)	25(22.3%)

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT	PRIMAXIN POSSIBLY	PROBABLY	DEFINITELY
Phlebitis/thrombo- phlebitis	6(5.9%)	1(1.0%)		3(3.0%)	2(1.9%)

	NO.		GENTAMICIN/CLINDAMYCIN	PROBABLY	DEFINITELY
Infused vein pain	2(1.8%)			2(1.8%)	
Vein induration	1(0.9%)			1(0.9%)	
Phlebitis/thrombo- phlebitis	2(1.8%)			1(0.9%)	1(0.9%)

SYSTEMIC SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	7(7.0%)		4(4%)	3(3%)	
Vomiting	3(3.0%)		2(2%)	1(1%)	
Diarrhea*	9(9.0%)	7(7%)		2(2%)	
Abdominal pain	1(1.0%)			1(1%)	
Hiccups	1(1.0%)	1(1%)			
Increased salivation	1(1.0%)			1(1%)	
Fever	1(1.0%)		1(1%)		
Chills	1(1.0%)	1(1%)			
Rash	3(3.0%)		3(3%)		
Headache	1(1.0%)	1(1%)			
Chest discomfort	1(1.0%)	1(1%)			
Hypotension	1(1.0%)			1(1%)	
Vaginal candidiasis	1(1.0%)		1(1%)		
Hemoptysis	1(1.0%)	1(1%)			
Anxiety	1(1.0%)	1(1%)			

GENTAMICIN/CLINDAMYCIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	1(0.9%)	1(0.9%)			
Vomiting	1(0.9%)	1(0.9%)			
Diarrhea	10(8.9%)	6(5.3%)	1(0.9%)	2(1.8%)	1(0.9%)
Hiccups	2(1.8%)	2(1.8%)			
Increased salivation	1(0.9%)	1(0.9%)			
Fever	2(1.8%)		2(1.8%)		
Chills	1(0.9%)	1(0.9%)			
Rash	8(7.1%)	1(0.9%)	2(1.8%)	3(2.6%)	2(1.8%)
Urticaria	1(0.9%)	1(0.9%)			
Headache	2(1.8%)	2(1.8%)			
Dizziness	1(0.9%)			1(0.9%)	
Dyspnea	1(0.9%)	1(0.9%)			
Hearing loss	2(1.8%)			2(1.8%)	
Oral candidiasis	1(0.9%)			1(0.9%)	

*One patient with diarrhea had positive C. difficile toxin in the stools.

Deaths: Two patients in the Primaxin group died during the study. Both deaths were considered by the investigators definitely not drug related.

Three patients in the Gentamicin/Clindamycin group died during the study or within 14 days after termination of therapy. Two of these deaths were considered definitely not drug related and one probably not drug related.

Abnormal Laboratory Tests

TEST	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
RBC	(D) 1	(D) 3
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
WBC	(D) 1	-
Eosinophils	(I) 2	(I) 1
Platelet count	-	(I) 2
Platelet estimate	(I) 4	(D) 1
Positive Coombs' Test	2	2
BUN	(I) 1	(I) 2
Blood urea	(I) 1	(I) 2
Creatinine	(I) 4	(I) 22
Serum uric acid	-	(I) 6
SGOT (ASAT)	(I) 9	(I) 10
SGPT (ALAT)	(I) 12	(I) 11
Bilirubin	(I) 1	(I) 1
Alk. phosphatase	(I) 7	(I) 6
Serum potassium	(I) 1	(I) 2
	(D) 1	(D) 1
Serum chloride	(D) 1	(D) 4
Urine protein	(I) 1	(I) 5
Urine WBCs	(I) 3	(I) 8
Urine RBCs	(I) 1	(I) 2
Urine casts	(I) 3	(I) 13

Summary and Conclusions: This was an open, randomized, controlled multicenter study comparing Primaxin and gentamicin plus clindamycin in the treatment of infections caused by susceptible bacteria.

A total of 102 patients, 64 males and 38 females, ranging in age from 15 to 79 years were enrolled in the Primaxin group. A total of 112 patients, 57 males, and 55 females, ranging in age from 16 to 84 years were enrolled in the Gentamicin/Clindamycin group.

Seventy patients with 77 sites of infection in the Primaxin group and 80 patients with 85 sites of infection in the gentamicin/clindamycin group were acceptable for evaluation of drug efficacy.

All patients were considered in assessing safety.

Clinical cure or improvement occurred in 75/77 (97%) infections in the Primaxin treated patients and in 77/85 (91%) infections in the gentamicin/clindamycin treated patients.

A favorable bacteriological outcome (eradication) was achieved in 104 (90%) of 115 organisms isolated in the Primaxin treated patients and in 112 (78%) of 144 organisms isolated in the gentamicin/clindamycin treated patients.

Systemic side effects were reported in 16.7% of the patients in the Primaxin group and in 22.3% of the patients in the gentamicin/clindamycin group. Local side effects were reported in 5.9% of the patients in the Primaxin group and in 4.5% of the patients in the gentamicin/clindamycin group.

The laboratory test abnormalities reported were similar in both treatment groups; however, there were more patients with elevated serum creatinine, serum uric acid, and urine casts in the gentamicin/clindamycin group than in the Primaxin group.

There were two deaths in the Primaxin group; both were considered definitely not-drug related. There were three deaths in the gentamicin/clindamycin group; two were considered definitely not drug related and one probably not drug related.

Results of this study demonstrate that Primaxin was safe and effective in the treatment of infections caused by susceptible bacteria. The combination of gentamicin plus clindamycin was somewhat less effective particularly in infections caused by E. coli, H. influenzae, and Enterobacter species.

Clinical Studies (Foreign)

II. Uncontrolled

Protocol No. 536
Title: "A Multiclinic Open Study of the Efficacy, Safety, and Tolerance of Primaxin (imipenem/cilastatin) in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

Study Design
This was a noncomparative, variable dosage, bacteriologically controlled evaluation of Primaxin in the intravenous therapy of hospitalized patients with infections casued by susceptible bacteria.

Procedure
All patients accepted for entry into this study were required to sign an informed consent form.
Each patient provided a complete clinical history and underwent a physical examination. Primaxin was administered at a total daily dosage of 1.5 grams (500 mg q 8 h) or 2.0 grams (500 mg q 6 h), depending on the severity of the infection. Each dose was given by intravenous infusion over a 15-minute period.

During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded. A daily infusion tolerance record of the study drug was kept.
Standard diagnostic tests of hematology, renal, and hepatic function were carried out before study drug therapy and were repeated during and after completion of therapy. Additional diagnostic tests (e.g. x-ray, sonography) were performed as indicated.
Bacteriologic cultures were obtained prior to, during, and after completion of therapy, except in cases in which cultures were impossible to obtain by virtue of a healed site. Gram stain and standard bacteriologic susceptibility tests were performed in all cultures by either disc or MIC method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

Investigators
Twenty-five investigators (23 from Germany and 2 from Austria) participated in this multiclinic study.

Overall Summary of Studies Conducted Under Protocol No. 536

TOTAL NO. OF PATIENTS: 234

AGE RANGE (years):   16-87

MEAN AGE (years):   51.7

SEX
    Male: 137

    Female: 97
EVALUATION

EFFICACY
NO. OF CASES EVALUABLE: 165
NO. OF SITES OF INFECTION EVALUABLE: 180
NO. OF CASES UNEVALUABLE: 69

REASONS CASES UNEVALUABLE
No pretreatment pathogen   41
Treatment course too short   13
Inadequate bacteriologic cultures   10
Effective concomitant antimicrobial therapy   4
Diagnosis not clear   1

DURATION OF TREATMENT
  (Evaluable cases)

DAYS	NO. OF PATIENTS
5-14	159
15-30	6

RESULTS

		CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE	44	34 (77.3%)	8 (18.2%)	2 (4.5%)
(Wound infection, abscess, cellulitis, carbuncle/furuncle, decubitus & other skin ulcers				

(Continued)

BONE/JOINT (Pyogenic arthritis)	1	1 (100%)		
LOWER RESPIRATORY (Pneumonia, empyema, bronchitis)	20	11 (55.0%)	7 (35.0%)	2 (10.0%)
GYNECOLOGIC (PID, endometritis, tubo-ovarian abscess)	10	10 (100%)		
INTRA-ABDOMINAL (Peritonitis, abscess, liver abscess, cholangitis, gall bladder empyema	46	44 (95.6%)	1 (2.2%)	1 (2.2%)

RESULTS

		CLINICAL RESPONSE		
	NO.	CURE	IMPROVE	FAIL
UTI (Uncomplicated) (Cystitis, pyelonephritis)	5	5 (100%)		
UTI (Complicated) (Cystitis, pyelonephritis renal abscess)	35	19 (54.3%)	16 (45.7%)	
INFECTION BACTERIAL SEPTICEMIA	19	18 (94.7%)	1 (5.3%)	

ORGANISM		BACTERIOLOGIC RESPONSE
SKIN & SKIN STRUCTURE	NO.	ERADICATED
Gemella	1	1 (100%)
S. aureus[S]	5	5 (100%)
S. aureus[R]	9	8 (89.9%)
S. epidermidis	4	3 (75%)
Streptococcus spp.	2	2 (100%)
Streptococcus (Group A)	3	3 (100%)
Streptococcus (Group C)	1	1 (100%)
Streptococcus (Group D) Enterococci)	6	4 (66.7%)
Streptococcus faecalis	2	2 (100%)
Streptococcus viridans	2	2 (100%)
Beta-hemolytic streptococci	3	3 (100%)

(Continued)	NO.	ERADICATED
Acinetobacter spp.	1	0
Enterobacter spp.	4	3 (75%)
Enterobacter aerogenes	1	0
Escherichia coli	19	12 (63.2%)
Klebsiella oxytoca	1	0
Morganella morganii	1	1 (100%)
Proteus mirabilis	3	1 (33.3%)
Proteus vulgaris	1	1 (100%)
Pseudomonas aeruginosa	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	3	3 (100%)
Fusobacterium spp.	1	1 (100%)
Acidaminococcus fermentans	1	1 (100%)

ORGANISM BONE/JOINT	NO.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus[R]	1	1 (100%)

INTRA-ABDOMINAL

	NO.	ERADICATED
S. aureus[S]	3	3 (100%)
S. aureus[R]	3	3 (100%)
S. epidermidis	4	4 (100%)
Streptococcus spp.	1	1 (100%)
Streptococcus (Group D) Enterococci)	3	3 (100%)
Streptococcus faecalis	1	1 (100%)
Streptococcus viridans	5	5 (100%)
Non-hemolytic streptococci	2	2 (100%)
Citrobacter freundii	2	1 (50%)
Enterobacter spp.	1	1 (100%)
Enterobacter cloacae	1	1 (100%)
Escherichia coli	27	24 (88.9%)
Klebsiella pneumoniae	2	2 (100%)
Lactobacillus	1	1 (100%)
Morganella morganii	3	2 (66.7%)
Proteus mirabilis	2	2 (100%)
Proteus vulgaris	3	2 (66.7%)
Providencia rettgeri	1	1 (100%)
Pseudomonas spp.	1	1 (100%)
Pseudomonas aeruginosa	2	1 (50%)
Serratia liquefaciens	1	1 (100%)
Clostridium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	6	5 (83.3%)
Bacteroides fragilis	1	1 (100%)

LOWER RESPIRATORY	NO.	ERADICATED
S. aureus^S	4	4 (100%)
S. aureus^R	2	2 (100%)
S. epidermidis	1	0
Streptococcus spp.	1	1 (100%)
S. pneumoniae	2	2 (100%)
Streptococcus (Group D) Enterococci)	3	2 (66.7%)
Escherichia coli	3	2 (66.7%)
Haemophilus influenzae	4	3 (75%)
Klebsiella pneumoniae	2	1 (50%)
Pasteurella multocida	1	1 (100%)
Proteus vulgaris	1	0
Pseudomonas aeruginosa	6	4* (66.7%)
Corynebacterium (acnes)	1	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Fusobacterium spp.	1	1 (100%)

*Two patients with pneumonia in whom P. aeruginosa persisted in the sputum were considered clinically cured by the investigator. Both these patients were in the sa intensive care unit where P. aeurginosa was frequently isolated.

ORGANISM		BACTERIOLOGIC RESPONSE
GYNECOLOGIC	NO.	ERADICATED
Streptococcus (Group D) Enterococci)	1	1 (100%)
Escherichia coli	7	5 (71.4%)
Proteus vulgaris	1	1 (100%)
Neisseria gonorrhoeae	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	2	2 (100%)

UTI (Uncomplicated)

S. aureus^R	1	1 (100%)
Streptococcus (Group D Enterococci)	1	1 (100%)
Escherichia coli	4	4 (100%)
Proteus vulgaris	1	1 (100%)
Enterobacter spp.	1	1 (100%)
Klebsiella oxytoca	1	1 (100%)

UTI (complicated)	NO.	ERADICATED
S. aureus[R]	5	5 (100%)
S. epidermidis	4	4 (100%)
Streptococcus (Group D Enterococci)	5	5 (100%)
Streptococcus faecalis	1	0 -
Escherichia coli	13	6 (46.2%)
Proteus mirabilis	4	1 (25%)
Enterobacter spp.	1	1 (100%)
Citrobacter freundii	1	0 -
Klebsiella pneumoniae	1	0 -
Pseudomonas aeruginosa	3	2 (66.7%)

BACTERIAL SEPTICEMIA

	NO.	ERADICATED
S. aureus[S]	3	3 (100%)
S. aureus[R]	2	2 (100%)
S. epidermidis	2	2 (100%)
Streptococcus pneumoniae	1	1 (100%)
Streptococcus (Group D Enterococci)	1	1 (100%)
Streptococcus faecalis	1	1 (100%)
Acinetobacter spp.	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Escherichia coli	6	6 (100%)
Klebsiella pneumoniae	1	1 (100%)
Salmonella (Group A)	1	1 (100%)
Bacteroides spp.	1	1 (100%)

Six patients were designated by the investigators as developing superinfections. Four of these occurred at the site of the primary infection and two at a different site.
Four patients healed spontaneously, and two required additional antibiotic therapy. Only one patient with a bronchopneumonia developed a superinfection with a Primaxin-resistant P. aeruginosa. The organism was successfully eradicated with a combination of tobramycin and piperacillin.

SAFETY

TOTAL NO. OF PATIENTS: ------------------------ 234

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS ---- 24 (10.3%)

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS ------- 27 (11.5%)

SIDE EFFECTS
SYSTEMIC

	No.	Probably Not Related	Possible Related	Probably Related	Definitely Related
Diarrhea	11 (4.7%)		2 (0.8%)	6 (2.6%)	3 (1.3%)
Nausea	10 (4.3%)		2 (0.8%)	5 (2.1%)	3 (1.3%)
Vomiting	6 (2.6%)		1 (0.4%)	2 (0.8%)	3 (1.3%)
Heartburn	1 (0.4%)			1 (0.4%)	
Abdominal pain	1 (0.4%)		1 (0.4%)		
Brown tongue	3 (1.3%)			3 (1.3%)	
Allergic dermatitis	1 (0.4%)			1 (0.4%)	
Pruritus	1 (0.4%)			1 (0.4%)	
Rash	1 (0.4%)				1 (0.4%)
Dizziness	3 (1.3%)			1 (0.4%)	2 (0.8%)
Hypotension	1 (0.4%)			1 (0.4%)	
Dyspnea	1 (0.4%)		1 (0.4%)		

LOCAL

	No.	Probably Not Related	Possible Related	Probably Related	Definitely Related
Pain	9 (3.8%)	4 (1.7%)	3 (1.3%)	1 (0.4%)	1 (0.4%)
Induration	11 (4.7%)	7 (3%)	4 (1.7%)		
Erythema	12 (5.1%)	6 (2.5%)	6 (2.5%)		
Phlebitis/ thrombo- phlebitis	5 (2.1%)		4 (1.7%)	1 (0.4%)	

Deaths
Three deaths were reported in this study. Two were considered by the investigator as definitely not related and one as probably not drug related.

Abnormal Laboratory Tests

Test		
WBC	(D)	1
Monocytes	(I)	8
Eosinophils	(I)	6
Basophils	(I)	3
Prothrombin time	(I)	2
Positive Coombs' test		2
Creatinine	(I)	1
SGOT (AST)	(I)	6
SGPT (ALT)	(I)	11
Alkaline phosphatase	(I)	4

Overall Summary of the Efficacy and Safety of Primaxin in Controlled and Uncontrolled Studies (Compassionate Protocol Excluded)

	CONTROLLED	UNCONTROLLED
NO. OF STUDIES	6	3
NO. OF INVESTIGATORS	58	78

DEMOGRAPHIC SUMMARY OF PATIENTS

TOTAL NO. OF PATIENTS   1,656

AGE RANGE (years)   12 - 101

SEX

    Male   994
    Female   662

EVALUATION

EFFICACY

TOTAL NO. OF PATIENTS   1,656

NO. OF PATIENTS EVALUABLE   1,116

NO. OF SITES OF INFECTION EVALUABLE   1,253

RESULTS

INFECTION	NO.	CLINICAL RESPONSE CURE	IMPROVE	FAIL
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess)	214	115 (53.7%)	72 (33.6%)	27 (12.6%)
URINARY TRACT – UNCOMPLICATED (Cystitis, pyelonephritis)	41	38 (92.7%)	2 (4.9%)	1 (2.4%)
URINARY TRACT – COMPLICATED (Cystitis, pyelonephritis) renal or perinephric abscess)	139	90 (64.7%)	42 (30.2%)	7 (5.1%)

	NO.	CURE	IMPROVE	FAIL
INTRA-ABDOMINAL (Abscess, peritonitis, cholecystitis, cholangitis, liver abscess, perirectal abscess)	156	112 (71.8%)	32 (20.5%)	12 (7.7%)
ENTERITIS	1	1 (100%)		
GYNECOLOGIC (Endometritis, pelvic cellulitis, pelvic inflammatory disease, tubo-ovarian abscess, pelvic abscess	95	75 (78.9%)	16 (16.8%)	4 (4.2%)
BACTERIAL SEPTICEMIA	164	138 (84.1%)	20 (12.2%)	6 (3.7%)
BACTEREMIA	24	15 (62.5%)	8 (33.3%)	1 (4.2%)
ENDOCARDITIS	11	11 (100%)		
BONE/JOINT Infectious arthritis, osteomyelitis)	72	32 (44.4%)	35 (48.6%)	5 (6.9%)
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/furuncle, infected decubitus and other skin ulcers)	328	204 (62.2%)	110 (33.5%)	14 (4.3%)
OTITIS	4	2 (50%)	1 (25%)	1 (25%)
UPPER RESPIRATORY	2		1 (50%)	1 (50%)
MEDIASTINITIS	1	1 (100%)		
BRAIN ABSCESS	1	1 (100%)		

ORGANISM LOWER RESPIRATORY	NO.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus^{S*}	7	7 (100%)
S. aureus^{R**}	9	9 (100%)
S. epidermidis	2	0
S. pneumoniae	49	49 (100%)
Streptococcus (Group A)	2	2 (100%)
S. viridans group	1	1 (100%)
Beta-hemolytic streptococcus not Group A	2	2 (100%)
S. bovis	1	1 (100%)
Other streptococcus species	9	9 (100%)
Group D streptococcus (enterococcus)	7	4 (57%)
Branhamella catarrhalis	2	2 (100%)
N. meningitidis	1	1 (100%)
H. influenzae	52	45 (87%)
H. parainfluenzae	5	5 (100%)
E. coli	18	16 (89%)
P. mirabilis	17	5 (29%)
P. vulgaris	1	0
K. pneumoniae	23	19 (83%)
K. oxytoca	1	1 (100%)
K. ozaenae	1	1 (100%)
Klebsiella spp.	1	1 (100%)
E. aerogenes	3	2 (67%)
E. cloacae	10	9 (90%)
E. agglomerans	1	1 (100%)
Hafnia alvei	1	0
Providencia stuartii	1	1 (100%)
P. multocida	2	2 (100%)
Citrobacter freundii	1	0
Citrobacter spp.	1	1 (100%)
P. aeruginosa	54	18 (33.3%)***

*S = Penicillin-sensitive   **R = Penicillin-resistant
*** = Forty of the 54 patients with lower respiratory tract infections had serious underlying lung diseases (e.g. COPD, cystic fibrosis, cancer of the lung), and 21 required some degree of respiratory assistance during study drug therapy. These patien had failed previous courses of antibiotic therapy.

All these factors contributed to the low eradication rate of P. aeruginosa (as it is usually the case). However, 67% of the patients were considered to have had a satisfactory clinical response.

ORGANISM LOWER RESPIRATORY	NO.	BACTERIOLOGIC RESPONSE ERADICATED
Pseudomonas spp.	1	1 (100%)
A. hydrophilia	1	1 (100%)
S. marcescens	6	4 (67%)
Alcaligens spp.	1	1 (100%)

(Continued)

ORGANISM		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	NO.	ERADICATED
A. calcoaceticus	4	4 (100%)
Acinetobacter spp.	2	2 (100%)
Corynebacterium acnes	1	1 (100%)
Peptostreptococcus spp.	3	3 (100%)
Fusobacterium spp.	1	1 (100%)
Bacteroides spp.	3	3 (100%)
Eikenella corrodens	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
	NO.	ERADICATED
URINARY TRACT (UNCOMPLICATED)		
S. aureus[S]	1	1 (100%)
Group D Streptococcus (enterococci)	1	1 (100%)
S. faecalis	1	1 (100%)
E. coli	32	29 (91%)
P. mirabilis	3	3 (100%)
P. vulgaris	2	2 (100%)
K. pneumoniae	2	2 (100%)
K. oxytoca	1	1 (100%)
E. cloacae	2	2 (100%)
Enterobacter spp.	1	1 (100%)
P. aeruginosa	1	1 (100%)
URINARY TRACT (COMPLICATED)		
S. aureus[R]	6	5 (83%)
S. epidermidis	4	4 (100%)
Group B Streptococcus	2	2 (100%)
Group D Streptococcus (enterococci)	10	9 (90%)
S. faecalis	2	1 (50%)
E. coli	43	26 (60%)
P. mirabilis	12	6 (50%)
P. vulgaris	1	0
P. rettgeri	3	2 (67%)
M. morganii	3	3 (100%)
K. pneumoniae	8	7 (87.5%)
K. oxytoca	1	1 (100%)
E. aerogenes	1	1 (100%)
E. cloacae	7	6 (85.7%)
Enterobacter spp.	1	1 (100%)
Providencia stuartii	4	1 (25%)

		BACTERIOLOGIC RESPONSE
ORGANISM	NO.	ERADICATED

URINARY TRACT
COMPLICATED)

ORGANISM	NO.	ERADICATED
Providencia spp.	1	0
Citrobacter diversus	2	0
Citrobacter freundii	2	0
Citrobacter spp.	1	1 (100%)
P. aeruginosa	43	36 (84%)
Pseudomonas spp.	2	2 (100%)
S. marcescens	2	1 (50%)
Serratia spp.	1	1 (100%)
Bifidobacterium spp.	1	1 (100%)
Peptococcus spp.	1	1 (100%)

INTRA-ABDOMINAL

ORGANISM	NO.	ERADICATED
S. aureus^S	3	3 (100%)
S. aureus^R	6	5 (83%)
S. epidermidis	6	6 (100%)
Streptococcus (Group A)	1	1 (100%)
S. viridans group	15	14 (93%)
Alpha-hemolytic streptococus	1	1 (100%)
Beta-hemolytic streptococcus	2	2 (100%)
Non-hemolytic streptococcus	2	2 (100%)
S. intermedius	4	4 (100%)
S. mitis	1	1 (100%)
S. salivarius	1	1 (100%)
S. sanguis	1	1 (100%)
S. morbillorum	2	2 (100%)
S. bovis	1	1 (100%)
S. faecium	1	1 (100%)
Other streptococus spp.	9	9 (100%)
Group D streptococcus (enterococcus)	13	11 (85%)
S. faecalis	10	7 (70%)
Haemophilus spp.	1	1 (100%)
E. coli	89	74 (83%)
P. mirabilis	9	6 (67%)
P. vulgaris	4	3 (75%)
P. rettgeri	1	1 (100%)
M. morganii	5	4 (80%)
K. pneumoniae	20	18 (90%)
K. oxytoca	3	3 (100%)
Klebsiella spp.	1	1 (100%)

ORGANISM INTRA-ABDOMINAL	NO.	BACTERIOLOGIC RESPONSE ERADICATED
Enterobacter aerogenes	3	3 (100%)
E. cloacae	6	4 (67%)
Enterobacter spp.	1	1 (100%)
Enterobacter agglomerans	2	2 (100%)
Hafnia alvei	1	1 (100%)
P. multocida	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	3	2 (67%)
Citrobacter spp.	3	3 (100%)
Acinetobacter calcoaceticus	2	2 (100%)
P. aeruginosa	18	12 (67%)
P. alcaligenes	1	1 (100%)
Pseudomonas spp.	1	1 (100%
Salmonella typhi	1	1 (100%)
Salmonella choleraesuis	1	1 (100%)
Serratia liquefaciens	1	1 (100%)
Lactobacillus	3	3 (100%)
Eubacterium lentum	1	1 (100%)
Eubacterium spp.	2	2 (100%)
Propionibacterium acnes	3	3 (100%)
Propionibacterium spp.	1	1 (100%)
C. perfringens	4	4 (100%)
Clostridium spp.	22	22 (100%)
Bifidobacterium adolescentis	1	1 (100%)
Bifidobacterium spp.	1	1 (100%)
Peptococcus spp.	6	6 (100%)
Peptostreptococcus spp.	9	8 (89%)
Bacteroides spp.	21	20 (95%)
B. fragilis	35	34 (97%)
B. melaninogenicus	1	1 (100%)
B. ruminicola	1	1 (100%)
B. bivius	1	1 (100%)
Fusobacterium spp.	9	9 (100%)
Veillonella parvula	1	1 (100%)
Veillonella spp.	1	1 (100%)

ENTERITIS		
Campylobacter spp.	1	1 (100%)
Salmonella type B	1	0

| ORGANISM | BACTERIOLOGIC RESPONSE | |
GYNECOLOGIC	NO.	ERADICATED
S. aureus^{S*}	3	3 (100%)
S. aureus^{R*}	8	7 (88%)
S. epidermidis	17	17 (100%)
Alpha-hemolytic streptococus	3	3 (100%)
S. viridans group	2	2 (100%)
Non-hemolytic streptococcus	3	3 (100%)
Group B streptococcus	20	20 (100%)
Other streptococcus spp.	7	7 (100%)
Group D streptococcus (enterococcus)	14	12 (86%)
S. faecalis	11	10 (91%)
H. influenzae	1	1 (100%)
E. coli	33	28 (85%)
Proteus mirabilis	6	5 (83%)
Proteus vulgaris	1	1 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	6	6 (100%)
Klebsiella spp.	1	1 (100%)
Enterobacter aerogenes	2	2 (100%)
Enterobacter cloacae	1	1 (100%)
Enterobacter agglomerans	1	1 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Pseudomonas aeruginosa	1	0
N. gonorrhoeae	3	3 (100%)
Propionibacterium granulosum	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Bifidobacterium spp.	3	3 (100%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	5	5 (100%)
Peptostreptococcus spp.	9	9 (100%)
Bacteroides fragilis	9	8 (89%)
Bacteroides spp.	31	29 (94%)
Veillonella parvula	2	2 (100%)
Gardnerella vaginalis	7	7 (100%)
M. hominis	1	1 (100%)
Ureaplasma urealyticum	2	2 (100%)

		BACTERIOLOGIC RESPONSE
ORGANISM		
BACTERIAL SEPTICEMIA	NO.	ERADICATED
S. aureus[S]	7	7 (100%)
Micrococcus	1	1 (100%)
S.aureus[R]	21	19 (90%)
S. epidermidis	6	6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic streptococcus	1	1 (100%)
Beta-hemolytic streptococcus	1	1 (100%)
Group A streptococcus	1	1 (100%)
Streptococcus sanguis	1	1 (100%)
Streptococcus bovis	1	1 (100%)
Other streptococcus spp.	10	10 (100%)
Group D streptococcus (enterococcus)	4	4 (100%)
S. faecalis	3	3 (100%)
Bacillus subtilis	1	1 (100%)
H. influenzae	2	2 (100%)
E. coli	45	44 (98%)
P. mirabilis	2	2 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	8	8 (100%)
K. oxytoca	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Enterobacter cloacae	3	3 (100%)
Providencia stuartii	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Acinetobacter spp.	2	2 (100%)
Yersinia enterocolitica	1	1 (100%)
Pseudomonas aeruginosa	3	3 (100%)
Serratia marcescens	6	5 (83%)
Serratia spp.	1	1 (100%)
N. gonorrhoeae	1	1 (100%)
Salmonella spp.	3	3 (100%)
Clostridium bifermentans	1	1 (100%)
Clostridium spp.	1	0
Corynebacterium acnes	1	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides corrodens	1	1 (100%)
Bacteroides melaninogenicus	1	1 (100%)
Bacteroides spp.	4	4 (100%)
Fusobacterium spp.	2	2 (100%)
Flavobacterium spp.	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
BACTEREMIA	NO.	ERADICATED
S. aureus[S]	1	1 (100%)
S. aureus[R]	2	2 (100%)
S. epidermidis	1	1 (100%)
S. pneumoniae	1	1 (100%)
Group D streptococcus (enterococcus)	1	1 (100%)
H. influenzae	1	1 (100%)
E. coli	7	7 (100%)
E. cloacae	3	3 (100%)
Providencia stuartii	1	1 (100%)
Citrobacter diversus	1	1 (100%)
P. aeruginosa	4	4 (100%)
Bacteroides bivius	1	1 (100%)
ENDOCARDITIS		
S. aureus[S]	1	1 (100%)
S. aureus[R]	6	6 (100%)
S. pneumoniae	1	1 (100%)
S. sanguis	1	1 (100%)
Streptococcus spp.	1	1 (100%)
S. viridans group	1	1 (100%)
BONE/JOINT		
S. aureus[S]	8	8 (100%)
S. aureus[R]	23	22 (96%)
S. epidermidis	5	5 (100%)
S. pyogenes	1	1 (100%)
Beta-hemolytic streptococcus	2	2 (100%)
Streptococcus spp.	12	12 (100%)
Group D Streptococcus (enterococci)	5	5 (100%)
S. faecalis	5	5 (100%)
E. coli	5	4 (80%)
P. mirabilis	8	5 (63%)
P. vulgaris	2	1 (50%)
M. morganii	3	3 (100%)
Proteus spp.	1	0
Providencia stuartii	1	0
Enterobacter aerogenes	3	3 (100%)
Enterobacter cloacae	6	6 (100%)
Citrobacter diversus	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
P. aeruginosa	28	22 (79%)

ORGANISM		BACTERIOLOGIC RESPONSE
BONE/JOINT	NO.	ERADICATED
Serratia marcescens	3	1 (33%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides spp.	3	2 (67%)
Fusobacterium spp.	1	1 (100%)

SKIN & SKIN STRUCTURE

Gemella	1	1 (100%)
S. aureus^S	25	21 (84%)
S. aureus^R	116	98 (84%)
S. epidermidis	23	18 (78%)
Alpha-hemolytic streptococcus	11	11 (100%)
S. viridans	3	3 (100%)
Beta-hemolytic streptococcus	24	22 (92%)
Group A streptococcus	28	26 (93%)
Group B streptococcus	13	11 (85%)
Group C streptococcus	1	1 (100%)
S. intermedius	1	1 (100%)
Streptococcus spp.	38	35 (92%)
Group D streptococcus	30	24 (80%)
S. faecalis	22	19 (86%)
Corynebacterium spp.	5	5 (100%)
E. coli	59	49 (83%)
P. mirabilis	37	20 (54%)
P. vulgaris	7	6 (86%)
P. rettgeri	3	3 (100%)
Proteus spp.	1	1 (100%)
M. morganii	14	12 (86%)
K. pneumoniae	11	9 (82%)
K. oxytoca	12	11 (92%)
Klebsiella spp.	2	2 (100%)
Providencia stuartii	3	3 (100%)
P. multocida	1	1 (100%)
Enterobacter aerogenes	8	7 (88%)
Enterobacter cloacae	13	13 (100%)
Enterobacter agglomerans	1	1 (100%)
Enterobacter spp.	5	4 (80%)
Citrobacter freundii	4	4 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter spp.	2	2 (100%)
Acinetobacter calcoaceticus	6	6 (100%)

| ORGANISM | | BACTERIOLOGIC RESPONSE |
SKIN & SKIN STRUCTURE	NO.	ERADICATED
Acinetobacter spp.	2	1 (50%)
Alcaligenes odorans	1	1 (100%)
Alcaligenes spp.	1	1 (100%)
P. aeruginosa	56	37 (66%)
Pseudomonas spp.	1	1 (100%)
Aeromonas hydrophilia	4	3 (75%)
Serratia marcescens	9	8 (89%)
Serratia spp.	2	2 (100%)
Vibrio parahemolyticus	1	1 (100%)
Lactobacillus	1	1 (100%)
Gaffkia anaerobia	1	1 (100%)
Clostridium p .fringens	1	1 (100%)
Peptococcus spp.	22	22 (100%)
Peptostreptococcus spp.	13	13 (100%)
Eubacterium spp.	1	1 (100%)
A. eriksonii	1	1 (100%)
Bacteroides fragilis	27	27 (100%)
B. melaninogenicus	3	3 (100%)
B. bivius	1	1 (100%)
Bacteroides spp.	32	32 (100%)
Eikenella corrodens	1	1 (100%)
Eikenella spp.	1	1 (100%)
A. fermentans	1	1 (100%)
Fusobacterium spp.	5	5 (100%)
Fusobacterium rusii	1	1 (100%)
Veillonella parvula	2	2 (100%)
Mixed anaerobes	2	2 (100%)
OTITIS		
S. pneumoniae	1	1 (100%)
UPPER RESPIRATORY		
S. aureus[R]	1	1 (100%)
Streptococcus spp.	1	1 (100%)
E. aerogenes	1	1 (100%)
K. pneumoniae	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	1	1 (100%)
Fusobacterium spp.	1	1 (100%)
MEDIASTINITIS		
S. aureus[R]	1	1 (100%)

BRAIN ABSCESS	NO.	ERADICATED
S. aureus[R]	1	1 (100%)

SAFETY

NO. OF CASES EVALUABLE ------------------------------ 1,696

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS ----------- 79 (4.7%)

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS --------- 181 (10.7%)

LOCAL SIDE EFFECTS

	NO.	Probably Not	Possibly	Probably	Definite
Infused vein pain	17 (1.0%)	5 (0.3%)	4 (0.2%)	5 (0.3%)	3 (0.2
Infused vein induration	11 (0.6%)	7 (0.4%)	4 (0.2%)		
Infused vein infection	3 (0.2%)	2 (0.1%)	1 (0.1%)		
Erythema I.V. site	13 (0.8%)	7 (0.4%)	6 (0.4%)		
Phlebitis/ thrombophlebitis	56 (3.3%)	3 (0.2%)	24 (1.4%)	22 (1.3%)	7 (0.4

SYSTEMIC SIDE EFFECTS

	NO.	Probably Not	Possibly	Probably	Definite
Anxiety	1 (0.05%)	1 (0.05%)			
Confusion	4 (0.2%)	3 (0.15%)	1 (0.05%)		
Seizures	11 (0.6%)	4 (0.2%)	3 (0.15%)	4 (0.2%)	
Encephalopathy	1 (0.05%)			1 (0.05%)	
Dizziness	6 (0.3%)	1 (0.05%)	1 (0.05%)	1 (0.05%)	3 (0.1
Vertigo	2 (0.1%)		2 (0.1%)		
Headache	5 (0.3%)	3 (0.15%)	2 (0.1%)		
Myoclonus	2 (0.1%)			2 (0.1%)	
Meningitis	1 (0.05%)		1 (0.05%)		
Intracerebral hemorrhage	1 (0.05%)	1 (0.05%)			
Paresthesia	1 (0.05%)				1 (0.
Somnolence	3 (0.15%)		1 (0.05%)	2 (0.1%)	
Nystagmus	1 (0.05%)	1 (0.05%)			
Asthenia/weakness	2 (0.1%)		1 (0.05%)		1 (0.
Chest discomfort/pain	4 (0.2%)	3 (0.15%)	1 (0.05%)		
Syncope	1 (0.05%)	1 (0.05%)			
Hypotension	10 (0.6%)	4 (0.2%)	3 (0.15%)	3 (0.15%)	
Palpitation	2 (0.1%)		2 (0.1%)		
Tachycardia	1 (0.05%)		1 (0.05%)		
Apnea	2 (0.1%)	2 (0.1%)			
Dyspnea	2 (0.1%)	1 (0.05%)	1 (0.05%)		
Hyperventilation	1 (0.05%)				1 (0.
Hemoptysis	1 (0.05%)	1 (0.05%)			
Respiratory distress syndrome	1 (0.05%)	1 (0.05%)			

SYSTEMIC SIDE EFFECTS

	NO.	Probably Not	Possibly	Probably	Definit
Cyanosis	1 (0.05%)		1 (0.05%)		
Septic Shock	2 (0.1%)	2 (0.1%)			
Flushing	1 (0.05%)				1 (0.0
Fever	10 (0.6%)	2 (0.1%)	5 (0.3%)	1 (0.05%)	2 (0.1
Chills	2 (0.1%)	2 (0.1%)			
Hyperhydrosis	2 (0.1%)	1 (0.05%)	1 (0.05%)		
Facial edema	1 (0.05%)			1 (0.05%)	
Pruritus	6 (0.3%)	1 (0.05%)	1 (0.05%)	3 (0.15%)	1 (0.(
Rash	17 (1.0%)	1 (0.05%)	8 (0.5%)	5 (0.3%)	3 (0.
Urticaria	3 (0.15%)			2 (0.1%)	1 (0.
Erythema multiforme	1 (0.05%)				1 (0.
Polyarthropathy	1 (0.05%)		1 (0.05%)		
Thoracic spine pain	1 (0.05%)				1 (0.
Pharyngeal pain	1 (0.05%)			1 (0.05%)	
Increased salivation	1 (0.05%)			1 (0.05%)	
Glossitis	1 (0.05%)				1 (0.
Brown tongue	3 (0.2%)			3 (0.2%)	
Heartburn	2 (0.1%)		1 (0.05%)	1 (0.05%)	
Hiccups	1 (0.05%)	1 (0.05%)			
Nausea	38 (2.2%)	3 (0.2%)	14 (0.8%)	16 (0.9%)	5 (0
Vomiting	31 (1.8%)	6 (0.4%)	11 (0.6%)	6 (0.4%)	8 (0
Diarrhea	45 (2.7%)	15 (0.9%)	14 (0.8%)	10 (0.6%)	6 (C
Abdominal pain	3 (0.15%)	1 (0.05%)	1 (0.05%)	1 (0.05%)	
Pseudomembranous colitis	3 (0.15%)			3 (0.15%)	
Hemorrhagic colitis	1 (0.05%)			1 (0.05%)	
Oral candidiasis	1 (0.05%)				1 ((
Vaginal candidiasis	1 (0.05%)		1 (0.05%)		
Pruritus vulvae	1 (0.05%)		1 (0.05%)		
Menorrhagia	1 (0.05%)	1 (0.05%)			
Dysuria	1 (0.05%)	1 (0.05%)			
Oliguria and anuria	2 (0.1%)	1 (0.05%)		1 (0.05%)	
Polyuria	1 (0.05%)			1 (0.05%)	
Fullness in ears	1 (0.05%)	1 (0.05%)			
Hearing loss	3 (0.15%)	2 (0.1%)	1 (0.05%)		
Tinnitus	1 (0.05%)		1 (0.05%)		

	NO.	Definitely Not	Probably Not	Probably
DEATHS	88 (5.3%)	83 (5.0%)	4 (0.2%)	1 (0.1%)

Abnormal Laboratory Tests

	NO ABNORMAL (%)
Decreased RBCs	1 (0.1%)
Decreased hemoglobin	17 (1.0%)
Decreased hematocrit	14 (0.8%)
Decreased WBC	22 (1.3%)
Decreased neutrophils	10 (0.6%)
Increased lymphocytes	2 (0.1%)
Increased monocytes	13 (0.8%)
Increased eosinophils	69 (4.1%)
Increased basophils	3 (0.2%)
Increased platelets	27 (1.6%)
Decreased platelets	12 (0.7%)
Prothrombin time (abnormal)	13 (0.8%)
Increased BUN	10 (0.6%)
Increased blood urea	4 (0.2%)
Increased creatinine	13 (0.8%)
Increased bilirubin	13 (0.8%)
Increased AST (SGOT)	76 (4.5%)
Increased ALT (SGPT)	83 (4.9%)
Increased alkaline phosphatase	61 (3.6%)
Increased LDH	6 (0.4%)
Increased blood glucose	2 (0.1%)
Increased potassium	1 (0.1%)
Decreased potassium	1 (0.1%)
Increased chloride	4 (0.2%)
Decreased chloride	1 (0.1%)
Positive Coombs' test	33 (1.9%)
Urine protein	7 (0.4%)
Urine RBCs	6 (0.4%)
Urine WBCs	9 (0.5%)
Urine epithelial cells	1 (0.1%)
Urine casts	5 (0.3%)
Urine bilirubin	3 (0.2%)
Urine urobilinogen	4 (0.2%)

Summary of Safety Update Report

The Safety Update Report includes information on 1502 patients in MSDRL-sponsored studies for whom information was available between the U.S. NDA cutoff (November 7, 1983) and September 30, 1984. All adverse experiences from both domestic and foreign studies are included.

The adverse experiences of 1369 patients treated with multiple doses of Primaxin are reported separately from those which occur in 133 patients who received the study drug in pharmacokinetic studies (mainly single doses).

Adverse Experiences in 1369 Patients

	NO.	Probably Not	Possibly	Probably	Definite
LOCAL SIDE EFFECTS					
Infusion site ulcer	1 (0.07%)			1 (0.07%)	2 (0.1%
Infused vein induration	1 ((0.07%)			1 (0.07%)	
Erythema I.V. site	5 (0.4%)	3 (0.22%)	2 (0.15%)		
Phlebitis/thrombophlebitis	53 (3.9%)	12 (0.9%)	13 (1.0%)	21 (1.5%)	7 (0.5%
SYSTEMIC SIDE EFFECTS					
Nervousness	1 (0.07%)			1 (0.07%)	
Insomnia	1 (0.07%)			1 (0.07%)	
Disorientation	1 (0.07%)		1 (0.07%)		
Tremor	2 (0.15%)		2 (0.15%)		
Hallucinations	1 (0.07%)		1 (0.07%)		
Grand mal seizures	1 (0.07%)		1 (0.07%)		
Convulsive disorder	7 (0.5%)	3 (0.22%)	3 (0.22%)	1 (0.07%))	
Asterixis	1 (0.07%)		1 (0.07%)		
Hemiplegia	1 (0.07%)	1 (0.07%)			
Vertigo	1 (0.07%)	1 (0.07%)			
Headache	3 (0.22%)	2 (0.15%)		1 (0.07%)	
Chest discomfort	1 (0.07%)	1 (0.07%)			
Asthma	1 (0.07%)	1 (0.07%)			
Pulmonary embolism and infarction	1 (0.07%)	1 (0.07%)			
Cardiac arrest	1 (0.07%)	1 (0.07%)			
Cardiogenic shock	1 (0.07%)	1 (0.07%)			
Tachycardia	2 (0.15%)		1 (0.07%)	1 (0.07%)	
Atrial fibrillation	1 (0.07%)	1 (0.07%)			
Transient ischemic shock	1 (0.07%)	1 (0.07%)			
Myocardial infarction	1 (0.07%)	1 (0.07%)			
PVCs	1 (0.07%)	1 (0.07%)			
Fever	3 (0.22%)		1 (0.07%)	1 (0.07%)	1 (0
Hyperhydrosis	2 (0.15%)		1 (0.07%)		1 (0
Edema	1 (0.07%)			1 (0.07%)	
Fluid overload	1 (0.07%)		1 (0.07%)		
Peripheral edema	2 (0.15%)			2 (0.15%)	
Petechiae	1 (0.07%)	1 (0.07%)			
Pruritus	7 (0.5%)		2 (0.15%)	5 (0.4%)	
Drug eruption	1 (0.07%)			1 (0.07%)	
Rash	33 (2.4%)	4 (0.3%)	12 (0.9%)	15 (1.1%)	2 (
Urticaria	5 (0.4%)	2 (0.15%)	2 (0.15%)		1 (
Toxic erythema	1 (0.07%)			1 (0.07%)	
Skin inflammation	1 (0.07%)			1 (0.07%)	
Intertrigo	1 (0.07%)			1 (0.07%)	

Adverse Experiences in 1369 Patients

SYSTEMIC SIDE EFFECTS	NO.	DRUG RELATIONSHIP			
		Probably Not	Possibly	Probably	Definitely
Pharyngeal discomfort	1 (0.07%)		1 (0.07%)		
Dry-mouth	2 (0.15%)		2 (0.15%)		
Glossitis	2 (0.15%)			2 (0.15%)	
Heartburn	1 (0.07%)			1 (0.07%)	
Nausea	38 (2.8%)	1 (0.07%)	13 (0.9%)	23 (1.7%)	1 (0.07%
Vomiting	19 (1.4%)	1 (0.07%)	5 (0.4%)	12 (0.9%)	1 (0.07%
Diarrhea	38 (2.8%)	9 (0.6%)	16 (1.2%)	11 (0.8%)	2 (0.15%
Gastroenteritis	1 (0.07%)		1 (0.07%)		
Abdominal cramps	2 (0.15%)			1 (0.07%)	1 (0.07%
Abdominal pain	5 (0.4%)	2 (0.15%)	1 (0.07%)	2 (0.15%)	
Pseudomembranous colitis	2 (0.15%)			1 (0.07%)	1 (0.07%
Oral candidiasis	4 (0.3%)			4 (0.3%)	
Taste perversion	4 (0.3%)	1 (0.07%)	2 (0.15%)	1 (0.07%)	
Visual disturbance	1 (0.07%)		1 (0.07%)		
Paralytic lens	1 (0.07%)			1 (0.07%)	
Tooth discoloration	1 (0.07%)	1 (0.07%)			
Hematuria	2 (0.15%)	1 (0.07%)	1 (0.07%)		
Abnormal urine color	3 (0.22%)	1 (0.07%)	1 (0.07%)	1 (0.07%)	

Adverse Experiences in 133 Patients (usually one dose)

SYSTEMIC SIDE EFFECTS	NO.	DRUG RELATIONSHIP			
		Probably Not	Possibly	Probably	Definitel
Chills	3 (2.3%)			3 (2.3%)	
Abdominal pain	1 (0.8%)		1 (0.8%)		
Nausea	2 (1.5%)			2 (1.5%)	
Oral candidiasis	1 (0.8%)		1 (0.8%)		
Vomiting	1 (0.8%)	1 (0.8%)			
Euphoria	1 (0.8%)		1 (0.8%)		
Dizziness	1 (0.8%)			1 (0.8%)	
Hyperhydrosis	2 (1.5%)			2 (1.5%)	
Urticaria	1 (0.8%)		1 (0.8%)		
Taste perversion	1 (0.8%)		1 (0.8%)		
Headache	1 (0.8%)	1 (0.8%)			

Deaths

There were 113 deaths reported, all of which were considered not drug related. Of these, 25% occurred in patients under compassionate protocols.

The adverse experiences reported in the post NDA patients were, in general, similar to those reported in the NDA studies.
The predominant nervous system adverse experiences in the post NDA patients related to seizures and occurred at about the same frequency as in the NDA patients.
One patient with renal failure and one with marked renal insufficiency were inadvertently given four times the recommended maximum dose of study drug and had seizures. Both patients were treated under the compassionate protocol and had significant background CNS disturbances. Four other patients who had seizures had marked renal impairment and major CNS background disturbances and were given more study drug than defined for their level of renal function.
The frequency of seizures during Primaxin therapy appears to be similar to that for other antibiotics in general. However, as with beta-lactams in general, the administration of Primaxin may be associated with grand mal seizures.

In general, the majority of the patients who developed seizures had pre-existing CNS disturbances.

Clinical Development Study Program (CDSP)

A total of 760 patients entered the CDSP in Germany as of September 30, 1984. Eighty-six investigators participated in these studies and contributed patients to this program. All patients enrolled were evaluated for safety. A total of 37 deaths were reported, and according to the investigators none of the deaths were drug related. These patients had severe infections and serious concomitant diseases and many of them received Primaxin as a "last resort" antibiotic with the hope that the patient would survive.

Based on the type of patients treated, the number of deaths in the program was not considered unexpected. There were no unusual or high frequency adverse experiences noted.

Japan Studies

As of September, 1984, Primaxin had been administered to 1,227 adult patients in open clinical studies in Japan.
The overall incidence of adverse clinical experiences was 4.6% (56/1,227), and the most frequent events reported were nausea 1.7%, diarrhea 0.8%, skin eruption 0.7%, and vomiting 0.7%. None of the patients experienced a seizure. The most frequent abnormal laboratory findings were elevation of SGOT - 6.2%, SGPT - 6.1%, alkaline phosphatase - 2.4%, and gamma - GTP - 1.7%. None of these patients experienced serious hepatic dysfunction. Eosinophils were increased in 2.0% of the cases and BUN in 1.0%, but no patient had renal function compromised by Primaxin. A total of 18 deaths were reported; none was considered drug related.

LABORATORY VARIATIONS FROM THE NORMAL RANGE
POST NDA SAFETY UPDATE
1369 PATIENTS

	If. Not	Prob. Not	Poss.	Prob.	Def.	Total	%
Hemoglobin decrease	2	4	1	1	0	8	.58
Hematocrit decrease	1	5	2	0	0	8	.58
WBC decrease	3	2	6	3	1	15	1.1
WBC increase	4(1)	4	1	0	0	9(1)	.66
Neutrophils decrease	0	0	1	0	0	1	.07
Seg. Neutrophils decrease	1	1	4	5	0	11	.80
Lymphocytes decrease	0	3	0	0	0	3	.22
Monocytes increase	2	1	4	1	0	8	.58
Eosinophils increase	1	4	27	13	2	47	3.4
Atypical Lyc	0	1	0	0	0	1	.07
Platelets decrease	4(1)	6(2)	6(1)	2(1)	0	18(5)	1.3
Platelets increase	2	13	21	10	0	46	3.4
SED Rate increase	0	1	3	0	0	4	0.3
Pro Time (abnormal)	2	6(1)	4	1	0	13(1)	.95
RBC Morph. Abnormal	1	1	0	0	0	2	.15
BUN increase	7(2)	8(3)	2(1)	0	0	17(6)	1.2
Creatinine increase	7(2)	12(2)	7(2)	1	0	27(6)	2.0
Bilirubin increase	4	5(1)	2	1	0	12(1)	.88
AST increase	6(1)	17	30	14	0	67(1)	4.9
ALT (abnormal)	10(1)	11	25	12	1	50(1)	3.7
Alkaline Phosphatase	7	17(1)	32	9	0	65(1)	4.7
GGT	0	0	0	1	0	1	.07
Bl. Glucose	1(1)	1	0	0	0	2(1)	.15
S. Lactate	0	1(1)	0	0	0	1(1)	.07
S. Uric Acid	1	0	0	0	0	1	.07
S. Sodium	1	0	0	0	0	1	.07
S. Potassium	2(1)	5(1)	2	0	0	9(2)	.66
S. Chloride	0	1	4	1	0	6	.44
Magnesium	1(1)	0	0	0	0	1(1)	.07
Coombs (+)	1	1	8	17	0	27	2.0
Urine Protein	1	2	4	1	0	8	.58
Urine WBCs	5	2	4	0	0	11	.80
Urine RBCs	5	4	0	0	0	9	.66
Urine Epithelial Cells	2	0	0	0	0	2	.15
Urine Casts	0	0	1	0	0	1	.07
WBC Casts	0	0	1	0	0	1	.07
Calcium Oxalate Crystals	0	1	0	0	0	1	.07
Urine Yeast	0	0	1	0	0	1	.07
C. difficile (stool)	0	0	0	2(2)	0	2(2)	.15

The counts not in parenthesis represent total counts, including serious and non-serious laboratory results. The counts in parenthesis are serious laboratory results only.

Other Studies

In addition to the MSDRL - Japan and the CDSP studies in Germany, local
studies to support registration are on-going in Italy, Spain, France, and the
United Kingdom.
Of the total 339 patients entered in these studies, there were four deaths
(all considered not drug related), and the only adverse experiences considered
to be probably drug related were leukopenia and hypotension. Both patients
recovered.

Marketing of Primaxin Outside the United States

On October 5, 1984, Merck notified the DAIDP that the West German Federal
Health Authority (the BGA) had suspended the registration of Primaxin. This
action was taken prior to the initial marketing of the drug by Merck. The
reason given for the suspension was that the BGA desired to have more time to
review data which Merck provided at their request.

On April 8, 1985, Merck informed the DAIDP that the BGA had completed its
review of the information provided, and that the suspension of the
registration had been removed. Therefore, Merck was to initiate marketing of
Primaxin in West Germany in April, 1985.

Conclusions

The results obtained in controlled and uncontrolled studies conducted by
well-qualified investigators demonstrate that Primaxin (imipenem/cilastatin)
given in appropriate dosages is safe and effective in the treatment of serious
infections caused by susceptible strains of the designated microorganisms in
the conditions listed below:

1. Lower Respiratory Tract Infections caused by S. aureus (penicillinase
    producing strains), E. coli, Klebsiella species, Enterobacter species,
    P. aeruginosa, H. influenzae, H. parainfluenzae, Acinetobacter species,
    S. marcescens.

2. Urinary Tract Infections (complicated and uncomplicated) caused by
    S. aureus (penicillinase producing strains), Group D streptococci
    (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus
    vulgaris, Providencia rettgeri, M. morganii, P. aeruginosa.

3. Intra-Abdominal Infections caused by S. epidermidis, Group D streptococci
    (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus
    species (indole positive and indole negative), M. morganii, P. aeruginosa,
    Citrobacter species, Clostridium species, Gram-positive anaerobes,
    including Peptococcus species, Peptostreptococcus species and
    Propionibacterium species, Bacteroides species, including B. fragilis, and
    Fusobacterium species.

4. Gynecologic Infections caused by S. aureus, (penicillinase producing strains), S. epidermidis, Group B streptococci, Group D streptococci (enterococci), E. coli, Klebsiella species, Proteus species (indole positive and indole negative), Enterobacter species, Gram-positive anaerobes, including Peptococcus species, Peptostreptococcus species, Propionibacterium species and Bifidobacterium species, Bacteroides species, including B. fragilis, and Gardnerella vaginalis.

5. Bacterial Septicemia caused by S. aureus (penicillinase producing strains), Group D streptococci (enterococci), E. coli, Klebsiella species, P. aeruginosa, Serratia species, Enterobacter species, Bacteroides species, including B. fragilis.

6. Bone and Joint Infections caused by S. aureus (penicillinase producing strains), S. epidermidis, Group D streptococci (enterococcis), Enterobacter species, P. aeruginosa.

7. Skin and Skin Structure Infections caused by S. aureus (penicillinase producing strains), S. epidermidis, Group D streptococci (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus vulgaris, P. rettgeri, M. morganii, P. aeruginosa, Serratia species, Citrobacter species, Acinetobacter species, Gram-positive anaerobes, including Peptococcus species and Peptostreptococcus species, Bacteroides species, including B. fragilis, and Fusobacterium species.

8. Endocarditis due to S. aureus (penicillinase producing strains).

9. Polymicrobic Infections

Review of Package Insert
The proposed package insert for Primaxin was discussed with representatives from MSDRL during conferences held April 20, 1985 and June 5, 1985 (see memos of conferences). Subsequently, a revised copy of the insert, dated June 18, 1985, was submitted for further evaluation.

The following labeling revisions should be made:

Page 7, under Susceptibility Testing, first paragraph, imipenem spelling should be corrected.

Page 8, underline E. coli, S. aureus, S. faecalis and Pa. aeruginosa.

Page 9, under Urinary Tract Infections, page 10, under Intra-Abdominal and Gynecologic Infections, page 11, under Bacterial Septicemia and Bone and Joint Infections and page 12 under Skin and Skin Structure Infections change Group D streptococcus (enterococcus) to Group D streptococci (enterococci).

Page 10, under <u>Intra-Abdominal Infections</u> underline <u>Peptococcus</u>,
<u>Peptostreptococcus</u>, <u>Eubacterium</u>, <u>Propionibacterium</u>, <u>Bifidobacterium</u>,
<u>Bacteroides</u>, and <u>Fusobacterium</u>.

Page 10, under <u>Gynecologic Infections</u>, change Group B streptococcus to Group B
streptococci and underline <u>Peptococcus</u>, <u>Peptostreptococcus</u>, <u>Propionibacterium</u>
and <u>Bifidobacterium</u>.

Page 12, under <u>Skin and Skin Structure Infections</u>, underline <u>Peptococcus</u> and
<u>Peptostreptococcus</u>.

Other than for the above revisions, the insert appears adequate; however,
final approval is deferred pending evaluation by other reviewers.

Recommendations
Based on the clinical data contained in Antibiotic Form 5 50-587, it is
recommended that Primaxin (imipenem/cilastatin) be approved for the
indications listed under <u>Conclusions</u>.
MSDRL should be notified of the above labeling revisions.

Mercedes S. Albuerne, M.D.

cc:
Orig Form 5
HFN-815
HFN-815/CSO
HFN-815/Micro
HFN-178
HFN-815/MAlbuerne:js/6/24/85
3748b

Drug Control Review Notes #3

NDA #50-587

Dosage Form: Injectable combination of imipenem and cilastatin sodium

Submissions Reviewed:

   a. Original dated: May 3, 1984
   b. Amendments dated: August 22, 1985
   c. Providing for: Draft Labeling

Names:

   a. Trade: Primaxin
   b. Non-proprietary: imipenem and cilastatin

Remarks:

1- The applicant has completed labeling deficiencies by submission of an adequate draft package insert, dated May 3, 1984. This submission provides adequate labeling from the manufacturing controls viewpoint. All outstanding microbiological issues concerning spectrum, in vitro susceptibility testing breakpoints have been rectified and the statements in the labeling are satisfactory.

2- A satisfactory CGMP evaluation was received, dated July 26, 1985.

3- The certification monographs have not been negotiated with the applicant. However, the applicant has provided approvable manufacturing and controls commitments.

Conclusions: The manufacturing and controls provided by the applicant are approvable, pending successful negotiation of a proposed draft certification monograph.

James R. King 9/13/85

James R. King, 9/12/85

cc: Orig. NDA 50-587
HFN-815, HFN-815/CSO
HFN-178, HFN-235
HFN-815/JRKing/9/13/85/dv
R/D: init. by RNorton/9/12/85

June 11, 1985

Addendum to Medical Officer's Reivew of NDA 50-587

Date of Submission: June 7, 1985

Applicant: Merck Sharp & Dohme Research Laboratories
            West Point, PA

Name of Drug: PRIMAXIN (imipenem/cilastatin sodium)

On June 7, 1985, Merck submitted case report forms for 14 additional patients
who had endocarditis caused by <u>Staphylococcus aureus</u>.

The cases were provided by the following investigators: Byungse Suh, M.D.,
Assistant Professor of Microbiology and Immunology, Temple University.

Gordon Dickinson, M.D., Assistant Professor of Medicine, University of Miami.

Jay Jacobson, M.D., Assistant Professor of Medicine, Division of Infectious
Diseases, University of Utah College of Medicine.

Louis D. Saravolatz, M.D., Head, Division of Infectious Diseases and Hospital
Epidemiology, Henry Ford Hospital, Detroit, Michigan.

Stephen S. Hawkins, M.D., Assistant Professor of Medicine, Division of
Infectious Diseases, University of Tennessee.

All 14 patients were adults ranging in age from 25 to 42 years, with a mean
age of 30.8 years.
There were 9 males and 5 females.
All patients were known to be I.V. drug abusers.

Twelve patients were treated with Primaxin at a total daily dose of 2 grams
(500 mg q 6 hours) by intravenous infusion. The duration of treatment ranged
from 18 to 38 days. Two patients were treated with a total daily dose of 3
grams (500 mg q 4 hours) by intravenous infusion, for 8 and 25 days,
respectively.

All 14 patients were considered adequate for the evaluation of drug efficacy
and safety.

RESULTS

EFFICACY

INFECTION	NO	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
Endocarditis	14	11 (79%)	2 (14%)	1 (7%)

Organism		BACTERIOLOGIC RESPONSE	
		ERADICATED	NO ERADICATED
S. aureus(S)	3	3 (100%)	
S. aureus(R)	11	10 (91%)	1 (9%)

(S) = Penicillin sensitive
(R) = Penicillin resistant

SAFETY

Two of the 14 patients were reported to have had some side effects during treatment. One patient had headache, diaphoresis, dyspnea and tachycardia; the other patient had nausea and vomited once.

The following abnormal laboratory test values were reported:

Decreased hemoglobin   - 1

Decreased hematocrit   - 1

Increased eosinophils   - 1

Increased platelets   - 2

Increased SGOT   - 1

Increased SGPT   - 1

Positive Coombs' test   - 4

Conclusions

The 14 cases provided in this submission plus the 7 cases provided in the original NDA submission add up to a total of 21 cases of endocarditis due to S. aureus.

The results obtained in these 21 cases were as follows:

		Clinical Response		
INFECTION	No.	Cure	Improve	Fail
Endocarditis	21	18 (86%)	1 (9%)	1 (5%)

Organism	No.	Eradicated
S. aureus(S)	4	4 (100%)
S. aureus(R)	17	16 (94%)
Total	1	20 (95%)

The results demonstrate that Primaxin is effective in the treatment of endocarditis caused by S. aureus.

Mercedes S. Albuerne, M.D.

CHEM REV

Form 5 # 50-587   Rx thienamycin derivative/
                                                 dihydropeptidase inhibitor

Applicant: Merck, Sharp, & Dohme Research Laboratories
             West Point, PA 19486

Submission Reviewed:

    a. Original Dated: May 3, 1984
    b. Amendment Dated: Jan. 2, 1985
    c. Providing for: In vitro Microbiology data

Names:

    a. Trade: Primaxin
    b. Non proprietary: Imipenem/cilastatin sodium

Remarks:

The applicant responded to a request for additional in vitro data
addressing each of 3 topics.

1- Susceptibility data were supplied for a list of pathogens for
inclusion in the package insert. These organisms had been previously
deleted as a part of the review of the package insert. This submission
provided sufficient in vitro evidence that only "▓▓▓▓▓▓▓▓▓▓▓▓▓
▓▓▓▓▓▓▓▓▓" should be deleted from the original draft package insert
submitted May 3, 1984. ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓" data
have been supplied to justify inclusion of the list of microorganisms in
the review dated 6/13/84.

2- Minimal quality control data were provided for susceptibility testing
imipenem diffusion and dilution procedures. In lieu of the company's
data for diffusion procedures, I reviewed the recommendation provided to
the National Committee for Clinical Laboratory Standards (NCCLS) by the
Collaborative Antibiotic Susceptibility Testing (CAST) group. The study
is documented as Item # 6 of a Disk Diffusion Susceptibility Meeting on
April 30, and May 1, 1984. The CAST group recommends that the 10 mcg
disk have the following quality control breakpoints:

	Breakpoints
Pseudomonas aeruginosa ATC 27853	20 - 28 mm.
Escherichia coli ATCC 25922	27 - 31 mm.

No Staphylococcus aureus ATCC 25923 breakpoints were recommended,
probably because zones were extremely large (ranging from 36 to 48 mm).
If the disk content remains at 10 mcg, the Pseudomonas and E. coli are
satisfactory quality control organisms.

The company also supplied MIC quality control data. The paucity of data
precludes drawing a reasonable conclusion. ████████████████████████████
███
████████████ The company supplied the mode MIC values, but final decision
will have to await receipt by the FDA of an adequate quantity of data for
the dilution testing quality control breakpoints.

3- █

Conclusions:

Manufacturing and Controls are inadequate.

1- Exhibit samples have been received and are undergoing Methods
Validation.

2- No satisfactory CGMP evaluation has been received from the Division
of Drug Quality Compliance.

✓ 3- The term ███████████████████████████ is the only listed organism
in the in-vitro section which should be deleted from the original draft
package insert submitted May 3, 1984.

4- Susceptibility testing quality control breakpoints should be
established for the 10 mcg imipenem disk as follows:

Pseudomonas aeruginosa ATCC 27853   20 - 28 mm.

Escherichia coli ATCC 25922   27 - 31 mm.

5- Additional data should be supplied to establish quality control
breakpoints for dilution susceptibility testing procedures. Data from
the CAST group should be satisfactory.

Page 3

6- Establishment of interpretive breakpoints for diffusion and dilution susceptibility testing procedures will be defered until the Medical Officer's review has been completed.

James R. King 3/15/85

James R. King, 1/10/85

cc: Orig. Form 5 #50-587
      HFN-815, HFN-815/CSO
      HFN-815/MO
      HFN-178, HFN-235
      HFN-815/JRKing/3/15/85/dv
      RD: init. by RNorton/3/13/85

DRUG CONTROL REVIEW NOTES

1. TYPE ☐ IND ☐ •	**2. NO.** 50-587

3. SPONSOR

Merck, Sharp & Dohme Research Laboratories

5. SUBMISSIONS REVIEWED

a. ORIGINAL DATED May 3, 1984

b. AMENDMENTS DATED

4. ADDRESS

West Point, PA   19486

5c. PROVIDING FOR

6. NAME(S)

a. TRADE

Primaxin

b. NON-PROPRIETARY

imipenem and cilastatin

**c. CHEMICAL** N-formimidoylthienamycin monohydrate and [Z,7(R), 2(S)]-7-[(2-amino-2-carboxyethyl)thio]-2-[[(2,2-dimethylcyclopropyl) carbonyl]amino]-2-heptanoic ac___ monosodium salt

d. ESTAB

none designated

e. USAN

imipemide/none designated

f. WHO

none designated

7. STRUCTURAL FORMULA

8. DOSAGE FORM

injectable combination
250 + 500 mg strengths

9. ☒ RX   ☐ OTC

10. FAMILY OR TYPE OF DRUG

thienamycin derivative/
dihydropeptidase inhibitor

11. RELATED NDA, IND, MF, FORM 5'S

12. REMARKS

13. CONCLUSIONS

Manufacturing and Controls are inadequate.

1. No certification monograph has been negotiated because exhibit samples had not been received as of 5/31/84.

2. No satisfactory CGMP evaluation has been received from the Div. of Drug Quality Compliance (mailed May 31, 1984).

14. DATE REVIEWED	**15. REVIEWER**
6/13/84	James R. King R. King 6/23/84

FORM FDH-1742
5/65

RNorton/init. r/d by: 6/22/84   Duplicate IND HFN-815, HFN-815/CSO, HFN-178
Triplicate IND HFN-235
HFN-815/JRKing/6/25/84/dv

Conclusions:

3. The applicant should be notified to provide raw data, if necessary to provide for inclusion in the package insert of the microorganisms list in review section 8 as well as data to support interpretive breakpoints and Q C data for susceptibility testing.

Bulk Imipenem sterile
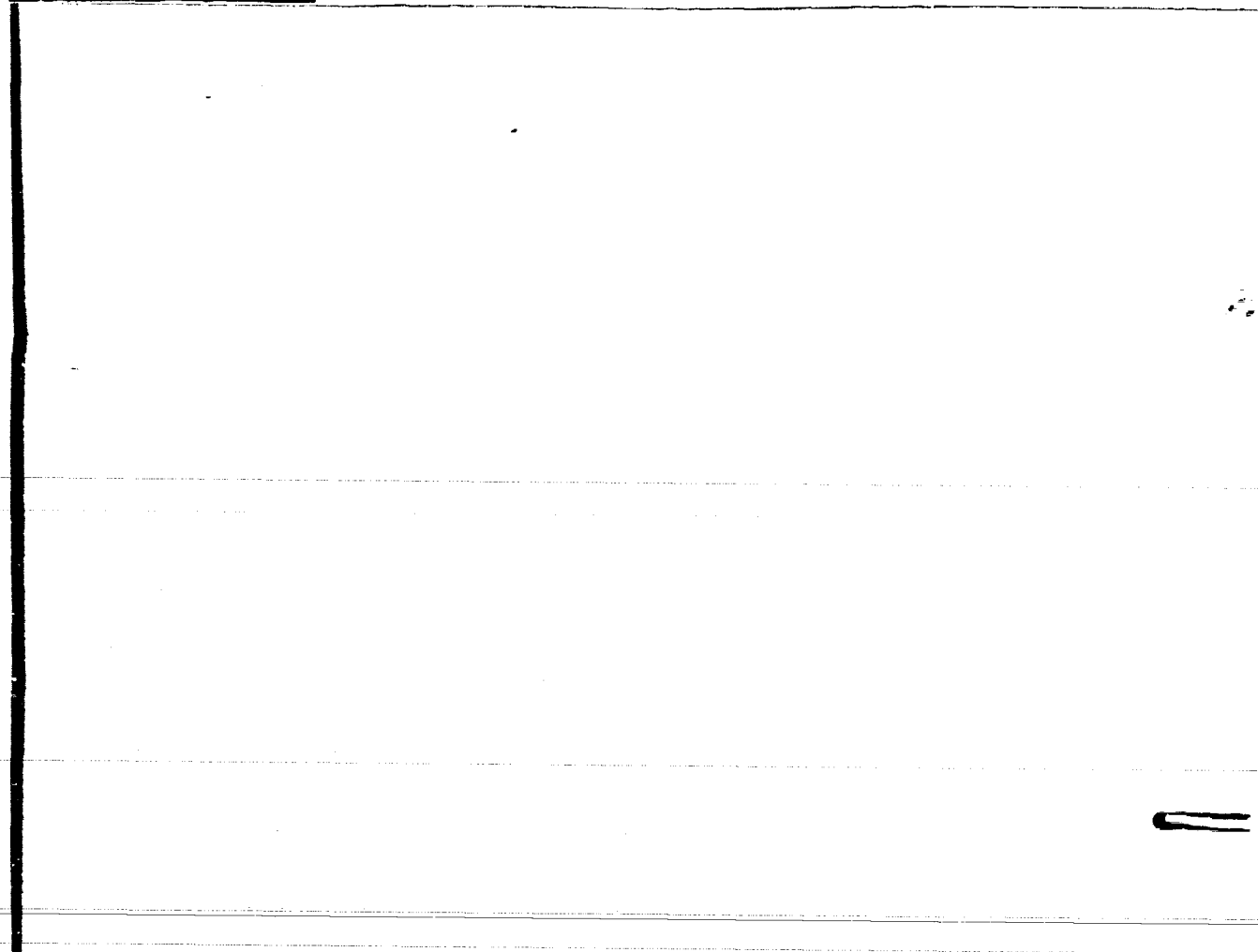
4- Manufacturing and Processing   Inadequate

See attached listing of manufacturing procedures and locations.

A CGMP evaluation request was mailed to the Manufacturing Review Branch
of Division of Drug Quality Compliance on May 31, 1984.

5- Laboratory Controls   Adequate for in-house release

1- <u>Components and Composition</u>   <u>Adequate</u>

2- <u>Source and Synthesis</u>   <u>Adequate</u>

✓ 3- <u>Raw Materials</u>   <u>Adequate</u>

6- <u>Stability</u>   <u>Adequate for a shelf-life of 18 months</u>

7- <u>Control Numbers</u>   <u>Adequate</u>

8- <u>Labeling</u>   <u>Inadequate</u>

a- <u>Draft vial and carton labels</u>

Adequate draft vial and carton labels were filed.

b- <u>Package Insert</u>

The firm has requested that a very long list of microorganisms be included in the <u>in vitro</u> Microbiology section. Data were not submitted to allow inclusion of the following microorganisms in the <u>in vitro</u> Microbiology section of the package insert.

<u>Streptococcus agalactiae</u> (Group B)
<u>Streptococcus</u> Group C
<u>Streptococcus</u> Group G

Salmonella spp.
<u>Citrobacter</u> spp.
<u>Enterobacter</u> agglomerans
<u>Hafnia alvei</u>
<u>Yersinia enterocolitica</u>
<u>Yersinia pseudotuberculosis</u>
<u>Bordetella bronchiseptica</u>
<u>Haemophilus parainfluenzae</u>
<u>Gardnerella</u> spp.   *should get G. vaginalis not G. sp.*
<u>Campylobacter</u> spp.
<u>Acinetobacter</u> spp.
<u>Achromobacter</u>
<u>Alcaligenes</u> spp.
<u>Moraxella</u> spp.

Section 3a

3a. <u>Name and location of each plant conducting the operations.</u>

Bacteroides asaccharolyticus
B. bivius
B. disiens
B. distasonis
B. ovatus
B. vulgatus
Peptococcus spp.

Acinomyces spp.

In addition, inadequate regression curve data were filed to support the interpretive zone diameter breakpoints as well as the MIC breakpoints. Only limited summary data were provided to establish these zone diameter breakpoints. No strains were utilized in the regression studies with susceptibilities in the intermediate range. Adequate data should be filed for this region of the regression curve to allow intelligent establishment of breakpoints.

Furthermore, no data for quality control studies were filed for disks or MIC measurements.

9- **Containers and closures**   **Adequate**

Bacteroides asaccharolyticus
B. bivius
B. disiens
B. distasonis
B. ovatus
B. vulgatus
Peptococcus spp.

Acinomyces spp.

In addition, inadequate regression curve data were filed to support the interpretive zone diameter breakpoints as well as the MIC breakpoints. Only limited summary data were provided to establish these zone diameter breakpoints. No strains were utilized in the regression studies with susceptibilities in the intermediate range. Adequate data should be filed for this region of the regression curve to allow intelligent establishment of breakpoints.

Furthermore, no data for quality control studies were filed for disks or MIC measurements.

9- __Containers and closures__   __Adequate__

PHARM
REV

NDA 50-587   (Original Submission)

Date Review Completed: 6/18/85

Applicant: Merck Sharp & Dohme

Drug: Primaxin[R] (Imipenem/Cilastatin Sodium; MK 789/MK-791)

Category: Broad spectrum beta-lactam antibiotic/enzyme inhibitor combination

Chemical Names:

   Imipenem: [5 R - [5 a, 6a (R*)]] -6-(1-hydroxyethyl) -3- [[2-[(iminomethyl) amino] ethyl] thio] -7-oxo-1- azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate

   Cilastatin: [Z, 7 (R),2(S)]-7-[(2-amino-2-carboxyethyl) thio]-2-[[(2,2-dimethyl-cyclopropyl)carbonyl]amino]-2-heptenoic acid monosodium salt"

Chemical Structures:
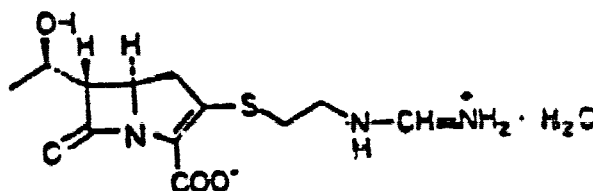
   Imipenem:
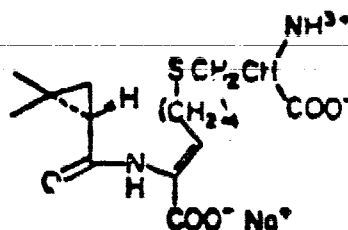
   Cilastatin:

Composition of Bottles & Vials to be Marketed: The drug [Primaxin^{TM} (imipenem/cilastatin; 1/1)] will be supplied by the sponsor to hospitals only. Two doses will be available in both bottles (120 ml) and vials (13 ml), i.e., 250 & 500 mg. In the bottles which already have the drug(s) in them, 100 ml of the solvent(s) should be added. If the drug is already in the vials (either dose), the vials should be filled with approx. 10 ml of the diluent and shaken to make a suspension. This suspension should be transferred to a 120 ml empty bottle, and the bottle filled with the diluent "ad 100 ml". As a result, 2 different doses (250 & 500 mg) will be available in the same volume (100 ml).

Diluents: These will not be supplied by the sponsor; however, they list several:

    0.9% Sodium Chloride Injection
    5% or 10% Dextrose Injection
    5% Dextrose Injection with 0.02% sodium bicarbonate solution
    5% Dextrose & 0.9% Sodium Chloride Injection
    5% Dextrose Injection with 0.225% or 0.45% saline solution
    NORMOSOL+-M in D5-W
    5% Dextrose Injection with 0.15% potassium chloride solution
    Mannitol 2.5%, 5% & 10%

The attending physician will determine the diluent of choice.

Proposed Clinical Use: Treatment of infection due to sensitive organisms

Related Submission: IND 18,538 (Primaxin)

Preclinical Studies: [The order of this review will follow the order in which the pharm/tox data are contained in the "Antibiotic Certification Request" (Form 5).]

I.   MICROBIOLOGY

II.   BIOCHEMICAL, METABOLIC & PHARMACOLOGIC STUDIES

Animals: rabbit, rhesus monkey, rat

Reason for Creating Imipenem from Thienamycin: The NH_3^+ group of thienamycin is highly ionizable in aqueous sol'n; therefore, its relatively high alkaline pH is high enough to induce the hydrolysis of the beta-lactam ring leading to the inactivation of the antibiotic.

Solution: By creating a formamidine derivative of thienamycin via the NH_3^+ group, the ionization of the alkaline moiety of thienamycin is wiped out. Note that this alkyl end of the drug shows a new pharmacologically active moiety, an amidine; however, since this amidine is attached by its nitrogen atom to the alkyl chain of the very right ring, we should call this derivative an alkylated amidine. The well known effects of the amidine, guanidine group of drugs (particularly di-) is not evident from the results of pharmacological studies. There is no reason to be concerned.

Systemic Persistence of Imipenem vs. Urinary Persistence: It became evident quite early that imipenem gives a satisfactory systemic effect for all viscera but the urinary system.   It was also evident that the drug is metabolized virtually completely by the kidney, which explains its very low availability for the urinary system, and the problem of inactivation of the antibiotic is magnified with the severe tubular toxicity induced by the drug.   The toxicity of the drug was not the result of hydrolysis of the lactam ring.   The approach to the sol'n was the finding of the mammalian enzyme responsible for the hydrolysis of the lactam ring in the kidney.   Dehydropeptidase-I (DHP-I) was found to be the hydrolyzing enzyme.   (In certain articles, this enzyme is also called mammalian beta-lactamase.   This is a brush border enzyme.)

The search for a more or less specific enzyme inhibitor resulted in the sol'n to both problems.   The inhibitor not only inactivated DHP-I, but protected the kidney against the toxicity of the drug.   The inhibitor was named "cilastatin".

Search for the Inhibitor: In a beautifully planned, organized and executed study, the search began by testing the simplest compound possessing the necessary chemical structure (configuration) as thienamycin or imipenem fitting the receptors of DHP-I.   Interestingly, the inhibitor does not contain a beta-lactam ring, but a peptide (carboxamide) in which the nearest 2 carbon atoms (to the peptide bond) of the amino acid are dehydrogenated.   That is why the enzyme which is inhibited by the discussed chemical moiety is called "dehydropeptidase-I".   Consequently, the inhibitor is named a "DHP-I inhibitor".   So to conclude, by feeding the enzyme with a false (open) dehydropeptide (without a beta-lactam ring attached), though only the receptors of the tubular epithelium (brush border) enzyme (DHP-I), specific for the very right-hand ring (which possess the dehydropeptide moiety) are blocked by the inhibitor (cilastatin); paradoxically, another activity of this complex and highly unusual mammalian renal brush border enzyme, the beta-lactamase function is inhibited.   I consulted a world-known enzymologist about this interesting enigmatic double activity of the enzyme, whose answer was that it is fascinating and "I would love to solve this problem."   There are countless questions to be answered, but these are more academic than practical; therefore, they will not be discussed here.   My view is that by introducing imipenem to medical practice, besides its excellent antibiotic effects, it is a new chemical moiety (not named by the applicant) which, by itself, is known to have profound biological effects on various cellular functions, including nuclear metabolism.

There are numerous requirements for a good inhibitor which had to be satisfied.   Of a series of compounds tested, the best appeared to be cilastatin.   These requirements were:

1.   relatively low toxicity;

2.   if coadministered with imipenem, a substantial increase in urinary recovery of the antibiotic (intact);

3.   virtually no influence on plasma level (systemic availability) of imipenem;

4. blockage of the metabolism of the drug by two routes: (a) glomerular filtration, and (b) tubular excretion (secretion?)*;

5. retention of a high enough conc'n in the blood until the next dose is administered;

6. total lack of local (urinary tract) irritating effects;

7. relative metabolic stability or conversion into such a compound which is an equipotent or more active inhibitor;**

8. compatibility of the two drugs, i.e., noninterference with the in vitro or in vivo activity of the other.

*If thienamycin (imipenem) is given alone, only 25% of the filtered fraction escapes metabolism. The tubular secretum is almost completely metabolized.

**The bulk metabolite (in the kidney) is the acetyl derivative of cilastatin, which is even more active than cilastatin itself.

All of the above requirements are necessary for the inhibition of the inactivation of imipenem in the urinary system. Cilastatin has all of these qualities.

Prevention of Nephrotoxicity by DHP-I Inhibitors:

Previous toxicity studies in rabbits showed that imipenem, at single doses of 90 mpk or higher, induced proximal tubular endothelial necrosis. The same lesion occurs in the rhesus monkey at 180 mpk or higher. A penem antibiotic, cephaloridine, induces a similar nephropathology in rabbits at about the same doses as imipenem, but at even lower doses in the rhesus monkey.

The Mechanism of Toxic Action of Both Antibiotics

1. Cephaloridine: Its toxicity is associated with the high cortical conc'n of the drug. An active anionic pump carries the drug into the proximal tubular epithelial cells, from which the egress is very slow. This indicates that the nephrotoxicity of the drug is related to its accumulation in the proximal tubular epithelium.

2. Imipenem is not accumulated in the above cells, since it freely passes them, and is completely metabolized in the lumen. It as also shown that high definitely nephrotoxic doses, coadminstered with DHP-I inhibitors, did not cause any nephrotoxicity. It was once suspected that the degradates from the enzymatic metabolism of imipenem might be trapped in the tubular epithelium and exert their toxic effects there. It was established that the prevention of nephrotoxicity was not due to inhibition of the DHP-I enzyme, but to the competitive exclusion of the drug from entering the tubular epithelial cells at the level of transport.

Further Proof of the Above Mechanism of Action of Nephrotoxicity-preventing Effects of Cilastatin

1. It equally prevents th   ephrotoxicity of cephaloridine.

2. The D(-) isomer of c   statin has no enzyme-inhibiting activity, but is still capable of pr   ting nephrotoxicity of both imipenem & cephaloridine by b   ..ng their entry into the tubular epithelial cells. The metabolism o   ipenem is not inhibited this way at all.

Imipenem Metabolites & Their Role in Nephrotoxicity: The retention of radioactivity (RA) from radiolabeled imipenem was measurable in the rabbit & rat. The activity was only a fraction of the total RA, but the rabbit retained 1Cx more RA than the rat. That is the answer to the lack of nephrotoxicity in the rat. Kidney cortex homogenates were prepared for studying the individual metabolites: Metabolite I is the hydrolysis product (lactam) of the action of DHP-I on imipenem. The admin. c an inhibitor prevents the formation of this metabolite. It is not con:. iered to be nephrotoxic. The identity of metabolite II is unknown. I. is a minor metabolite which is generated during the action of DHP-I enzyme or spontaneously from metabolite I. Metabolites III & IV are important, since they are formed independently from the action of DHP-I, and from metabolite I. Both are cysteine adducts. Metabolite III is only the cysteine adduct of imipenem; metabolite IV is the glutathione conjugate of metabolite III, and gives rise to metabolite III spontaneously. IV injection of all the metabolites did not induce nephrotoxicity.

The applicant's final conclusion about the mechanism of action of the nephrotoxicity of imipenem is quoted as follows: "Since imipenem is secreted when its metabolism is blocked by DHP-1 inhibitors, or is so rapidly metabolized in the tubular cells in the absence of inhibitor, it cannot be the nephrotoxic agent per se. At this point, all the degradates produced by imipenem may be ruled out as the toxic agents. Further experimentation will continue to explore the mechanism of this nephrotoxicity. What is clear at this point is that cilastatin Na prevents the nephrotoxicity of imipenem in animal models by excluding the antibiotic competitively at the secretory site, thereby preventing its entry into the tubular cells, the site of nephrotoxicity.

Physiological Disposition of Radiolabeled Imipenem

Species Used: rabbit, rat, rhesus monkey, man

Procedure: Radiolabeled imipenem (^{35}S & ^{14}C) alone or in combination (1:1) with unlabeled cilastatin was administered IV at doses of 5, 10, 20 or 40 g/kg of either drug entity to animals; in humans, the dose was 500 mg of ^{14}C-imipenem alone or in combination with 500 mg of cilastatin Na.

Major Mechanism of Elimination

Renal Excretion: Greater than 85% of the RA was recovered in the urine within 6 hrs in all animal species, except the rat, which does not develop

renal pathology. The coadministration of cilastatin had no effect on the excretion pattern of RA.

Radioactivity in the Feces: Negligible

Man: Urinary recovery of intact imipenem was 20% The coadministration of cilastatin raised the amount of intact imipenem to 70%. The corresponding renal clearance estimates of imipenem were 74 & 182 ml/min. 95% of the RA in human urine was associated with intact imipenem & metabolite I.

The ratio of intact imipenem to metabolite I in human urine with or without coadministered cilastatin was determined by using combined radiometric & chromatographic analysis. With imipenem alone, greater than 80% of the RA derived from metabolite I. After coadministering cilastatin, 70% of the dose was identified as intact imipenem.

Rat, Rabbit & Monkey: The chromatogram exhibited 2 peaks. One (major) corresponded to the imipenem & metabolite I peak; the other (minor) to the cysteine adduct (III) peak.

Plasma Levels in Animals & Man: Plasma levels of RA disappeared rapidly. AUCs of plasma RA were similar for a given species (except man) when imipenem was given alone or in combination with cilastatin Na. In man, cilastatin coadministration decreased the plasma clearance of intact imipenem by 20%.

Tissue Distribution Studies in Rats: The RA of imipenem (^{14}C & ^{35}S) alone was distributed primarily in the kidneys & liver. The disappearance of RA from these tissues paralleled that from plasma. Analysis of selected tissues for the intact imipenem and metabolite indicated that cilastatin drastically increased the level of intact imipenem, and decreased the level of metabolite I in these tissues. The disappearance pattern of imipenem & metabolite I from the tissues was similar to that from plasma.

Physiological Disposition of Radiolabeled Cilastatin Sodium

Species Used: rhesus monkey, rat, rabbit, dog & man

Administration: Radiolabeled cilastatin Na alone or in combination with an equal dose of nonradioactive imipenem was administered IV at doses of 5, 10 or 40 mpk of either drug in animals. Humans were given 250 mg of ^{14}C-cilastatin Na alone or in combination with 250 or 1000 mg of imipenem.

Renal Excretion: In monkey, rabbit & man, this was the sole route of elimination of cilastatin Na drug-related materials. (The RA found in the feces was negligible.) In the rat & dog, though renal excretion was over 50%, fecal excretion was also substantial (approx. 40%). In the rat, biliary excretion was significant, and enterohepatic circulation was evident.

Imipenem does not alter the excretion of intact cilastatin Na. Approx. amounts of intact cilastatin Na excreted in the urine were 15% for the rabbit, 45% for the monkey & 77% for man, whether or not imipenem was coadministered. For a given species, renal clearance of intact cilastatin Na are similar

between treatments; the values for the rabbit, monkey & man are estimated to be 10, 30 & 180 ml/min., respectively. In man, N-acetyl cilastatin Na accounted for 10% of the dose in the presence or absence of imipenem. Plasma RA levels decreased rapidly in all species; greater than a 100-fold reduction occurred within 6 hrs, with or without the coadministration of imipenem. The metabolism of cilastatin Na in primates appears to be mainly acetylation to the N-acetyl conjugate. In the rat, lower urinary recoveries of ^{35}S-RA vs. ^{14}C-RA suggest cleavage of the cysteinyl moiety of cilastatin Na.

There was no accumulation of radiolabeled material by rat tissues. Liver, kidney & small intestine gave the highest tissue-plasma ratios. Although the levels were high in the early time periods, the tissue conc'ns of RA decreased rapidly, concomitantly with the decrease in plasma RA. Parallel studies conducted following coadministration of unlabeled imipenem resulted in no significant change in the disposition profiles of RA.

Imipenem did not alter the renal excretion or plasma clearance of intact cilastatin Na in any of the species studied. In man, no change was noted in the extent of the N-acetyl conjugate formed.

III. SECONDARY PHARMACOLOGY

IMIPENEM

G.I. System

Imipenem, at an oral dose of 20 mpk in fistula dogs, significantly reduced gastric volume evoked by gastrin tetrapeptide in the period of 0-30 min. after stimulation. However, the integrated secretion over 0-90 min. did not differ from the placebo trial. In a second trial at 10 mpk, output volume response was increased during the first collection period. Imipenem at either dose level did not affect basal gastric secretion.

At IV doses up to 100 mpk, it did not affect basal gastric secretion in pylorus-ligated rats as measured by pH, acidity, volume or acid pepsin output.

Imipenem did not alter the transit time of charcoal test meal in mice at doses up to 20 mpk SC & 100 mpk IV.

Cardiovascular System

Blood pressure, heart rate & autonomic activity in anesthetized dogs were not altered by imipenem at 4 mpk IV. The autonomic response of BP to high IV doses of imipenem were measured in the anesthetized dog. At doses up to 100 mpk, it did not affect autonomic activity.

Tested at 20 mpk IP in 5 spontaneously hypertensive rats, it did not significantly lower BP. It did, however, cause a slight, transient pressor response.

The effects of high doses of imipenem (20 & 100 mpk IV) on BP, resp. rate & lead II of ECG were studied in anesthetized dogs. No effects were observed at

25 mpk or in 2/3 dogs at 100 mpk; the third dog at 100 mpk had a transient increase in resp. rate, systolic BP & HR.

Central Nervous System

In a standard pharmacometric screen for CNS effects in the mouse, imipenem gave no significant effects at doses of 6, 30 & 150 mpk IP.

Imipenem had no behavioral or overt effects in squirrel monkeys trained in the Sidman avoidance procedure.

The effects of high doses (50 & 200 mpk IV) on the spontaneous EEG or EEG arousal were observed at 50 mpk. Seizure discharge in the hippocampus occurred in 1/5 rabbits given 200 mpk. EEG arousal was increased 45 min. after admin. of 200 mpk.

The effects of high doses of imipenem on locomotor activity and normal body temp. in rats at doses up to 100 mpk were little or none. Doses of 100 mpk had no effect on the neuromuscular junction of rats.

Respiratory System

In the anesthetized dog, imipenem had no effect on respiratory parameters observed (tidal vol., resp. rate, total lung resistance or dynamic compliance) at IV doses of 2.5 or 10 mpk.

Renal System

No diuretic activity was observed in conscious rats at doses of 1.25-10 mpk IP, or in conscious dogs at 5 mpk IV.

CILASTATIN

G.I. System

Basal & gastrin-stimulated gastric secretion in dogs was not significantly changed by 1 mpk of cilastatin Na given IV.

IV doses up to 100 mpk did not affect basal gastric secretion in pylorus-ligated rats as measured by pH, acidity vol. or acid pepsin output.

Intestinal propulsion of charcoal test meal in mice was not affected at doses up to 100 mpk IV.

Cardiovascular System

Arterial BP in spontaneously hypertensive rats was not affected by cilastatin at doses up to 10 mpk IP. In 3 dogs treated at 10 mpk IV, the compound did not alter BP or HR and it neither blocked nor enhanced any of a variety of autonomic stimuli.

The autonomic responses of BP to high IV doses were measured in the anesthetized dog. Cilastatin did not affect BP, HR, resp. rate or ECG.

Central Nervous System

Cilastatin Na was tested at doses of 6, 30 & 150 mpk IP in the pharmacometrics procedure, a battery of tests useful for detecting various types of actions in the CNS in mice. The compound was essentially inactive.

At cumulative oral doses of 5, 10 & 20 mpk in squirrel monkeys, it did not cause any alteration in continuous avoidance responding or any overt signs of CNS activity.

The effect of high doses were studied on locomotor activity & normal body temp. in rats. Doses up to 100 mpk had little or no effect.

A dose of 100 mpk had no effect on the neuromuscular junction of rats.

Respiratory System

Cilastatin Na at 10 & 40 mpk IV was tested in anesthetized dogs for possible effects on various respiratory system parameters. Changes, if any, were minimal and generally no different from those occurring in dogs receiving the drug solvent (water injected IV).

Renal System

Urinary electrolyte excretion in 6 conscious dogs was unaffected by cilastatin Na at 10 mpk IV.

IMIPENEM/CILASTATIN

G.I. System

IV doses up to 100 mpk each of imipenem & cilastatin Na in combination did not affect basal gastric secretion in pylorus-ligated rats, as measured by pH, acidity, volume or acid pepsin output.

Intestinal propulsion of a charcoal test meal in mice was not affected by cilastatin combined with imipenem at doses up to 100 mpk.

Cardiovascular System

The autonomic responses of BP to high doses of the combination were measured in the anesthetized dog. At doses of 25:25 or 100:100 mpk, there was no sig. inhibition of the carotid sinus reflex which may be related to a decrease in mean BP.

When studied for effect on BP, HR, resp. rate & ECG in anesthetized dogs, the combination at 100:100 mpk IV slightly decreased mean BP; lower doses (25:25 mpk) had no effect on BP or other parameters.

Central Nervous System

In mice, the combination in doses up to 100:100 had no effect on gross behavior or pupil size and possessed no anticonvulsant activity.

The effect of the combination was studied in rats in locomotor activity and normal body temp. Doses of 100:100 mpk had no effect on the neuromuscular junction of rats.

CONCLUSIONS

Imipenem

- Devoid of any pronounced actions on the G.I. tract.
- Lacked important actions on the CVS.
- Produced no noteworthy actions in the CNS.
- Produced no major effects on the respiratory system.
- Devoid of sig. actions in the renal system.

Cilastatin Sodium

- Devoid of sig. effects on G.I. acid secretion.
- Produced no sig. action on the CVS.
- Possessed no marked or pronounced actions on the CNS.
- Did not affect renal function.
- Produced no sig. change on respiratory parameters.

Imipenem/Cilastatin Sodium

- Inhibited the carotid sinus reflexes and slightly decreased mean BP.
- Showed no sig. effect on the CNS.
- Produced no appreciable change in HR, resp. rate or ECG.

IV.   GENERAL TOXICITY

Introduction: The bulk of the studies were reviewed in my pharm. rev. of IND 18,538. The applicant submitted the results of newer studies in this NDA. For a better overview of the toxicity, the results of all toxicity studies will be summarized here, following that of the applicant.

A. Studies with Imipenem

The acute parenteral toxicity of imipenem was evaluated in rats & mice. No oral toxicity studies were performed, as the drug degrades extensively in the acid environment of the stomach. The IV LD_{50} values for imipenem in both species ranges approx. 1500 to greater than 2000 mpk with no sex- or species-related differences apparent.

Rats administered imipenem alone at dosage levels up to 180 mpk/day for 6 mos. showed no evidence of adverse effects. Renal tubular necrosis was observed in monkeys after single or multiple doses of imipenem of 180 mpk/day. Some variability & sensitivity to this renal effect is seen in this species, as some animals receiving this dose level survived for 5 wks of continuous daily admin. with no histomorphologic evidence of renal damage. It is noteworthy that admin. of imipenem to this same species at a level of 120 mpk/day for 6 mos. produced no evidence of renal damage. Thus, a rather high threshold exists for induction of nephrotoxicity by this antibiotic in this species.

B. Studies with Cilastatin

The low order of toxicity of cilastatin Na was demonstrated initially in acute toxicity tests. Oral LD_{50} values in mice & rats are greater than 10 gm/kg. IV LD_{50} values for both species are greater than 5 gm/kg.

Cilastatin Na has been administered to rats & rhesus monkeys IV at doses up to 500 mpk/day; rats received daily admin. for up to 3 mos. and monkeys received daily admin. for up to 5 wks. No evidence of treatment-related adverse effects was observed in either species. Admin. of cilastatin Na SC to rats for 5 wks at doses up to 3125 mpk/day produced renal changes characterized by very slight vacuolar degeneration in the proximal tubular epithelial cells at 1250 mpk & higher. In addition to these changes, slight-moderate tissue damage was observed at the site of SC injection, indicating slight local irritation produced by this route of admin. This route was necessitated by the high viscosity of the dosing sol'ns required to achieve these conc'ns. In addition, slight decreases in serum protein & albumin conc'ns were observed at the highest dose level. No other evidence of adverse effects was seen in this study.

C. Studies with Imipenem/Cilastatin Combination

The acute toxicity of imipenem/cilastatin was evaluated in rats & mice. In contrast to the protective effects observed with coadministration of these 2 agents to rabbits or monkeys, the acute toxicity of the combination was slightly greater than that observed with imipenem alone and significantly greater than with cilastatin alone. The IV LD_{50} values ranged from approx. 900-1200 mpk/day in mice & rats.

SC studies in rhesus monkeys with imipenem/cilastatin revealed a protective effect of coadministration of the DHP inhibitor similar to that observed in rabbits. Admin. of a nephrotoxic dose (180 mpk/day) or imipenem with an identical dose level of cilastatin produced no evidence of renal damage after daily admin. for up to 6 mos. [The reader should keep this in mind; in my "Comments & Recommendations", I will discuss the increased sensitivity (at least 4-5 fold) of pregnant rabbits to the drug combination.]

Imipenem/cilastatin has been administered to rats at doses up to 320 mpk/day of each drug for up to 6 mos. without evidence of sig. toxicity. Although slight elevation of kidney weights was observed in animals given this high dose level of each drug for 3 mos., no similar changes were observed at lower dose levels. No other evidence of adverse effect was observed with this combination of drugs in this species.

D. Studies in Infant Monkeys

The toxicity of imipenem/cilastatin Na was evaluated in neonatal & infant rhesus monkeys at dosage levels up to 180:180 mpk/day. In the former study, drug admin. was begun within 3 days of birth and continued for 10-12 wks. The latter study began within 6-8 wks of age and continued for 14 wks. No evidence of induced toxicity was observed in either study.

V.   REPRODUCTION STUDIES

IMIPENEM - IV Teratology in the Rat & Rabbit

A.   Rats: No evidence of adverse effects on the embryo were observed and no
     evidence of teratogenicity was seen. The rats received up to 900 mpk/day
     during the period of organogenesis. The rat, being the least sensitive
     animal to the toxicity of the drug, showed an unusually high level of
     tolerance, even in these studies.

B.   Rabbits: Dosage levels up to 60 mpk/day during organogenesis did cause
     embryo- & fetotoxicity at maternotoxic dose levels, but no evidence of
     fetal malformation. The level tolerated by the dams & embryos/feti was 30
     mpk/day.

CILASTATIN SODIUM

A.   SC Teratology in the Rat: Doses of 40, 200 & 1000 mpk administered during
     the period of major organogenesis.

B.   IV Teratology in Rabbits: Doses of 30, 100 & 300 mpk/day during
     organogenesis.

Results: No evidence of embryo- or fetotoxicity was observed in either
species, and no drug-induced fetal malformations were seen.

IMIPENEM/CILASTATIN COMBINATION

A.   Male & Female Fertility in Rats (IV; SC)

     Dosage & Admin.: Doses up to 320:320 mpk/day, IV/SC to M for 12 wks prior
     to mating & throughout mating; to F, the same doses IV/SC for 15 days
     prior to mating through Day 19 of gestation.

     Results: No evidence of drug-induced adverse effects was observed on
     fertility or fetal viability.

B.   Effect on Fetal Development in Rats & Mice

     N.B.: The applicant's remarks: "Excessive toxicity observed in rabbits at
          low dosage levels in range finding studies precluded the use of this
          species for evaluation." (Though the details of the range-finding
          study are submitted, the study will not be reviewed until the
          problem is resolved.)

     Reviewer's Comments: This unusual change of toxicity in the same species
     (40:40 mpk/day = nephrotoxicity) vs. other rabbit studies where the "no
     nephrotoxicity dose effect level" was 320:320 mpk/day (single dose,
     180:180 mpk/day for 6 mos.) is presently discussed with the reviewing
     group and Dr. Blois of MSD. Though this appears to be a cosmetic problem,
     it is not. If there is so much difference in nephrotoxicity among
     rabbits, the same thing might happen in humans. Dr. Blois called me

recently. I explained the problem and asked him to give me an acceptable argument for the increased sensitivity of the pregnant rabbit to the drug combination. He promised to call again the next day.

Three studies will be reviewed below in one paragraph.

1. IV Teratology Study in the Mouse
2. IV/SC Teratology Study in the Rat
3. IV/SC Range-finding Study in Pregnant Rabbits

"Dosage levels employed for both mice & rats ranged up to 320:320 mpk/day. Slight decreases in fetal wt were observed for rats at this high dose level; no similar change was seen in mice. No evidence of embryo- or fetotoxicity was observed at lower dose levels and no treatment-related fetal malformations were observed. A slight increase in age of testes descent was seen in F_1 pups at 80:80 mpk/day. Although no consistent similar response was observed at higher dose levels, it is not possible to exclude this slight effect as a possible treatment-related change. No other evidence of adverse effect on postnatal growth or behavior was observed in rats. The effect of imipenem/cilastatin Na on the fetus/neonate when administered late in gestation and during lactation was evaluated in rats at dose levels up to 320:320 mpk/day. No evidence of adverse effects was observed."

VI. GENETIC TOXICITY

A. Studies with Imipenem: V-79 mammalian cell; forward mutation; with & without metabolic activation.

Results: No evidence of mutagenesis.

B. Studies with Cilastatin Na: Bacterial cell (Ames); reverse mutation; with & without metabolic activation.

Results: No evidence of mutation.

C. Studies with Imipenem/Cilastatin Na

1. V-79 mammalian cell; forward mutation; without metabolic activation.

Results: No evidence of mutation.

2. Hepatocyte unscheduled DNA synthesis; without metabolic activation.

Results: No evidence of mutagenesis; no clastogenic potential.

Conclusions: "The results of in vitro & in vivo assays with imipenem and cilastatin Na alone and in combination have revealed no potential for interaction with genetic material."

VII. SPECIAL TOXICITY STUDIES

In the write-up of these studies, the applicant repeats certain data which are evident from the "Biochemical, Metabolic & Pharmacologic Studies", reviewed above. For "Introduction", please refer to that section of the review.

A. Nephrotoxic Potential of Imipenem

The Study Proper: Renal damage after high dose levels of imipenem alone has been demonstrated in rabbits & rhesus monkeys. This effect is seen after single or multiple doses and with IV or SC admin. The renal toxicity seen is quantitatively & qualitatively identical in both species after SC or IV admin of the same dose level.

Exploration of the time course of renal tubular change produced by a nephrotoxic dose at the light & electron microscopic level revealed that the earliest change was visible as early as 0.5 hrs after treatment. This change was characterized by swelling & loss of the parallel configuration of the basilar cytoplasmic compartments, as well as increased electron density of cytoplasm. These changes progressed through vacuolation of the apical portion of the cell accompanied by loss of microvilli, distention of the citernae of the rough endoplasmic reticulum, and loss of ribosomes; mitochondrial injury was not apparent until 8 hrs after treatment.

To more closely approximate the clinical dosage regimen, the nephrotoxic potential of imipenem in a split dose regimen was evaluated in rabbits. A series of studies explored the effects of a nephrotoxic dose split into 2 or 3 equal doses spaced 2 or 6 hrs apart. Although this split dose regimen clearly reduced the severity of renal damage, tubular necrosis was still evident.

B. Effect of Cilastatin Na on Imipenem-induced Nephrotoxicity

A series of studies was performed to evaluate the effect of cilastatin on the nephrotoxic potential of imipenem. Coadministration of a frankly nephrotoxic dose of imipenem to rabbits with increasing dose level of cilastatin produced decreasing degrees of renal damage; at a ratio of 1:1, no evidence of renal damage was seen. Protection was apparent at this ratio, regardless of the total dose of antibiotic given. In addition, complete protection was also observed in the split-dosage regimen referred to above with both agents coadministered in a 1:1 ratio.

Multiple-dose nephrotoxicity studies in rabbits evaluated nephrotoxicity potential of repeated admin. of imipenem/cilastatin Na.

In a range-finding study in rabbits prior to a proposed teratology study, mortality & renal tubular degeneration were observed at relatively low dose levels (40:40 mpk/day). The morphologic appearance of these changes was different from that observed in rabbits receiving imipenem alone. In addition, no evidence of renal damage was observed in rabbits given the combination at much higher dose levels (up to 360:360 mpk). The additional multiple dose nephrotoxicity studies described in this volume

reproduced the mortality & renal functional changes, but renal tubular degeneration was not observed. Rabbits in both of these studies had diarrhea. The renal changes observed in tne range-finding study were thus considered secondary to excessive toxicity produced in this species as a result of alteration of gut flora. These studies further support the statement that the rabbit is an inappropriate species for multiple-dose teratology studies of antibiotics.

The inhibitory effect of cilastatin Na on renal DHP, and thus the inhibition of imipenem metabolism by this enzyme, is documented in the "Biochemical, Metabolic & Pharmacologic Studies" section of this review.

The protective effect of cilastatin on imipenem-induced nephrotoxicity led to a suggestion that inhibition of nephrotoxicity was a result of inhibition of metabolism. This protective effect appears to be a function of exclusion of the antibiotic from the renal tubule in a manner analogous to that proposed for probenicid & cephaloridine.

Studies were performed in rabbits to evaluate the nephrotoxic potential of the principal metabolites of imipenem. Metabolites were administered IV at doses shown to achieve sig. intracellular conc'ns in the kidney cortex. No evidence of renal damage was observed.

Further studies were performed to explore the relationship between nephrotoxicity & alterations in tissue glutathione levels. Treatments designed to alter the intracellular content of glutathione had no effect on degree of renal damage.

In vitro studies performed to explore the mechanism of imipenem induced nephrotoxicity were conducted in rabbit kidney cortex slices & cortical mitochondria. Studies with both preparations indicated that sig. changes in PAH accumulation & mitochondrial respiration were not observed until relatively high conc'ns of drug were used in incubation media. Although these studies are clearly not definitive, they suggest that alteration of mitochondrial respiration does not play a sig. role in initiating the nephrotoxic response to high dose levels of imipenem.

The hemolytic activity of imipenem & cilastatin alone and in combination was evaluated in vitro. No evidence of hemolytic activity was observed. Conc'ns of imipenem alone at 10 mg/ml & higher produced a positive direct Coomb's test; no similar results was observed at lower conc'ns.

Ocular & dermal irritation studies were done in rabbits with imipenem or cilastatin Na. Very slight dermal irritation was observed with either agent after placing 500 mg of the test agent in direct contact with abraded skin for 24 hrs; no irritation was observed in intact skin.

Ocular irritancy of the bulk compound was evaluated by placing 100 mg of the dry powder into the conjunctival sacs of rabbits. The eye was closed for 60 secs., then degree of irritancy assessed. Moderate irritation with cilastatin & slight irritation with imipenem were observed.

COMMENTS & RECOMMENDATIONS

Introduction: After reviewing all the preclinical studies pertaining to pharmacology/toxicology, I found the drug relatively safe for human use. This is based on (in the applicant's order of presentation) Biochemical, Metabolic & Pharmacologic Studies, Primary & Secondary Pharmacologic Studies, Genetic Toxicity Studies & Special Toxicity Studies. However, there are some discrepancies in the submission with respect to the General Toxicity & Reproduction Studies, i.e , the data are acceptable as such, but not so after comparing certain data with those derived from similar studies in pregnant rabbit studies. (The results of the 2 studies are contradictory, and this needs clarification.) In the following paragraphs, I will not only discuss these discrepancies, but will summarize the results and my request for repetition of toxicity studies in pregnant rabbits. (This is in the framework of the teratogenicity studies which will include an extra group of nonpregnant F rabbits otherwise receiving the same treatment as the pregnant rabbits.)

Reason for the Study: In the above pregnancy range-finding study, the applicant found & reported moderate-severe nephropathology in the rabbits treated at 40:40 mpk/day parenterally. The elaboration of the applicant on the etiology of the lesions is quite tranquilizing, but unacceptable. This elaboration indicates that the nephropathology of the treated pregnant rabbits is the result of drug-induced dehydration & diarrhea commonly associated with antibiotic testing, and the pregnancy played no role in this seemingly pregnancy-related increased sensitivity.

I called an emergency meeting on 6/28/85 with Drs. Blois & Bokelman and the Chief Toxicologist at MSD (see my review of Reproduction Studies) to discuss this phenomenon, which in my view, cannot be neglected. At this meeting, I said that the neither study (single-dose 360:360 mpk/day or 6-mo. 180:180 mpk/day multiple-dose) showed any nephrotoxicity; therefore I feel that the 40:40 mpk/day multiple-dose pregnant rabbit study indicates pregnancy-related increased sensitivity to the drug. The toxicologist tried to white-wash this phenomenon, but when Dr. Bokelman saw my insistence on the repetition of this study, and since I stated that the drug could be approved while the study is under preparation or in progress, they suddenly changed their attitude and shared my view on the potential hazard of the drug in pregnant women. They also agreed that this is most likely the result of an endotoxic shock due to the sudden death of endotoxin-producing gram-negative bacteria in the intestine, caused by the antibiotic. N.B.: A simple and reliable test is used in human medicine for the indication of nonspecific endotoxemia. If the shock is already manifested, a simple drug treatment might be life-saving.

The gravity of potential endotoxic shock in humans, and in particular pregnant women, needs no explanation. However, the point I would like to make here is that endotoxic shock treated properly and on time is not always fatal. In spite of this, endotoxic shock resulting from an intrauterine accident in pregnant women is almost always fatal. If the patient recovers from the acute episode, the extent of the nephrocortical necrosis might be very great, i.e., the 2 outer thirds of the cortex of the kidney(s) might undergo irreversible necrosis. This might also be superimposed with a very well known complicating syndrome leading to a severe endocrinopathy, consequently making the fatal outcome more certain.

The investigation of the above phenomenon in rabbits is probably the most suitable for elucidation of the problem. The conduction of the recommended study is a medical/ethical must. The species indicating the above hazards being the rabbit is fortunate, since for both phenomena discussed above, the rabbit is the animal model accepted by world authorities.

The applicant promised to submit a written commitment to undertake the rabbit study during the first week of July, 1985. Since the results will not be available at the time of approval of the drug, the package insert should be slightly changed, allowing leeway for the implicit expression of this potential hazard(s).

The following are my recommendation for changes in the labeling:

A. Pregnancy

1. Until the results of adequate, well-controlled studies are available, I recommend this drug be categorized in Pregnancy Category "C". The reason for this is that in the IV/SC Teratology Study in the rat, "Slight decreases in fetal weight were observed for rats at 320:320 mpk/day. No evidence of embryotoxicity was observed at lower dosage levels, and no treatment-related fetal malformations were observed. A slight increase in the age of testes descent was seen in F_1 male pups at 80:80 mpk/day. Although no consistent similar response was observed at higher dosage levels, it is not possible to exclude this slight effect as a possible treatment-related change."

2. Additionally, "Excessive nephrotoxicity in rabbits at low dosage levels (40:40 mpk/day)* in range-finding studies for teratogenicity studies precluded the use of this species for evaluation." As I explained at our meeting the the applicant (6/28/85), the nephrotoxicity of the drug might be very well due to endotoxic shock induced by the antimicrobial effects of the drug on gram-negative bacteria living in any healthy mammalian intestine, leading to endotoxin liberation. The applicant agreed with this potential mechanism of this indirect nephrotoxicity, and promised to elucidate the problem. For more information, the reader is referred to my comments on this problem in an earlier chapter of this review.

    *Note that the rabbit dose is very close to the actual human dose.

B. Warnings: Whether or not a warning is justified, in my view, is up to the judgment of the reviewing Medical Officer.

C. Drug Interaction: My concern is the potential interaction of theophylline with primaxin, with particular attention to the convulsigenic effects of primaxin itself. As I understand it, the applicant is planning special human studies for this. I leave the inclusion of this potential interaction also to the MO.

D. The Use of the Term "Polyarthropathy": This term is interpreted in animal pathology as degenerative joint disease. Except with urinary

quinolone-azaquinolone antibacterials, there is no other drug-induced "honest-to-goodness" arthropathy known in animals. I know of no drug-induced human arthropathy. For the purpose of academic precision, the above term is justified if the gross and/or micropathology confirms the existence of the entity. Since animal arthropathy is a synonymous term with the human osteoarthritis, the indiscriminate use of the two terms might c 'fuse the attending physician. Without knowing the histopathology of the above "polyarthropathy", I would go no further with my clinical terminology than "polyarthralgia". Dr. Albrecht should be consulted about this.

Lorant Buko, D.V.M., M.Sc.

cc: Orig. NDA
HFN-815
HFN-815/MO
     CSO
HFN-340
HFN-815/LBuko/smc/8/27/85
R/d init.by:JMDavitt
0045p

STAT REV

Statistical Review and Evaluation

Date: AUG 29 1985

NDA #: 50-587/Drug Class: 1b

Applicant: Merck Sharp & Dohme Research Laboratories

Name of Drug: Primaxin (Imipenem/Cilastatin Sodium)

Documents Reviewed: Biostatistical Volumes 1-4 dated 2/20/85, and
Volumes 2.30, 2.32, 2.37 dated 5/3/84.

This review pertains to clinical studies evaluating the safety and efficacy of Primaxin for treatment of various systemic and urinary tract infections.

The medical officer for this NDA is M. Albuerne, M.D. (HFN-815) who provided clinical input to this review.

Background

Primaxin is a 1:1 formulation of imipenem and Cilastatin sodium. Cilastatin sodium, which is an inhibitor of renal dehydropeptidase, is added to achieve antibacterial levels in the urine. Imipenem is a beta-lactam antibiotic.

Study Design

These studies were open, randomized, multi-center, parallel group trials in hospitalized patients with proven or suspected bacterial infections in which the pathogen was presumed susceptible to both Primaxin and control agent. Infection sites included lower respiratory tract, upper urinary tract, skin and skin structures, bone and joint, biliary tract, intra-abdominal and gastrointestinal tract, gynecologic, and systemic infections.

Patients were excluded from entry if they were less than 12 years of age; had a high probability of death within 48 hours; had received effective anti-microbial therapy 72 hours preceding initiation of study drug treatment; hypersensitive to any beta-lactam antibiotic; likely to require higher doses or longer duration than allowed by the protocol; pregnant or nursing; infected with an organism known to be resistant to either study drug; likely to require treatment with high and/or repeated doses of potent loop diuretics; or had an uncomplicated bacteruria or uncomplicated infected decubitus ulcer.

Each patient in the study was designated as either evaluable or not evaluable based on the following criteria:

1. The infection was bacteriologically proven.

2. The clinical diagnosis was clear.

3. The patient did not receive effective antimicrobial therapy for any period of time prior to entry into the study.

4. The patient did not receive concomitant effective antimicrobial therapy.

5. The patient received study drug for a duration appropriate to the site and severity of infection.

6. Bacteriologic outcomes were assigned and justified based on follow-up cultures at the infection site, when appropriate.

Response to treatment was assessed by both clinical and bacteriological outcomes at end of therapy (usually 14 days). The sponsor has categorized the responses for analysis as follows:

Favorable clinical outcome

--- cure (Investigator's judgment that the signs and symptoms of the infection were resolved.)

--- improvement (Investigator's judgment that infection was brought under control and the need for further intravenous therapy was not indicated.)

Unfavorable clinical outcome included

--- no improvement

--- died of infection primarily (with or without a contributing background disease)

--- died of background disease (with or without a contributing infection).

Favorable bacteriologic outcome

--- eradication of the etiologic pathogen(s).

Unfavorable bacteriologic outcome

--- suppression of the etiologic pathogen(s) in whole or in part.

--- persistance of the etiologic pathogen(s) in whole or in part.

The sponsor tested whether treatment groups had comparable favorable clinical outcome rates and comparable bacteriological eradication rates using Chi-square tests.

Although the Statistical Methods subsection of the Materials and Methods section states that a rank sum test would be used to compare the distribution of patients by treatment and category of clinical/bacteriological responses and further that a Generalized Odds Ratio test would be used to see whether results were consistent across investigators, the results of these tests were

not provided in the original submission. The sponsor indicated that the rank sum test was not done and the Generalized Odds Ratio was only done for the Moxalactam study.

The sponsor has provided the results of the Generalized Odds Ratio for the Moxalactam study, at this reviewer's request.

Moxalactam-controlled Study

This open-labeled, randomized, multi-center study with 19 U.S. investigators was conducted on hospitalized patients with bacterial infections. The dose of Moxalactam was 2 gm. every 8 hours. Investigators were allowed by protocol amendment to use aminoglycoside or beta-lactam antibiotics. Thirteen (13) patients were treated under the protocol amendment. Since so few patients were so treated, the results from these patients will not be discussed in this review.

Of 428 patients enrolled, 300 were evaluable for efficacy (147 Moxalactam and 153 Primaxin). The reasons for non-evaluability seemed appropriate [e.g., bacteriologically not proven (85 patients, 66.4%), course of treatment too short (20 patients, 15.6%), inadequate bacteriology cultures (13 patients, 10.1%)] and did not seem to favor either treatment.

The evaluable patients had a variety of infections, the largest being skin and skin structures (28.7%), gynecologic (18.0%), lower respiratory (16.0%) and intra-abdominal (8.3%). The sponsor provided an overall analysis and an analysis of bacteremia/septicemia separately, but did not provide separate analyses or tabulations for the other types of infection.

The treatment groups were comparable at baseline with respect to age-sex distribution, primary diagnosis distribution, and severity of infections.

There were 271 (89.4%) of 303 pathogens eradicated with Primaxin as compared to 192 (92.3%) of 208 eradicated with Moxalactam. For the infectious organisms sampled, Primaxin could be as much as 7.9% worse (with 95% confidence) than Moxalactam, or as much as 2.1% better.

The sponsor reported that 144 (94%) of 153 Primaxin patients had a favorable (cured/improved) clinical response compared to 129 (88%) of 147 Moxalactam patients. Although this difference is approaching significance (p=0.054), seven (7) of the 18 non-favorable clinical outcomes for Moxalactam came from Dr. Eron's clinic. The results from Dr. Eron's 30 patients showed 15(100%) of Primaxin patients with favorable clinical outcomes as opposed to 8 (53%) for Moxalactam.

The clinical improvement rates for evaluable patients whose infections were susceptible to both drugs were 81/86 (94%) and 90/99 (91%) for Primaxin and Moxalactam respectively.

The mean duration of therapy for the Primaxin patients was 11.0 days while that of the Moxalactam patients was only 8.8 days. The sponsor reported that there was a significant difference (p<0.05) between the Primaxin and Moxalactam treatment groups in the distribution of patients by duration of therapy. The distribution test used was not reported.

The sponsor reported that the proportion of patients who had phlebitis from their injection was significantly higher in the Primaxin group (12/218, 5.5%) than in the Moxalactam group (4/223, 1.3%).

Gentamicin/Clindamycin Study

This was an open, randomized, 8-center trial comparing Primaxin to Gentamicin/Clindamycin (G/C) in the intravenous treatment of hospitalized patients with infections caused by bacteria proven or presumed susceptible to both agents.

There were 150 evaluable subjects out of 214 total. The reasons for non-evaluability appear acceptable [infection not bacteriologically proven (44 patients, 70%), treatment course too short (14 patients, 22%) and inadequate bacteriologic cultures (5 patients, 8%)] and do not favor either treatment. The two treatment groups appeared comparable at baseline with respect to demographic and clinical characteristics. The sites of infection for the evaluable subjects were skin and skin structures (20%), lower respiratory tract (22%), intra-abdominal (31.3%), genitourinary tract (20%), bloodstream (11.3%) and other (2%).

There were too few patients having any particular site of infection to allow detection of site-specific differences between treatments in clinical efficacy. Overall, 68 of 69 (98%) Primaxin patients were clinically cured or improved as opposed to 72 of 81 (89%) G/C patients. This difference was significant (p=0.02). The relevance of this significance is somewhat weakened by the fact that 3 of the 9 clinical failures for G/C had diagnoses for which there were no Primaxin patients; likewise, no G/C patient had the diagnosis for which the Primaxin failure occurred. Considering only those evaluable patients with organisms susceptible to both drugs in vitro, no significant difference between drugs was detected (39 of 39 Primaxin patients and 41 of 45 G/C patients were clinically cured or improved).

The sponsor provided summarizations of bacteriological results within each site of infection. The only site showing a significant difference in eradication rates between treatments were for intra-abdominal infections, with 40/41 (98%) pathogens eradicated on Primaxin and 45/61 (74%) on G/C. This difference was significant (p=0.002). Overall, 102/112 (91.1%) of organisms were eradicated by Primaxin as opposed to 117/144 (81.2%) by G/C. Significant differences between drugs were not obtained for any particular pathogen.

Reinfections occurred in 9 cases (8 Primaxin and 1 G/C). This difference was statistically significant (p=.01). Superinfections were observed in 15 cases (3 Primaxin and 12 G/C). This difference was statistically significant (p=.03). However, two of the three Primaxin cases and 10 of the 12 G/C cases were in one study (Dr. Guerra) which makes it difficult to generalize this result.

No information on duration of therapy was presented.

Cefotaxime Study

This was an open, randomized, comparative trial against Cefotaxime, involving 13 centers. The dosage of Cefotaxime was 2 g. t.i.d.

There were 141 evaluable patients (70 Primaxin, 71 Cefotaxime) out of 234 total patients. The reasons for non-evaluability were infection not bacteriologically proven (43 patients, 47%), treatment course too short (21 patients, 23%), inadequate bacteriological cultures (19 patients, 21%) and other (9 patients, 10%). The reasons seem adequate and only for 'treatment course too short' (15 Primaxin, 6 Cefotaxime) was there a significant difference between treatments (p=.03). The evaluable patients in the different treatment groups were comparable at baseline with the exception that Primaxin patients had a significantly greater i. of prior diagnostic therapy procedures, polymicrobial infections a u abscesses than did the Cefotaxime patients.

The major primary diagnoses for the evaluable patients were septicemia (27%), wound infection (13%), pneumonia (16%), bronchopneumonia (7%), and intra-abdominal abscess (7%).

Sixty out of 70 (86%) of Primaxin patients were clinically cured or improved whereas 65 out of 71 (92%) were cured or improved on Cefotaxime. With 95% confidence, Primaxin could be as much as 16.26% worse than Cefotaxime or as much as 4.6% better with respect to clinical assessment for the patient population sampled in this trial.

The clinical improvement rates for evaluable patients whose infections were susceptible to both drugs were 42/48 (88%) and 51/55 (93%) for Primaxin and Cefotaxime respectively.

There were 103 (80.5%) of 128 pathogens eradicated with Primaxin as compared to 90 (88.2%) of 102 eradicated with Cefotaxime. For the infectious organisms sampled, Primaxin could be as much as 15.23% worse than Cefotaxime or 1.52% better.

Cefazolin Study

This was an open, randomized, 11-center trial comparing Primaxin to Cefazolin for the intravenous treatment of hospitalized patients with infections caused by bacteria proven or presumed susceptible to both agents.

There were 210 evaluable subjects out of 319 total patients. The reasons for non-evaluability included: injection not bacteriologically proven (55 patients, 50%), treatment course too short (33 patients, 30%), and inadequate bacteriologic cultures (16 patients, 15%). The reasons seem adequate and did not appear to favor either treatment. However, the evaluable subjects in the different treatment groups were not comparable at baseline. The Primaxin subjects were more severely infected (23% severe for Primaxin vs. 9% for Cefazolin) and more physiologically impaired (20.4% for Primaxin vs. 4.9% for

Cefazolin). The Primaxin group had a higher percentage of respiratory disorders as a secondary diagnosis and a higher incidence of bacteremia (13.9% to 4.9%).

There was no significant difference between treatment groups in the proportion of patients with favorable clinical response (cured/improved) [101/108 (93.5%) for Primaxin, 98/102 (96.1%) for Cefazolin]. Based on 95% confidence limits, Primaxin could be as much as 8.54% worse than Cefazolin, or as much as 3.42% better for the patient population sampled in this trial.

The clinical improvement rates for evaluable patients whose infections were susceptible to both drugs were 66/67 (98%) and 68/68 (100%) for Primaxin and Cefazolin respectively.

For those etiologic pathogens in evaluable patients shown to be susceptible to the study drug, 156/177 (88.1%) of pathogens were eradicated by Primaxin whereas 123/134 (91.8%) of the pathogens were eradicated by Cefazolin. The 95% confidence interval indicated that Primaxin could be as much as 8.62% worse than Cefazolin in eradication rates or as much as 4.7% better for the infectious organisms sampled in this trial.

The mean duration of therapy for Primaxin evaluable patients was 9.5 days whereas that for Cefazolin patients was 8.9 days.

Conclusions

1. In the Moxalactam-controlled study, 271 (89.4%) of 303 infections were eradicated with Primaxin as opposed to 192 (92.3%) of 208 infections eradicated by Moxalactam. With 95% confidence, Primaxin could be as much as 7.9% worse or 2.1% better than Moxalactam. In this study, 144 (94%) of 153 Primaxin patients had a favorable (cured/improved) clinical response compared to 129 (88%) of 147 Moxalactam patients. Although this result is approaching significance (p=0.054), it is largely attributable to significant results seen in Dr. Eron's study (15 of 15 favorable for Primaxin and only 8 of 15 favorable for Moxalactam).

The duration of therapy for Primaxin patients was longer than that for Moxalactam patients (11.0 days compared to 8.8 days) and the Primaxin group had more phlebitis due to their injection (5.5% compared to 1.8%).

2. In the Gentamicin/Clindamycin-controlled study, 68 (98%) of 69 Primaxin patients were clinically cured or improved as opposed to 72 (89%) of 81 G/C patients (p=0.02). The relevance of this significance is somewhat weakened by the fact 3 of of the 9 clinical failures for G/C occurred in diagnoses for which no Primaxin patients were represented. Significant differences in eradication rates favoring Primaxin over G/C were found for intra-abdominal infections [40/.1 (98%) for Primaxin vs. 45/61 (74%) for G/C] and for all infections combined [102/112 (91.1%) for Primaxin vs. 117/144 (81.2%) for G/C].

3. Although studies against Cefazolin and Cefotaxime showed numerically lower eradication rates and clinical improvement rates for Primaxin, the treatment groups were not comparable at baseline (Primaxin patients more seriously infected); it is therefore difficult to interpret these results.

There are no statistical comments to be conveyed to the firm at this time.

James R. Gebert, Ph.D.
Mathematical Statistician

cc:
Orig. NDA 50-587
HFN-815
HFN-815/Dr. Albuerne
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Gebert
Chron.
File: DRU 1.32 NDA
Dr. Gebert/x34594/njs/rp/08/27/85/#0327n

Concur: Dr. Johnson *MJ 8/28/85*

Dr. Dubey *8/28/85*

Table 1   Summary of Results for Evaluable Patients - All infectious organisms

Diagnosis	Drugs	N	# Pathogens	Eradicated	Clinically Improved	Duration of Therapy (days)
Skin & Skin Structures (29%)	Primaxin	153	303	89.4%	94%	11.0
Gynecologic (18%)	Moxalactam	147	208	92.3%	88%	8.8
Lower Respiratory (16%)						
Intra-Abdominal (8%)						
Intra-Abdominal (31%)	Primaxin	69	112	91.1%	98%	--
Lower Respiratory (22%)	Gent./Clind.	81	144	81.2%	89%	--
Skin & Skin Structures (20%)					(p=0.02)	
Genitourinary Tract (20%)						
Bloodstream (11%)						
Intra-Abdominal	Primaxin		41	98%		
Infections	Gent./Clind.		61	74%		
				(p=0.002)		
Septicemia (22%)	Primaxin	70	128	80.5%	86%	--
Pneumonia (16%)	Cefotaxime	71	102	88.2%	92%	--
Wound Infection (13%)						
Bronchopneumonia (7%)						
Intra-Abdominal (7%)						
Skin & Skin Structures (60%)	Primaxin	108	177	88.1%	94%	9.5
Lower Respiratory (14%)	Cefazolin	102	134	91.8%	96%	8.9
Upper Urinary Tract (9%)						

Table 2

Summary of Clinical Results for Evaluable Patients with Infections Susceptible to Both Drugs

Drugs	N	Clinically Improved
Primaxin	86	94%
Moxalactam	99	91%
Primaxin	39	100%
Gent./Clind.	45	91%
Primaxin	48	88%
Cefotaxime	55	93%
Primaxin	67	98%
Cefazolin	68	100%

BIO/DIS
REV

Imipenem/Cilastatin Sodium
Injection (I.V.)
Sterile Powder (250 mg & 500 mg)
Form 5 50-587;030885
Reviewer: Raja Velagapudi, Ph.D.
Wang
1-0

Merck Sharp & Dohme
Submission Dated:
March 8, 1985

FEB 14 1986

Review of Pharmacokinetic Data

Background:

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

This submission contained pharmacokinetic studies listed in the attached biopharmaceutic summary. This drug product has already been approved (11/26/85) for marketing by HFN-815 (Division of Anti-Infective Drug Products). The necessity (priority) to review the biopharmaceutic portion of this submission, is not being requested or required by the Division of Anti-Infective Drug Products at this time. Therefore, the Division of Biopharmaceutics will not undertake a formal review of this submission at this stage, until such time that HFN-815 finds it essential to request a formal review of this submission's biopharmaceutic portion.

Raja Velagapudi 2/14/86
Raja Velagapudi, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by J.P. Hunt
FT Initialed by J.P. Hunt

cc: Form 5 50-587 Orig., HFN-815(2 copies), HFN-226(Velagapudi, Hunt, Skelly), Chron, Drug and FOI Files.

RBV:dea:smj:5757x:2/14/86

Biopharmaceutics Summary

List of Attachments

Biopharmaceutics Summary

List of Attachments

| | VOLUME | STARTING PAGE |

Biopharmaceutics Summary

List of Attachments

4-10-84

Labeling in the Submission

Antibiotic Certification Request

NDA 50-587

Merck Sharp and Dohme Research Laboratories
Annotated Package Circular
PRIMAXIN™
(Imipenem/Cilastatin Sodium, MSD)

DESCRIPTION

PRIMAXIN* (Imipenem-Cilastatin Sodium, MSD) is a formulation of imipenem, a thienamycin antibiotic and cilastatin sodium, the inhibitor of the renal dipeptidase, dehydropeptidase I, with sodium bicarbonate added as a buffer.[1] PRIMAXIN is a potent broad spectrum antibacterial agent for intravenous administration.[2]

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*.[3] Its chemical name is (5 R - [5 , 6 (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:[4,5]

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[1]Item 2, Composition of the Drug
(Vol. 2.1 , Page N0002)

[2]Item 9.C.IV - Controlled Clinical Studies - Introduction
(Vol. 2.30 , page 10642)

[3]Item 9.B.1 - Microbiological Studies,
Kropp, et al. 1980. Antimicrobial Agents and Chemother.
17 (6); 6-3-1300.
(Vol. 2.7 , page 00587)

[4]Item 2, Composition of the Drug
(Vol. 2.1 , page 00003)

[5]Item 9.A.1 - Chemical Structural Formula
(Vol. 2.1 , page 00417)

-3-

Antibiotic Certification Request

NDA 50-587

Merck Sharp and Dohme Research Laboratories
Annotated Package Circular
PRIMAXIN™
(Imipenem/Cilastatin Sodium, MSD)

CLINICAL PHARMACOLOGY

Intravenous infusion of PRIMAXIN over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 mcg/ml for the 250 mg dose, from 21 to 58 mcg/ml for the 500 mg dose and from 41 to 83 mcg/ml for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 mcg/ml or less in 4 to 6 hours. The plasma half-life of each component is approximately 1 hour. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours, after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 mcg/ml can be maintained for up to 8 hours with PRIMAXIN at the 500 mg dose.[6,7,10,11]

[8]Item 9.C.II a) 2)
Metabolism - Imipenem ^{14}C
(Vol. 2.28 , page 10062)

[9]Item 9.C.II a) 3)
Pharmacokinetics - Imipenem/Cilastatin Sodium
(Vol. 2.22 , page 07382)

[10]Item 9.C.II a) 8)
Pharmacokinetics - Effect of Probenecid
(Vol. 2.24 , page 08856)

[11]Appendix IV - Biopharmaceutical Report, Section E.4.a
(Vol. 2.84 , page IV-0001)

NDA 50-587

Merck Sharp and Dohme Research Laboratories
Annotated Package Circular
PRIMAXIN™
(Imipenem/Cilastatin Sodium, MSD)

No accumulation of PRIMAXIN in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.[12,13,14,15]

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase,[16,17] resulting in relatively low levels in urine.[18,19,20,21]

[12] Item 9.C.11 a) 3)
Pharmacokinetics - Imipenem/Cilastatin Sodium
(Vol. 2.21 , page 07389)
[13] Item 9.C.11 a) 3)
Pharmacokinetics - Imipenem/Cilastatin Sodium
(Vol. 2.21 , page 07389)
[14] Appendix IV, Biopharmaceutics Report, Section E.4.b
(Vol. 2.94 , page IV-00028)
[15] Appendix IV, Biopharmaceutics Report, Section E.5.a
(Vol. 2.94 , page IV-00034)
[16] Item 9.B.11 - Biochemical, Metabolic & Pharmacological Studies
(Vol. 2.3 , page 00635)
[17] Appendix IV, Biopharmaceutics Report Section D
(Vol. 2.94 , page IV-00017)
[18] Item 9.C.11 a) 1) - Pharmacokinetics - Imipenem
(Vol. 2.20 , page 06773)
[19] Item 9.C.11 a) 4) - Pharmacokinetics - Effects of Probenecid
(Vol. 2.26 , page 09036)
[20] Appendix IV, Biopharmaceutics Report, Section E.2.a
(Vol. 2.94 , page IV-00022)
[21] Appendix IV, Biopharmaceutics Report, Section E.2.b
(Vol. 2.94 , page IV-00024)

NDA 50-587

Merck Sharp and Dohme Research Laboratories
Annotated Package Circular
PRIMAXIN™
(Imipenem/Cilastatin Sodium, MSD)

Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem[22,23] so that when imipenem and cilastatin sodium are given concomitantly fully adequate antibacterial levels of imipenem are achieved in the urine.[24,25] Peak plasma levels of cilastatin following a 20-minute intravenous infusion of PRIMAXIN, range from 15 to 25 mcg/ml for the 250 mg dose, from 31 to 49 mcg/ml for the 500 mg dose and from 56 to 88 mcg/ml for the 1000 mg dose.[26,27,28,29]

[22] Item 9.B.11, Biochemical, Metabolic & Pharmacological Studies
(Vol. 2.3 , page 00635)
[23] Appendix IV, Biopharmaceutics Report, Section D
(Vol. 2.94 , page IV-00017)
[24] Item 9.C.11 a) 3) - Pharmacokinetics - Imipenem/Cilastatin Sodium
(Vol. 2.21 , page 07389)
[25] Appendix IV, Biopharmaceutics Report, Section E.4.a
(Vol. 2.94 , page IV-00025)
[26] Item 9.C.11 a) 3) - Pharmacokinetics - Imipenem/Cilastatin Sodium
(Vol. 2.21 , page 07389)
[27] Item 9.C.11 a) 4) - Pharmacokinetics - Effect of Probenecid
(Vol. 2.26 , page 09036)
[28] Appendix IV, Biopharmaceutics Report, Section E.4.a
(Vol. 2.94 , page IV-00025)
[29] Appendix IV, Biopharmaceutics Report, Section E.5.a
(Vol. 2.94 , page IV-00017)
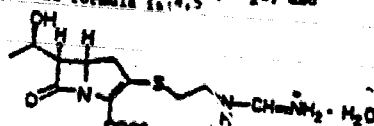
Merck Sharp and Dohme Research Laboratories
Annotated Package Circular
PRIMAXIN™
(Imipenem/Cilastatin Sodium, MSD)

Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of PRIMAXIN.[30,31,32,33]

Microbiology

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis.[34] Its greatest affinity is for penicillin binding proteins 1a, 1b, 2, 4, 5, and 6 of *Escherichia coli*, and 1A, 1b, 2, 4 and 5 of *Pseudomonas aeruginosa*.[35] Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms.[36,37]

[30]Item 9.C.11 c) 4) - Pharmacokinetics - Effects of Probenecid
(Vol. ___2.25___, page ___00256___)
[31]Item 9.C.11 c) 2)
Metabolism - Cilastatin - ^{14}C Sodium
(Vol. ___2.29___, page ___10236___)
[32]Appendix IV, Biopharmaceutics Report, Section 5.4.a
(Vol. ___2.64___, page IV-00025)
[33]Appendix IV, Biopharmaceutics Report, Section 5.5.a
(Vol. ___2.64___, page IV-00029)
[34]Item 9.B.1 Section I.A
(Vol. ___2.2___, page ___00417___)
[35]Item 9.B. Cilastatin Preclinical Bibliography
(Vol. ___2.19___, page ___00747-2___)
[36]Item 9.B.1 - Microbiological Studies
Kropp, et al. 1980, Antimicrob. Agents & Chemother.
17 (4): 993-1000
(Vol. ___2.2___, page ___00587___)
[37]Item 9.B.1 Section I.B
(Vol. ___2.2___, page ___00418___)

HOW SUPPLIED[109]

PRIMAXIN is supplied as a sterile powder mixture in vials and infusion bottles containing imipenem anhydrous and cilastatin sodium as follows:

No. XXXX - 250 mg imipenem equivalent and 250 mg cilastatin equivalent
NDC 0006-XXXX-XX in vials.
No. XXXX - 500 mg imipenem equivalent and 500 mg cilastatin equivalent
NDC 0006-XXXX-XX in vials.
No. XXXX - 250 mg imipenem equivalent and 250 mg cilastatin equivalent
NDC 0006-XXXX-XX in infusion bottles.
No. XXXX - 500 mg imipenem equivalent and 500 mg cilastatin equivalent
NDC 0006-XXXX-XX in infusion bottles.

MSD   MERCK SHARP & DOHME
       DIV OF MERCK & CO.,INC. WEST POINT, PA 19486, USA

[109]Item 4, Section 4.B
(Vol. ___2.1___, page ___00230___)

END
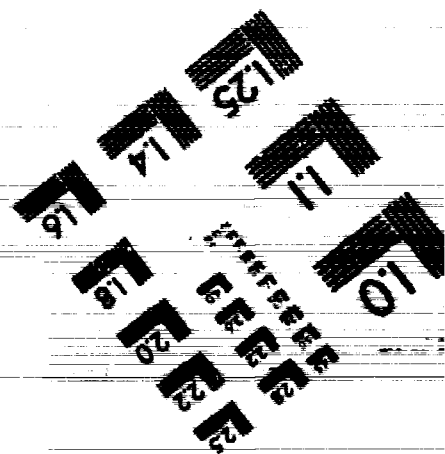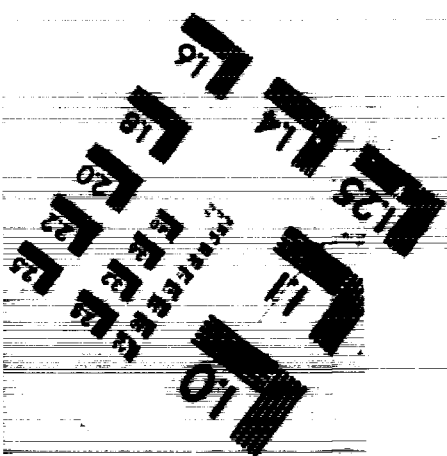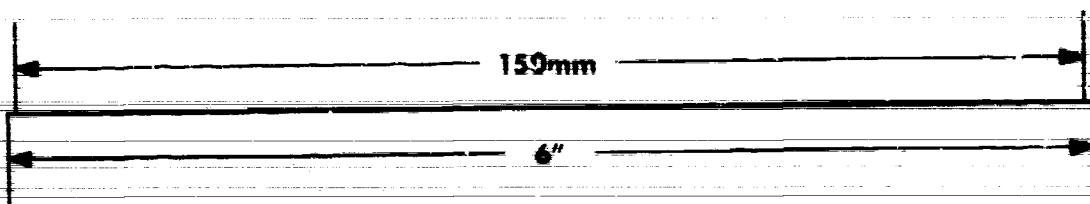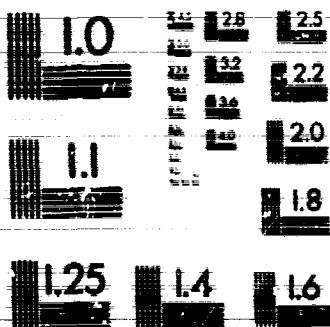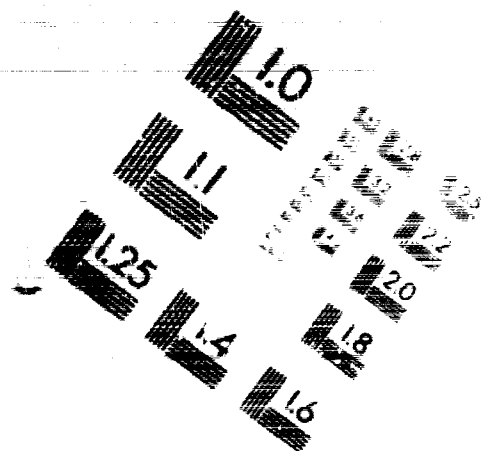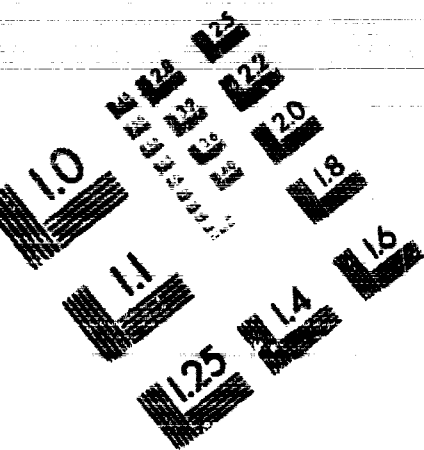
NDA

50-587

MOR

June 11, 1985

Addendum to Medical Officer's Reivew of NDA 50-587

Date of Submission: June 7, 1985

Applicant: Merck Sharp & Dohme Research Laboratories
             West Point, PA

Name of Drug: PRIMAXIN (imipenem/cilastatin sodium)

On June 7, 1985, Merck submitted case report forms for 14 additional patients
who had endocarditis caused by <u>Staphylococcus aureus</u>.

The cases were provided by the following investigators: Byungse Suh, M.D.,
Assistant Professor of Microbiology and Immunology, Temple University.

Gordon Dickinson, M.D., Assistant Professor of Medicine, University of Miami.

Jay Jacobson, M.D., Assistant Professor of Medicine, Division of Infectious
Diseases, University of Utah College of Medicine.

Louis D. Saravolatz, M.D., Head, Division of Infectious Diseases and Hospital
Epidemiology, Henry Ford Hospital, Detroit, Michigan.

Stephen S. Hawkins, M.D., Assistant Professor of Medicine, Division of
Infectious Diseases, University of Tennessee.

All 14 patients were adults ranging in age from 25 to 42 years, with a mean
age of 30.8 years.
There were 9 males and 5 females.
All patients were known to be I.V. drug abusers.

Twelve patients were treated with Primaxin at a total daily dose of 2 grams
(500 mg q 6 hours) by intravenous infusion. The duration of treatment ranged
from 18 to 38 days. Two patients were treated with a total daily dose of 3
grams (500 mg q 4 hours) by intravenous infusion, for 8 and 25 days,
respectively.

All 14 patients were considered adequate for the evaluation of drug efficacy
and safety.

RESULTS

EFFICACY

INFECTION	NO	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
Endocarditis	14	11 (79%)	2 (14%)	1 (7%)

Organism	NO	BACTERIOLOGIC RESPONSE	
		ERADICATED	NO ERADICATED
S. aureus(S)	3	3 (100%)	
S. aureus(R)	11	10 (91%)	1 (9%)

(S) = Penicillin sensitive
(R) = Penicillin resistant

SAFETY

Two of the 14 patients were reported to have had some side effects during treatment. One patient had headache, diaphoresis, dyspnea and tachycardia, the other patient had nausea and vomited once.

The following abnormal laboratory test values were reported:

Decreased hemoglobin   - 1

Decreased hematocrit   - 1

Increased eosinophils   - 1

Increased platelets   - 2

Increased SGOT   - 1

Increased SGPT   - 1

Positive Coombs' test   - 4

Conclusions

The 14 cases provided in this submission plus the 7 cases provided in the original NDA submission add up to a total of 21 cases of endocarditis due to S. aureus.

The results obtained in these 21 cases were as follows:

| INFECTION | No. | Clinical Response | | |
		Cure	Improve	Fail
Endocarditis	21	18 (86%)	1 (9%)	1 (5%)

Organism	No.	Eradicated
S. aureus$^{(S)}$	4	4 (100%)
S. aureus$^{(R)}$	17	16 (94%)
Total	1	20 (95%)

The results demonstrate that Primaxin is effective in the treatment of endocarditis caused by S. aureus.

Mercedes S. Albuerne

Mercedes S. Albuerne, M.D.

cc:
Orig Form 5
HFN-815
HFN-815/CSO
HFN-815/Micro
HFN-178
HFN-815/MAlbuerne:js/6/24/85
3748b

SRO 3July85 and 17July85 - see my attached ment
of 17 July 85

Applicant: Merck Sharp and Dohne Research Laboratories
             West Point, Pennsylvania

Date of Applicant: May 3, 1984

Date Review Started: July 30, 1984

Date Review Completed: March 29, 1985

1. General Information

    A) Name of Drug

        (1) Generic: Imipenem and Cilastatin Sodium
        (2) Trade: PRIMAXIN
        (3) Chemical:

             Imipenem
             [5R-[5α, 6 ∝, (R)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)
             amino] ethyl] thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-
             2-carboxylic acid monohydrate.

             Cilastatin Sodium
             [Z, 7 (R), 2(S) -7- [(2 – Amino – 2 – carboxyethyl) thio]-2 –
             [[2,2 – dimethylcyclopropyl) carbonyl] amino] – 2 – heptenoic
             acid, monosodium salt

             A brief glossary is provided below in order to clarify
             nomenclature which has changed during the course of these
             studies.

             Imipenem, also known as MK0787, is the approved name (USAN) for
             N-formimidoyl thienamycin, a broad spectrum antibiotic.

             Cilaslatin, also know as MK0791, is an inhibitor of renal
             dehydropeptidase.

             Thienamycin now refers only to a specific class of carbapenem
             antibiotics of which imipenem is the first to be tested and used
             in man.

             Imipenide was transiently used to refer to N-formimidoyl
             thienamycin by USAN but has been dropped.

             Primaxin, also known as MK0787/MK0791, is a broad spectrum,
             antibiotic consisting of equal parts of imipenem and cilastatin.

Applicant: Merck Sharp and Dohme Research Laboratories
            West Point, Pennsylvania

Date of Applicant: May 3, 1984

Date Review Started: July 30, 1984

Date Review Completed: March 29, 1985

1. General Information

    A) Name of Drug

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        (2) Trade: PRIMAXIN
        (3) Chemical:

             Imipenem
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             amino] ethyl] thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-
             2-carboxylic acid monohydrate.

             Cilastatin Sodium
             [Z, 7 (R), 2(S) -7- [(2 – Amino - 2 - carboxyethyl) thio]-2 –
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             Imipenide was transiently used to refer to N-formimidoyl
             thienamycin by USAN but has been dropped.

             Primaxin, also known as MK0787/MK0791, is a broad spectrum,
             antibiotic consisting of equal parts of imipenem and cilastatin.

(4) Chemical Structure

Imipenem

Cilastatin Sodium

B) **Pharmacologic Category**

Imipenem is a new broad spectrum beta-lactam antibiotic.

Cilastatin is an inhibitor of the renal dipeptidase, dehydropeptidase I.

C) **Proposed Indications:** Primaxin proposed indications are the treatment of the following infections caused by susceptible gram-positive and gram-negative aerobic and anaerobic microorganisms:

1. Lower respiratory tract infections
2. Genitourinary infections
3. Intra-abdominal infections
4. Gynecological infections
5. Bacterial septicemia
6. Endocarditis
7. Bone and Joint infections
8. Skin and Skin Structure infections

D) **Dosage Form:** Primaxin is supplied as a sterile powder mixture in vials and infusion bottles containing imipenem anhydrous 250 mg/250 mg cilastatin equivalent and imipenem anhydrous 500 mg/500 mg cilastatin equivalent.

E) **Route of Administration:** Intravenous infusion

F) **Related Drugs:** There are no pharmacologically or chemically analogous substances to imipenem or cilastatin sodium.

2. Manufacturing Controls: (Refer to Chemistry Review)

3. Pharmacology: (Refer to Pharmacology Review)

4. Microbiology: Thienamycin was discovered as a member of a complex of beta-lactam antibiotics produced in fermentation broths by the soil actinomycete, Streptomyces cattleya, itself a hitherto underscribed species.

Structurally, thienamycin is dissimilar (see chemical structure) from all other natural and synthetic beta-lactam antibiotics in the following respects:

(1) The five-membered fused ring lacks an S and, unlike the five-membered penicillins, has an enamine system typical of the six-membered cephalosporins. It is from the exocyclic S-substituent at C_3 that thienamycin derives its name.

(2) The six-position is directly alkylated by the side chain, in contrast to the acylamino group present at that position in all penicillins and cephalosporins.

(3) The configuration of the C6-side chain is trans with respect to the five-membered ring. In all other beta-lactam antibiotics, the relative configuration is cis.

Thienamycin, however, resembles the classical beta-lactam antibiotics in its mode of action, being a specific inhibitor of bacterial peptidoglycan "cell-wall" biosynthesis. At inhibitory concentrations, it induces the formation of bacterial spheroplasts whose subsequent lysis accounts for the bactericidal nature of thienamycin activity. Biochemical studies indicate thienamycin acts at a late stage of cell-wall synthesis, probably by inactivating one or more of the transpeptidases that have been implicated in the mode of action of penicillins.

Thienamycin and its derivative, imipenem, have a wide spectrum of antibacterial activity which includes bacteria inherently resistant to most beta-lactam antibiotics such as P. aeruginosa, the gram-negative anaerobes, and enterococci.
The antibiotic potency is virtually unaffected by the presence of beta-lactamases directed against one or more of the penicillins and cephalosporins.

The antibacterial spectra of imipenem, thienamycin, and several reference antibiotics are compared in Tables 1 and 2

TABLE 1

AGAR DILUTION SUSCEPTIBILITY TEST
MIC (mcg/ml) of

STRAIN	(105CFU)	IMIPENEM	THM	CFX	CEF	CAB	GEN
S. aureus	2985	0.01	0.02	3.2	0.2	0.63	0.32
S. aureus	210	0.02	0.04	3.2	0.4	1.3	0.32
S. aureus	2874	0.02	0.04	3.2	0.2	1.3	0.16
S. aureus	2314	0.04	0.04	6.3	0.8	20.0	0.63
S. aureus	2867	0.02	0.04	6.3	0.8	20.0	0.63
S. aureus	4428c	20.0	40.0	>100	>100	80.0	5.0
Enterococcus	2864	0.63	1.3	> 100	25.0	40.0	10.0
Enterococcus	2862	1.3	2.5	>100	25.0	40.0	˙ 20
Enterococcus	2863	40.0	40.0	>100	> 100	> 80	20.0
E. coli	2482	0.32	0.63	6.3	12.5	5.0	0.32
E. coli	2884	0.08	0.16	6.3	6.3	5.0	1.3
E. coli	2964	0.32	0.32	6.3	100	> 80	⌐ 20
E. coli	2891	0.16	0.16	50.0	>100	40.0	2.5
E. coli	2895	0.32	0.63	25.0	>100	> 80	1.3
Shigella spp.	2880	0.16	0.32	3.2	6.3	5.0	1.3
S. typhimurium	826	0.32	0.32	3.2	6.3	20.0	2.5
E. cloacae	2647c	0.16	0.32	12.5	12.5	20.0	1.3
E. cloacae	2646	0.63	0.63	> 100	> 100	> 60	1.3
E. cloacae	2828	1.3	2.5	>100	⌐100	20.0	0.63
Enterobacter spp.	2903	0.63	1.3	>100	>100	5.0	1.3
Enterobacter spp.	2902	1.3	2.5	>100	>100	20.0	1.3
E. aerogenes	2906	2.5	5.0	100	100	5.0	1.3
K. pneumoniae	2921	0.63	0.63	6.3	12.5	⌐ 80	1.3
K. pneumoniae	2922	0.63	0.63	6.3	100	> 80	> 20
Klebsiella spp.	2888	0.63	1.3	⌐100	>100	10.0	1.3
Klebsiella spp.	2890	1.3	1.3	⌐100	⌐100	10.0	1.3
Klebsiella. spp.	2889	2.5	5.0	⌐100	>100	10.0	1.3
Serratia spp.	2840	0.63	2.5	25.0	>100	10.0	2.5
Serratia spp.	2855	0.63	2.5	12.5	>100	> 80	1.3
P. mirabilis	3125	5.0	10.0	3.2	6.3	1.3	5.0
P. mirabilis	2831	2.5	5.0	25.0	50.0	2.5	10.0
P. mirabilis	2830	5.0	10.0	6.3	> 100	⌐ 80	2.5
P. morganii	2833	5.0	5.0	12.5	⌐100	> 80	2.5
P. morganii	2834	2.5	10.0	12.5	>100	1.3	0.32
Providencia spp.	2851	1.3	2.5	1.6	>100	1.3	0.63

a) Antibiotic Abbreviations: THM, thienamycin, CFX, cefoxitin, CEF,
    cephalothin, CAB, carbenicillin; GEN, gentamicin

b) Methicillin resistant

c) Beta-lactamase-negative mutant derived from parent strain 2646

TABLE 2

AGAR DILUTION SUSCEPTIBILITY OF PSEUDOMONAS ISOLATES

STRAIN	(10⁵CFU)	IMIPENEM	THM	CAB	GEN	AMK	PIP
			MIC (mcg/ml) of				
40		1.6	3.1	5.0	50	6.3	3.1
2824		0.63	0.63	30	2.5		
2835		2.5	5	80	5.0		
3350ᵇ		10	20	>80	>20		
3286		2.5	10	80	5.0	6.3	6.3
3287ᶜ		2.5	10	80	5.0		
3288ᵈ		20.0	40	80	5.0		
4293		6.3	25	100	12.5	25	6.3
4294		12.5	50	100	25	50	6.3

a) Antibiotic abbreviations: THM = thienamycin; CAB= carbenicillin; GEN = gentamicin; AMK = Anikacin; PIP = piperacillin.

b) Strain 3350 bears plasmid - mediated carbenicillin and gentamicin resistance.

c) Laboratory isolate from strain 3286, showing spontaneous resistance to carbenicillin.

d) Laboratory isolate from strain 3286, showing spontaneous resistance to thienamycin.

As shown in these tables, the potencies of the thienamycin antibiotics far exceed those of the other beta-lactam antibiotics against both gram-positive species, including enterococci, and gram-negative species, including Pseudomonas species. On the average, imipenem shows a two-fold advantage over thienamycin for the entire range of species. Isolates exhibiting beta-lactamase mediated resistance to one or more penicillins and cephalosporins are inhibited by the thienamycins at concentrations close to the MICs found for strains of the same species that are susceptible to beta-lactam antibiotics. An example of the absence of cross-resistance is seen by comparing Enterobacter #2646 with its beta-lactamase-negative isogenic derivative, Enterobacter #2647. Both strains have similar susceptibility to imipenem, showing the indifference of the antibiotic to - the beta-lactamase. All other beta-lactam agents tested, including the extended-spectrum cephalosporins, show much reduced activity on Enterobacter #2646. A single exception to the general absence of cross-resistance was obtained with a methicillin-resistant Staphylococcus isolate (#4428), whose intrinsic resistance to beta-lactam antibiotics is known to be unrealated to beta-lactamase activity. Cross-resistance did not occur between the thienamycins and carbenicillin for a P. aeruginosa isolate with heterotypic resistance to that antibiotic (#3287) nor was carbenicillin resistance found for thienamycin-resistant variant of P. aeruginosa (#3288). Both variants were isolated in in-vitro from the susceptible parental strain #3286.

A survey of 29 Bacteroides isolates showed that all have a very high susceptibility to imipenem (Table 3).

The median MIC for imipenem (0.25 mcg/ml) is comparable to clindamycin, 4-fold superior to thienamycin, and 64-fold superior to that of cefoxitin.

TABLE 3

Comparative Susceptibility Studies on 29
B. fragilis Strains to Imipenem and Three
Reference antibiotics
MIC (mcg/ml)

Compound	Range	For 50% of Strains	For 90% of Strains
Imipenem	0.13 to 1.0	0.25	1.0
Thienamycin	0.25 to 2.0	1.0	2.0
Clindamycin	0.06 to 4.0	0.13	2.0
Cefoxitin	8.0 to 32	16	32

Agar dilution susceptibility tests were conducted with 13 selected hospital isolates of Pseudomonas aeruginosa, of which 6/13 were judged resistant to carbenicillin (Table 4). Two inoculum levels, 10^5 and 10^7 CFU, were employed. Comparisons were made with two anti-pseudomonal cephalosporins, moxalactam and cefotaxime, and to gentamicin, amikacin, piperacillin, and carbenicillin. These isolates were uniformly susceptible to imipenem at both inoculum levels. Isolates resistant to carbenicillin were not significantly different in their susceptibility to the thienamycins. The median MICs for imipenem were superior both to thienamycins and to the reference antibiotics. At a higher inoculum level, the greater activity of imipenem is more pronounced.

TABLE 4

Effect of Inoculum Levels on Susceptibility
of 13 Clinical Pseudomonas aeruginosa Isolates
and Seven Reference Antibiotics
Agar Dilution MIC (mcg/ml)

Compound	10^5CFU Inoculum For % Strains Range	50	90	10^7CFU Inoculum For % Strains Range	50	90
Imipenem	0.8 - 12.5	3.1	6.3	3.1 - 25	6.3	12.5
Thienamycin	1.6 - 50	6.3	25	3.1 - 50	12.5	25
Moxalactam	12.5 - > 50	25	50	50 - 50	50	50
Cefotaxime	12.5 - > 100	25	100	50 - >100	100	100
Carbenicillin	50 - 400	100	400	100 - >400	200	400
Piperacillin	3.1 - >100	6.3	25	25 - >100	100	100
Gentamicin	1.6 - 50	6.3	50	6.3 - >50	6.3	50
Amikacin	1.6 - 50	6.3	25	6.3 - 50	12.5	50

A survey of 29 Bacteroides isolates showed that all have a very high susceptibility to imipenem (Table 3).

The median MIC for imipenem (0.25 mcg/ml) is comparable to clindamycin, 4-fold superior to thienamycin, and 64-fold superior to that of cefoxitin.

TABLE 3

Comparative Susceptibility Studies on 29
B. fragilis Strains to Imipenem and Three
Reference antibiotics
MIC (mcg/ml)

Compound	Range	For 50% of Strains	For 90% of Strains
Imipenem	0.13 to 1.0	0.25	1.0
Thienamycin	0.25 to 2.0	1.0	2.0
Clindamycin	0.06 to 4.0	0.13	2.0
Cefoxitin	8.0 to 32	16	32

Agar dilution susceptibility tests were conducted with 13 selected hospital isolates of Pseudomonas aeruginosa, of which 6/13 were judged resistant to carbenicillin (Table 4). Two inoculum levels, 10^5 and 10^7CFU, were employed. Comparisons were made with two anti-pseudomonal cephalosporins, moxalactam and cefotaxime, and to gentamicin, amikacin, piperacillin, and carbenicillin. These isolates were uniformly susceptible to imipenem at both inoculum levels. Isolates resistant to carbenicillin were not significantly different in their susceptibility to the thienamycins. The median MICs for imipenem were superior both to thienamycins and to the reference antibiotics. At a higher inoculum level, the greater activity of imipenem is more pronounced.

TABLE 4

Effect of Inoculum Levels on Susceptibility
of 13 Clinical Pseudomonas aeruginosa Isolates
and Seven Reference Antibiotics
Agar Dilution MIC (mcg/ml)

Compound	10^5CFU Inoculum For % Strains			10^7CFU Inoculum For % Strains		
	Range	50	90	Range	50	90
Imipenem	0.8 - 12.5	3.1	6.3	3.1 - 25	6.3	12.5
Thienamycin	1.6 - 50	6.3	25	3.1 - 50	12.5	25
Moxalactam	12.5 - >50	25	50	50 - >50	50	50
Cefotaxime	12.5 - >100	25	100	50 - >100	100	>100
Carbenicillin	50 - 400	100	400	100 - >400	200	>400
Piperacillin	3.1 - >100	6.3	25	25 - >100	100	>100
Gentamicin	1.6 - 50	6.3	50	6.3 - >50	6.3	>50
Amikacin	1.6 - 50	6.3	25	6.3 - 50	12.5	50

The effect of inoculum levels on both bacteriostatic and bactericidal activity
of imipenem was compared with that of cephalothin, carbenicillin, cefotaxime,
and moxalactam. A penicillin-sensitive Staphylococcus, beta-lactam resistant
enteric species (E. coli, E. cloacae, K. pneumoniae, P. morganii, S.
marcescens), and two carbenicillin-sensitive isolates of P. aeruginosa were
used. At the low and intermediate inoculum levels (10^3 and 10^5CFU per
microtiter well), imipenem is bactericidal at its MIC. At the high inoculum
level(10^7CFU), MICs and MBCs were elevated, generally four-fold.
This increase was less than that found for the reference agents which, in
several instances, lost their bactericidal effect or were overgrown at the
highest levels tested despite high potency apparent at the low inoculum levels.

Summary of Published In Vitro Microbiological Studies
of Imipenem by Independent (Non-Merck) Investigators

Samples of imipenem have been distributed to more than 500 university and
hospital microbiological laboratories around the world. These laboratories
have studied the drug in a large number of clinical isolates, and many of
these studies have been submitted to scientific journals.
Tables 6-15 are compilations of comparative in-vitro susceptibility data
described in 121 publications. A listing of the full spectrum of bacterial
species measured for susceptibility to imipenem is presented in Tables 5-15.

COMPARATIVE IN VITRO ACTIVITY OF MK0787 WITH
BETA-LACTAM AND AMINOGLYCOSIDE ANTIBIOTICS

TABLE 5   GRAM POSITIVE ORGANISMS

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml 50%	90%
STAPH. AUREUS	MK0787	14	379	$\leq$ 0.04	$\leq$ 0.06
	CEFOTAXIME	9	150	2.1	3.7
	CEFOXITIN	2	35	3.3	8.9
	CEPHALOTHIN	6	199	0.34	0.7
	CEFTAZIDIME	3	37	19.2	30.0
	MOXALACTAM	8	160	9.2	12.5
	PIPERACILLIN	3	160	5.8	30.2
	TOBRAMYCIN	1	69	0.12	0.5
STAPHYLOCOCCUS EPIDERMIDIS	MK0787	8	163	$\leq$ 0.06	0.44
	CEPHALOTHIN	5	105	$\leq$ 0.16	1.2
	CEFTAZIDIME	1	12	8.0	32.0
	MOXALACTAM	3	40	16.6	$\geq$ 45.0
	PENICILLIN G	6	117	0.69	5.8
	TOBRAMYCIN	1	18	0.25	> 32.0
STREPTOCOCCUS SPP.	MK0787	11	265	$\leq$ 0.02	$\leq$ 0.04
	CEPHALOTHIN	6	136	$\leq$ 0.16	$\leq$ 0.03
	MOXALACTAM	6	215	2.6	4.9
	OXACILLIN	3	32	0.13	0.21
	PENICILLIN G	9	170	$\leq$ 0.02	$\leq$ 0.05
	PIPERACILLIN	2	95	$\leq$ 0.06	$\leq$ 0.2
	TOBRAMYCIN	2	95	>32.0	>32.0
ENTEROCOCCUS	MK0787	9	307	1.17	2.1
	AMPICILLIN	3	94	1.15	1.4
	CARBENICILLIN	1	29	50.0	50.0
	CEFOPERAZONE	2	126	$\geq$ 34.0	$\geq$ 50.0
	PIPERACILLIN	3	110	5.4	20.5
	TICARCILLIN	1	29	100.0	200.00
	TOBRAMYCIN	1	26	>32.0	>32.0
	VANCOMYCIN	1	29	1.0	2.0

I = # OF INVESTIGATORS
N = # OF STRAINS EXAMINED

TABLE 5 (cont'd)   GRAM NEGATIVE ORGANISMS

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml 50%	90%
ESCHERICHIA COLI	MK0787	9	446	0.16	0.35
	CEFOPERAZONE	2	80	0.13	1.5
	CEFOTAXIME	4	160	0.05	0.10
	CEFOXITIN	3	97	3.5	6.4
	CEFTAZIDIME	1	60	0.12	0.5
	MOXALACTAM	4	243	0.10	0.21
	PIPERACILLIN	3	206	1.82	45.0
	AMIKACIN	3	88	2.4	8.0
ENTEROBACTER SPP.	MK0787	16	518	0.36	1.04
	CEFOTAXIME	7	371	0.09	0 61
	CEFOXITIN	7	281	12.0	124.0
	CEFTAZIDIME	1	34	0.5	16.0
	MOXALACTAM	7	313	0.13	0.76
	CARBENICILLIN	4	106	5.7	47.0
	PIPERACILLIN	6	171	2.3	15.1
	TICARCILLIN	7	134	5.3	87.0
	AMIKACIN	6	51	2.0	4.0
	TOBRAMYCIN	2	27	0.5	0.73
KLEBSIELLA SPP.	MK0787	11	315	0.17	0.47
	CEFOTAXIME	4	139	0.02	0.09
	CEFOXITIN	4	48	2.7	4.8
	CEFTAZIDIME	1	57	0.25	1.0
	MOXALACTAM	5	141	0.10	0.03
	CARBENICILLIN	3	96	631.06	631.0
	PIPERACILLIN	4	174	6.3	22.0
	AMIKACIN	4	48	1.3	4.6
SERRATIA SPP.	MK0787	11	214	0.68	1.3
	CEFOTAXIME	4	102	0.26	2.0
	CEFOXITIN	4	47	20.0	55.0
	CEFTAZIDIME	1	30	0.25	0.25
	MOXALACTAM	6	77	0.76	2.1
	CARBENICILLIN	2	70	22.0	578.0
	GENTAMICIN	3	47	4.2	51.0

TABLE 5 (cont'd)   GRAM NEGATIVE ORGANISMS

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml	
				50%	90%
ESCHERICHIA COLI	MK0787	9	446	0.16	0.35
	CEFOPERAZONE	2	80	0.13	1.5
	CEFOTAXIME	4	160	0.05	0.10
	CEFOXITIN	3	97	3.5	1.4
	CEFTAZIDIME	1	60	0.12	0.5
	MOXALACTAM	4	243	0.10	0.21
	PIPERACILLIN	3	206	1.82	45.0
	AMIKACIN	3	88	2.4	8.0
ENTEROBACTER SPP.	MK0787	16	518	0.36	1.04
	CEFOTAXIME	7	371	0.09	0.61
	CEFOXITIN	7	281	12.0	124.0
	CEFTAZIDIME	1	34	0.5	16.0
	MOXALACTAM	7	313	0.13	0.76
	CARBENICILLIN	4	106	5.7	47.0
	PIPERACILLIN	6	171	2.3	15.1
	TICARCILLIN	7	134	5.3	87.0
	AMIKACIN	6	51	2.0	4.0
	TOBRAMYCIN	2	27	0.5	0.73
KLEBSIELLA SPP.	MK0787	11	315	0.17	0.47
	CEFOTAXIME	4	139	0.02	0.09
	CEFOXITIN	4	48	2.7	4.8
	CEFTAZIDIME	1	57	0.25	1.0
	MOXALACTAM	5	141	0.10	0.03
	CARBENICILLIN	3	96	631.06	631.0
	PIPERACILLIN	4	174	6.3	22.0
	AMIKACIN	4	48	1.3	4.6
SERRATIA SPP.	MK0787	11	214	0.68	1.3
	CEFOTAXIME	4	102	0.26	2.0
	CEFOXITIN	4	47	20.0	55.0
	CEFTAZIDIME	1	30	0.25	0.25
	MOXALACTAM	6	77	0.76	2.1
	CARBENICILLIN	2	70	22.0	578.0
	GENTAMICIN	3	47	4.2	51.0

TABLE 5 (CONT'D)

ORGANISM	ANTIBIOTIC	I	N	GEOMETRIC MEAN MIC mg/ml 50%	90%
PROTEUS MIRABILIS	MK0787	7	210	1.4	3.0
	CEFOPERAZONE	2	74	0.61	2.0
	CEFOTAXIME	3	146	0.02	0.03
	CEFOXITIN	2	26	4.6	8.0
	CEFTAZIDIME	1	60	0.06	0.06
	MOXALACTAM	4	101	≤ 0.12	0.16
	CARBENICILLIN	1	33	0.78	0.78
	PIPERACILLIN	3	101	≤ 0.41	≤ 1.33
	TICARCILLIN	4	121	0.68	14.0
	TOBRAMYCIN	2	38	0.86	3.0
PROTEUS SPP. INDOLE (+)	MK0787	17	386	1.8	3.3
	CEFOPERAZONE	5	82	1.5	6.5
	CEFOTAXIME	11	318	≤ 0.04	0.4
	CEFOXITIN	6	215	4.3	> 15.0
	CEFTAZIDIME	4	60	0.12	0.21
	MOXALACTAM	10	265	0.11	0.20
	PIPERACILLIN	5	95	0.77	6.0
	TICARCILLIN	8	110	≥ 4.5	≥ 48.0
	AMIKACIN	4	38	2.3	5.8
PSEUDOMONAS AERUGINOSA	MK0787	12	590	1.5	4.9
	CEFOPERAZONE	5	254	3.9	22.4
	CEFOTAXIME	7	372	12.2	≥ 43.4
	CEFTAZIDIME	1	59	2.0	4.0
	CEFTIZOXIME	1	100	64.0	> 64.0
	MOXALACTAM	8	389	13.0	≥ 42.4
	CARBENICILLIN	4	198	75.0	563.0
	PIPERACILLIN	4	230	5.2	19.6
	GENTAMICIN	5	237	2.3	> 11.0
	TOBRAMYCIN	4	138	1.4	10.2
BACTEROIDES FRAGILIS	MK0787	5	345	0.15	0.4
	CEFOTAXIME	2	47	4.81	> 25.0
	CEFOXITIN	4	203	9.3	20.2
	MOXALACTAM	4	180	0.6	4.8
	CHLORAMPHENICOL	1	100	4.0	8.0
	CLINDAMYCIN	2	156	≤ 0.47	1.6
	METRONIDAZOLE	1	56	0.5	1.0

I = # OF INVESTIGATORS
N = # OF STRAINS EXAMINED

TABLE 6

MISCELLANEOUS SPECIES: SUSCEPTIBILITY TO MK0787

	N	GEOMETRIC MEAN MIC 90
AEROBES - GRAM-POSITIVE		
LISTERIA MONOCYTOGENES	11	0.125
MYCOBACTERIUM AVIUM - INTRACELLULARE	15	0.2(MIC 70)
NOCARDIA ASTEROIDES	8	1.56
AEROBES - GRAM-NEGATIVE		
ACINETOBACTER SPP	64	0.24
ALCALIGENES SPP	33	2.0
BRUCELLA MELITENSIS	98	2.0
HAEMOPHILUS INFLUENZAE	173	1.9
MORAXELLA SPP	28	0.125
NEISSERIA GONORRHOEAE	111	0.13
NEISSERIA MENINGITIDIS	93	0.04
SHIGELLA SPP	22	0.20
YERSINIA ENTEROCOLITICA	10	0.5
ANAEROBES - GRAM-POSITIVE		
CLOSTRIDIUM DIFFICILE	47	2.9
CLOSTRIDIUM PERFRINGENS	15	4.0
CLOSTRIDIUM SPP	100	0.25
EUBACTERIUM SPP	6	2.0
PEPTOCOCCUS SPP	49	0.07
PETOSTREPTOCOCCUS SPP	32	0.14
ANAEROBES - GRAM-NEGATIVE		
CAMPYLOBACTER FETUS SS. JEJUNI	36	0.03
CAMPYLOBACTER FETUS SS. INTESTINALIS	4	0.19
EIKENELLA CORRODENS	28	0.25
FUSOBACTERIUM SPP	57	0.5
VEILLONELLA SPP	23	0.25

SUSCEPTIBILITY DATA RECEIVED FROM NON-MERCK INVESTIGATORS. ON FILE AT MERCK
SHARP & DOHME RESEARCH LABORATORIES, RAHWAY, NJ

TABLE 7

Susceptibility of MK0787 (N-Formimidoyl thienamycin) to
Wild Type (W.T.) and Multiply Resistant Clinical Isolates

	I	N	GEOMETRIC MEAN MIC90 mg/ml
Gram-Positive			
Staphyloccus aureus (W.T.)	22	1063	$\leq$ 0.06
Staphylococcus aureus (Pen-R)	5	110	0.08
Enterococci	20	795	1.58
Nocardia asteroides	3	45	2.66
Mycobacterium avium	2	22	0.48 (MIC70)
Mycobacterium fortuitum	1	12	12.5
Gram Negative			
Pseudomonas aeruginosa (W.T.)	31	2278	3.54
Pseudomonas aeruginosa (A*-R)	9	317	3.80
Escherichia coli (W.T.)	22	1122	$\leq$ 0.26
Escherichia coli (Gen-R)	4	41	$\leq$ 0.70
Acinetobacter spp.	14	436	0.47
Campylobacter fetus	3	92	$\leq$ 0.07
Bacteroides fragilis	14	906	$\leq$ 0.33

I = Number of independent investigators
N = Number of clinical isolates tested
*A = Aminoglycosides, eg. Gentamicin, Amikacin, Tobramycin

TABLE 8

Comparative Activities Against <u>Streptococcus faecalis</u> Isolates
(n = 89)

Antibiotic	N	Geometric Mean MIC90, mg/ml
MKO787	89	0.9
Piperacillin	35	4.0
Cephalothin	54	32.0
Cefotaxime	89	> 128.0
Cefoperazone	39	34.3
Ceftazidime	54	> 128.0
Moxalactam	89	> 128.0
Cefsulodin	54	> 128.0
Ceftriaxone	54	> 128.0
Ceftizoxime	54	> 128.0
Cefuroxime	54	> 128.0
Gentamicin	35	15.0

TABLE 9

MKO787 Activity Against <u>P. aeruginosa</u> Isolates
Resistant to One or More Aminoglycosides or Penicillins

Antibiotic	No. of Isolates	MKO787 MIC90, mg/ml
Tobramycin (MIC $\geq$ 8)	15	8
Gentamicin (MIC $\geq$ 8)	65	4
Amikacin (MIC $\geq$ 32)	26	8
Azlocillin (MIC $\geq$ 128)	28	4
Ticarcillin (MIC $\geq$ 128)	29	8
	163	5.4 (Geom. Mean)

TABLE 10

Comparative Activities Against GEN-S and GEN-R P. aeruginosa Strains

Antibiotic	GEN-S, n = 29 MIC_{90}, mg/ml	GEN-R, n = 34 MIC_{90}, mg/ml
MKO787	2	8
Gentamicin	4	32
Amikacin	8	64
Tobramycin	2	8
Moxalactam	32	64
Cefoperazone	32	32
Cefotaxime	64	128
Piperacillin	16	32

TABLE 11

Carbenicillin-R. Pseucomonas aeruginosa Isolates

Cumulative Percentage (N = 20)
MIC, mg/ml

Antibiotic	3.13	6.25	12.5	25	50	100
MKO787	90	95	100			
Piperacillin			20	60	80	85
Cefotaxime					20	75
Moxalactam						5

TABLE 10

Comparative Activities Against GEN-S and GEN-R $\underline{P}$. $\underline{aeruginosa}$ Strains

Antibiotic	GEN-S, n = 29 MIC_{90}, mg/ml	GEN-R, n = 34 MIC_{90}, mg/ml
MK0787	2	8
Gentamicin	4	32
Amikacin	8	64
Tobramycin	2	8
Moxalactam	32	64
Cefoperazone	32	32
Cefotaxime	64	128
Piperacillin	16	32

TABLE 11

Carbenicillin-R. $\underline{Pseudomonas}$ $\underline{aeruginosa}$ Isolates

Cumulative Percentage (N = 20)
MIC, mg/ml

Antibiotic	3.13	6.25	12.5	25	50	100
MK0787	90	95	100			
Piperacillin			20	60	80	85
Cefotaxime					20	75
Moxalactam						5

TABLE 12

Comparative Activity Against Campylobacter fetus, supp. jejuni
$$n = 36$$

Antibiotic	MIC_{90}, mg/ml
MK0787	0.03
Ampicillin	4.0
Moxalactam	16.0
Cefotaxime	4.0
Erythromycin	0.5
Chloramphenicol	4.0
Rifampin	$\geq$ 128.0
Cefoperazone	$\geq$ 128.0
Vancomycin	$\geq$ 128.0

TABLE 14

Comparative Activity Against Acinetobacter spp.
$$n = 14$$

Antibiotic	MIC_{90}, mg/ml
MK0787	0.25
Amoxicillin	32.0
Cefotaxime	16.0
Moxalactam	64.0
Ceftazidime	8.0
Ticarcillin	32.0

TABLE 14

Comparative Activity Against Bacteroides fragilis Isolates
n = 100

Antibiotic	MIC_{90}, mg/ml
MK0787	0.25
Moxalactam	4.0
Piperacillin	64.0
Mezlocillin	128.0
Carbenicillin	> 256.0
Ticarcillin	> 256.0
Azlocillin	> 256.0
Cefoxitin	16.0
Cefotaxime	256.0
Cefoperazone	256.0
Cefamandole	> 256.0
Clindamycin	1.0
Metronidazole	1.0
Chloramphenicol	4.0

TABLE 14

Comparative Activity Against <u>Bacteroides fragilis</u> Isolates
$n = \overline{100}$

Antibiotic	MIC_{90}, mg/ml
MK0787	0.25
Moxalactam	4.0
Piperacillin	64.0
Mezlocillin	128.0
Carbenicillin	> 256.0
Ticarcillin	> 256.0
Azlocillin	> 256.0
Cefoxitin	16.0
Cefotaxime	256.0
Cefoperazone	256.0
Cefamandole	> 256.0
Clindamycin	1.0
Metronidazole	1.0
Chloramphenicol	4.0

TABLE 15

Susceptibility Reference List of MK0787 (N-Formimidoyl Thienamycin)

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC$_{50}$	MIC$_{90}$
Achromobacter Vd:				
Achromobacter Vd-1, Vd-2		10	2.0	2.0
Achromobacter xylosoxidans		7	2.0	4.0
Actinomyces spp.				
Actinomyces odontolyticus		5	0.06	0.13
Acinetobacter spp.	−	436	0.22	0.47
Acinetobacter calcoaceticus				
Acinetobacter calcoaceticus anitratus				
Acinetobacter calcoaceticus lwoffii				
Acinetobacter calcoaceticus haemolyticus				
Acinetobacter calcoaceticus alcaligenes				
Aeromonas hydrophilia	−	5	0.05	0.10
Alcaligenes spp.	−	86	0.97	2.04
Alcaligenes faecalis				
Bacteroides spp.	−	997	0.08	0.33
Bacteroides fragilis				
Bacteroides disiens				
Bacteroides distasonis				
Bacteroides melanin. melaninogenicus				
Bacteroides oralis				
Bacteroides ruminocola brevis				
Bacteroides thetaiotaomicron				
Bacteroides vulgatus				
Bacteroides ovatus				
Bacteroides uniformis				
Bordetella bronchicanis	−	13	4.0	4.0
Brucella melitensis	−	98	1.0	2.0
Campylobacter spp.	−	92	0.07	0.07
Campylobacter fetus jejuni				
Campylobacter fetus intestinalis				
Citrobacter/Salmonella	−	370	0.30	0.62
Citrobacter freundii				
Citrobacter diversus				
(Arizona hinshawii included)				
Clostridia spp.	+	292	0.31	1.14
Clostridium septicum				
Clostridium difficile				
Clostridium perfringens				
Clostridium bifermentans				
Clostridium botulinum				

TABLE 15 (CONT'D)

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC$_{50}$	MIC$_{90}$
			Geom. Mean	
Chlamidia trachomatis		7	cidal level =	27.8
Corynebacterium sp.	+	4	·32.0	32.0
E. coli	−	1122	0.14	0.26
Eikenella corrodens	−	56	0.15	0.22
Enterobacter spp.	−	1276	0.34	1.30
Enterobacter cloacae				
Enterobacter aerogenes				
Enterobacter agglomerans				
Erysipelothrix rhusiopathiae	+	2	⌐ 0.02	0.02
Eubacterium sp.	+	6	· 0.06	2.0
Flavobacterium spp.	−	23	⌐ 2.17	20.0
Flavobacterium IIb				
Fusobacterium sp.	−	57	0.03	0.50
Gardnerella vaginalis	−	25	−	0.50
Haemophilus influenzae		302	0.95	1.82
Hafnia spp.	−	14	⌐ 0.26	0.46
Hafnia alvei				
Klebsiella spp.	−	952	0.18	0.41
Klebsiella pneumoniae				
Klebsiella oxytoca				
Listeria monocytogenes	+	36	⌐ 0.08	0.11
Moraxella spp.	−	37	· 0.08	0.37
Moraxella osloensis				
Mycobacterium avium intracellulare	−	22		0.48
				(MIC$_{70}$)
Mycobacterium fortuitum	÷	12	3.12	12.50
Neisseria gonorrhoeae	−	387	⌐ 0.10	0.30
Neisseria meningitidis	·-	266	0.05	0.11
Nocardia spp.	+	45	⌐ 1.13	2.66
Nocardia asteroides				
Pasteurella multocida	−	10	0.50	1.00
Peptococcus/Petostreptococcus	+	87	⌐ 0.02	0.06
Peptococcus asaccharolyticus				
Peptococcus magnus				
Plesimonas shigelloides	−	15	0.13	0.25
Propionibacterium acnes	+	26	0.01	0.02
Proteus/Providencia spp.	−	1655	1.30	2.90
Proteus vulgaris				
Proteus mirabilis				
Proteus morganii				
Proteus rettgeri				
Prov. stuartii				
Staphylococcus aureus	+	1290	0.07	0.13
Staphylococcus epidermidis	+	509	0.09	1.33

TABLE 15 (CONT'D)

Bacterial Strain	Gram (+/-)	N	Geom. Mean (mg/ml) MIC$_{50}$	MIC$_{90}$
			Geom. Mean	
Chlamidia trachomatis		7	cidal level =	27.8
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Enterobacter spp.	-	1276	0.34	1.30
Enterobacter cloacae				
Enterobacter aerogenes				
Enterobacter agglomerans				
Erysipelothrix rhusiopathiae	+	2	⌐ 0.02	0.02
Eubacterium sp.	+	6	· 0.06	2.0
Flavobacterium spp.	-	23	⌐ 2.17	20.0
Flavobacterium IIb				
Fusobacterium sp.	-	57	0.03	0.50
Gardnerella vaginalis	-	25	-	0.50
Haemophilus influenzae		302	0.95	1.82
Hafnia spp.	-	14	⌐ 0.28	0.46
Hafnia alvei				
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Klebsiella pneumoniae				
Klebsiella oxytoca				
Listeria monocytogenes	+	36	⌐ 0.08	0.11
Moraxella spp.	-	37	0.08	0.37
Moraxella osloensis				
Mycobacterium avium intracellulare	-	22		0.48
				(MIC$_{70}$)
Mycobacterium fortuitum	+	12	3.12	12.50
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Neisseria meningitidis	-	266	0.05	0.11
Nocardia spp.	+	45	1.15	2.66
Nocardia asteroides				
Pasteurella multocida	-	10	0.50	1.00
Peptococcus/Petostreptococcus	+	87	0.02	0.06
Peptococcus asaccharolyticus				
Peptococcus magnus				
Plesimonas shigelioides	-	15	0.13	0.25
Propionibacterium acnes	+	26	0.01	0.02
Proteus/Providencia spp.	-	1655	1.30	2.90
Proteus vulgaris				
Proteus mirabilis				
Proteus morganii				
Proteus rettgeri				
Prov. stuartii				
Staphylococcus aureus	+	1290	0.07	0.13
Staphylococcus epidermidis	+	509	0.09	1.33

Bacterial Strain	Gram (+/–)	N	Geom. Mean (mg/ml) MIC$_{50}$	MIC$_{90}$
Pseudomonas spp.	–	2278	1.57	3.54
Pseudomonas aeruginosa				
Pseudomonas acidovorans				
Pseudomonas putrefaciens				
Pseudomonas stutzeri				
Pseudomonas fluorescens				
Pseudomonas cepacia		40	4.5	> 50.0
Pseudomonas maltophilia		118	> 64.0	> 128.0
Rhodococcus spp.	–	11	0.39	0.39
Serratia spp.	–	806	≤ 0.76	1.93
Serratia marcescens				
Shigella sp.	–	33	0.17	0.27
Streptococcus spp. (Grps. A,B,C,G)	+	1293	≤ 0.03	≤ 0.05
Streptococcus agalactiae				
Streptococcus pneumoniae				
Streptococcus durans				
Streptococcus pyogenes				
Streptococcus bovis				
Viridans streptococci	+	51	0.06	≤ 0.11
Streptococcus faecalis (Grp. D)	+	795	0.93	1.58
Streptococcus faecium	+	30	20.0	78.0
Veillonella spp.	–	23	0.05	0.25
Veillonella parvula				
Yersinia spp.	–	234	≤ 0.23	0.44
Yersinia enterocolitica				
Yersinia pseudotuberculosis				

Outstanding in-vitro potency is observed against gram-postive, gram-negative, aerobic and anerobic organisms. Worthy of particular note is the potent activity against P. aeruginosa, Serratia, Bacteroides, and enterococci organisms.

That imipenem is resistant to nearly all bacterial beta-lactamases has been confirmed in several of these studies. Thus, imipenem lacks cross-resistance with any other clinical or experimental antibiotic presently available. The only exceptions to the outstanding antimicrobical activity of imipenem are as follows: Pseudomonas maltophilia is the only organism which is fully resistant to imipenem. Although a large portion of methicillin-resistant S. aureus strains are susceptible to the antibiotic, these isolates do show a wide distribution of susceptibilities in contrast to wild-type strains which show a narrow distribution with low MICs (<0.1 mcg/ml). A portion of the methicillin-resistant S. aureus strains are considered resistart to imipenem (MIC > 8 mcg/ml). Occasionally, strains of S. epidermidis have been found to have high MICs; again, the majority of isolates have an MIC of < 0.1 mcg/ml.

Combinations of imipenem and aminoglycosides have been reported to be synergistic against several bacterial species, such as multiply-resistant P. aeruginosa, S. faecalis, L. monocytogenes, and Serratia species. The degree of synergy achieved varies with the aminoglycoside used in combination. A lack of synergy against some organisms was in most instances attributable to the efficiency of killing by imipenem alone. Antagonism between combinations of imipenem and aminoglycosides has not been observed. Kallick and associates measured the interaction of imipenem with aminocyclital antibiotics against numerous strains of P. aeruginosa and S. aureus isolated from patients with endocarditis. Imipenem in combination with tobramycin was rapidly bactericidal (e.g., 1000 – fold reduction in 4h), a marked improvement over a carbenicillin plus tobramycin combination observed for all strains of P. aeruginosa tested. Similarly the killing rates for imipenem plus tobramycin against S. aureus were significantly enhanced compared to those of individual antibiotics. Gombert and associates reported on the synergistic interaction of imipenem with amikacin and gentamicin against Streptococcus faecalis. Sixty percent of the synergistic combinations were totally bactericidal (produced sterile cultures) at 24 h.

Efficacy Studies in Experimental Infections in Animals.

Drs. D. Durack and J. Perfect of Duke University demonstrated therapeutic levels of imipenem in the cerebrospinal fluid (CSF) of rabbits with inflamed and uninflamed meninges. They also demonstrated that excellent bactericidal and inhibitory titers in plasma and CSF of rabbits are achievable against both methicillin-sensitive and methicillin-resistant clinical isolates of Staphylococcus aureus. Dr. George McCracken, Jr., at the University of Texas Health Science Center in Dallas has confirmed this work.

In a 1982 publication, Drs. McCracken and Putamasucon report that imipenem penetrates the CSF of rabbits with inflamed meninges, experimentally infected with Escherichia coli.

Three studies to measure the effectiveness of imipenem in the treatment of polymicrobial intraperitoneal infections in the rat have been performed; one by Drs. T. Hau and Reid Nishikawa, the others by Dr. A. Onderdonk at Tufts University, and Drs. Nord and Lahnburg at the National Bacteriological Laboratory in Stockholm, Sweden.
The results of these studies indicate significant survival and cure rates, as well as substantial reductions in abscess formation as a result of imipenem treatment.

Dr. J. Pennington from the Peter Bent Brigham Hospital in Boston reported on the excellent survival rates (70-75%) observed in his experimental pneumonia model in guinea pigs. In this animal model, imipenem was the only beta-lactam antibiotic that matched the effectiveness of aminoglycosides against Pseudomonas aeruginosa. Further, Drs. D. Johnson and S. Schimpf of the V.A. Medical Center and University of Maryland School of Medicine found that imipenem provided effective therapy of lethal Pseudomonas infections in neutropenic rats.

Data, from Dr. L. Guze's laboratory at the Wadsworth (V.A.) Medical Center in Los Angeles, describing the therapeutic effectiveness of the imipenem/cilastatin combination in a hematogenous pyelonephritis model in rats demonstrated the excellent efficacy achieved with imipenem in this animal model against both methicillin-sensitive and methicillin-resistant clinical isolates.

Imipenem was also evaluated for its potential in the treatment of bacterial endocarditis in rat and rabbit models. Dr. M. Scheld of the University of Virginia reported that imipenem was significantly more rapid and potent in its bactericidal action than nafcillin against strains of S. aureus isolated from endocarditis patients. This investigator also observed excellent activity of imipenem against a clinical isolate of S. faecalis in the same endocarditis rabbit model. In this study, imipenem, as a single agent, was equivalent to penicillin plus gentamicin therapy.

The effectiveness of imipenem, as a single agent in the treatment of endocarditis due to S. faecalis isolates expressing tolerance to this antibiotic (MIC 1.56, MBC 128 ucg/ml) was explored by Drs. Auckenthaler and Wilson at the Mayo Clinic. In the rabbit model, designed to simulate streptococcal prosthetic valve infections in man, the activity of imipenem (administered at 20 mg/kg) was found to be equal to procaine penicillin (administered at 720 mg/kg) but less active than a combined dose of procaine penicillin plus gentamicin.

Dr. Anthony Chow and his associates at the Department of Ophthalmology, University of British Colombia, Canada, reported on the intrathecal penetration of imipenem when administered alone or in combination with cilastatin sodium in normal rabbits. Imipenem penetrated uninflamed meninges, and peak concentrations were significantly increased by coadministration of cilastatin sodium.

Overall, the results of these animal studies reflect the excellent spectrum of antibacterial activity of imipenem and confirm the in-vitro susceptibility data. The ability of this antibiotic to penetrate body tissues and the CSF has been established from the animal studies.

Lack of Antibacterial Activity of Cilastatin

The lack of antibacterial activity of cilastatin was demonstrated by use of the sensitivity disk method, as well as by measuring the minimal inhibitory concentration (MIC) using the broth dilution (Mueller-Hinton) Microtiter technique. Cilastatin was tested against nine bacterial strains made up of five different genera (S. aureus, E. coli, Enterobacter, K. pneumoniae, P. aeruginosa).
Cilastatin showed no antibacterial activity at 10 mcg/ml (the highest level tested) against any of the nine strains.
In addition, a combination of imipenem and cilastatin in a ratio of 1: 6.25 was tested. No sign of synergistic activity was observed. No significant antagonism occurred -- only an occasional tube upward shift of the MIC for imipenem was observed.

Lack of antibacterial activity of cilastatin and lack of interference with the activity of imipenem was also demonstrated in disk diffusion studies where the individual components, at concentration of 25 mcg/disk of imipenem and 50 mcg/disk of cilastatin, and a combination of the two agents in a ratio of 2:1 (cilastatin : imipenem), were measured for antibacterial potency against 41 bacterial strains selected from 10 species (S. aureus, enterococcus, E. coli, Shigella species, Salmonella species, Enterobacter species, Klebsiella species, Serratia species, Proteus species, Providencia species, and Pseudomonas species). Again, no synergistic activity or antagonism was observed when the agents were combined.

Metabolism of Imipenem

Thienamycin and its derviative imipenem undergo extensive, species-variable metabolism as measured by the low urinary recovery of antibiotic.
Measures of the systemic bioavailability of thienamycin and imipenem, such as half-life and AUC, compare favorably (in the mouse, rabbit, dog, and chimpanzee) with those of nonmetabolized antibiotics and to those that undergo only minor metabolism.

However, the renal clearance rats were unusually low. In the dog, the renal clearance of imipenem was 0.49 ml/min/kg which is far below the glomerular filtration rate for this animal (4.9 ml/min/kg). An analogous low rate of renal clearance of imipenem was observed in the chimpanzee, a species having a similar excretion pattern to man.

This low renal clearance rate suggests that the antibiotic is destroyed during the process of excretion.
The major role of the kidney in metabolism was confirmed by the finding of prolonged plasma levels of antibiotic following bilateral ligation of the renal arteries in the rat and the rabbit.

Subsequent biochemical studies demonstrated that the bulk of metabolic inactivation results from the hydrolysis of the beta-lactam ring in imipenem by a renal dipeptidase. This enzyme was originally described 40 years ago and given the name Dehydropeptidase-I (DHP-I).

The subcellular localization of Dehydropeptidase-I on the lumenal surface (the brush-border) of the proximal renal tubular epithelium accounts for its impact on the disposition of imipenem. It has access to the antibiotic both in the glomerular filtrate and in the transcellular flux mediated by the secretory process between the blood and the lumen of the nephron.
In both cases, the antibiotic has eff_tively been cleared from the plasma by processes preceding, and independent of, the metabolic events that occur while it is in transit to the urine. Thus, systemic persistence is insulated from the major site of metabolism, whereas urinary tract bioavailability of the antibiotic is greatly reduced.

Clinical pharmacology studies in normal volunteers have confirmed the presence of extensive metabolism of imipenem similar to laboratory animals and particularly to the chimpanzee. The experience with imipenem in man is, therefore, entirely analogous to that observed in most animal species tested; while systemic bioavailability is adequate, urinary tract bioavailability may be inadequate.

This deficit in urinary tract bioavailability of imipenem could in principle be compensated for by increasing the dose rate and frequency of administration. However, in view of the nephrotoxic potential of the antibiotic, this approach would decrease the available safety margin. An alternative strategy, as described below, was to coadminister a selective inhibitor of the enzyme responsible for metabolism of the antibiotc.

Development of Cilastatin

Several compounds, selected on the basis of their chemical homology with dehydropeptidase, were screened for inhibitory action against a purified preparation of porcine renal DHP-I.

The compound selected from the screen was benzoyl-NH$_2$-2- acrylate.
Systemic chemical modification resulted in homologs with inhibitory constants
(K$_I$) < 0.03 mcM, a 1000-fold increase over the lead compound. These
inhibitors also exhibited a comparable potency against DHP-I purified from
human kidney.
The mechanism of inhibition was found to be competitive and reversible. The
specificity of several inhibitors of DHP-I was demonstrated by their lack of
significant inhibitory activity against several other zinc metalloenzyme
peptidases (Carboxypeptidase-A, Carboxypeptidase-B, leucine - amino-peptidase
and Acylase-I).

Inhibitors at 1 to 4 mg/kg, coadministered with imipenem, dramatically
increased the urinary recovery of the antibiotic, particularly in larger
animal species. For example, in the chimpanzee urinary recovery increased
from an average of 13.5% to 65-76%.

Enhanced urinary recovery is a necessary, but not sufficient, criterion of
efficacy for the inhibitors of antibiotic metabolism. The ideal inhibitor
must remain in the circulation at effective levels during an appreciable
fraction of the period that will elapse before the next dose is administered.
The desired goal of prolonged action was initially met by increasing the
length of the C$_3$ substituent, good activity being found with the n-pentyl
analog.
This inhibitor, MK-0789, was the predecessor to MK-0791 (cilastatin sodium).

Although well tolerated by 15 volunteers who received it, MK-0789 was
subsequently found to produce unacceptable local irritation in laboratory
animals. This local irritation phenomenon was attributed to the lipophilic
substituents of this inhibitor.
Effort turned to the synthesis of analogues whose long duration of action
would not depend upon lipophilic substituents.

With MK-0791 (cilastatin sodium), prolonged action was achieved by
introduction of a zwitterionic substituent, L-cysteine, which decreases the
rate of plasma clearance resulting from renal secretion. The in-vitro potency
of this inhibitor (0.11 mcM) is somewhat less than that of MK-0789 (0.08 mcM);
however, this slightly lower potency is offset partially by the much reduced
plasma binding of this agent (42% vs 96% for MK-0789).
An additional advantage of cilastatin sodium is its relative metabolic
stability. Only 30% of cilastatin sodium is metabolized in the Rhesus monkey
and the chimpanzee. Further, the N-acetyl metabolite that is formed from
cilastatin sodium is somewhat more potent in-vitro than the parent compound.
The acetylated compound is found primarily in the urine suggesting that
acetylation occurs during excretion.

Coadministration of 2 or 4 mg/kg of cilastatin sodium with 5 mg/kg of imipenem
in the chimpanzee resulted in urinary recoveries for imipenem of 63 and 75%,
respectively (vs 13% in controls).

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respectively (vs 13% in controls).

Cilastatin sodium was well tolerated both in acute and subacute toxicity studies. Importantly, no evidence of local irritation has been detected with its use.

Prevention of Nephrotoxicity of Imipenem by Coadministered Dehydropeptidase

Single large doses of imipenem induce proximal tubular necrosis in the rabbit at doses over 90 mg/kg and in the Rhesus monkey at doses of 180 mg/kg. Cephaloridine (a beta-lactam molecule resembling imipenem) produces a histomorphologically similar tubular lesion in the same two species. The mechanism of renal toxicity must be quite different for the two compounds. In the case of cephaloridine, nephrotoxicity has been correlated with high intracortical concentrations of intact antibiotic. They result from active anionic pumping of this agent into the proximal tubular epithelium followed by slow egress. With imipenem, however, the intact antibiotic does not accumulate to an appreciable extent within the tubular epithelium since the fraction transported into tubule from the plasma appears to be almost completely metaboli ed by DHP-I. Further, upon addition of low levels of dehydropeptidase inhibitors, transported fraction appears to be free to pass through the tublar epithelium and enter the lumen of the nephron. Therefore, imipenem is subject to conventional, net secretion and does not accumulate when protected from metabolism. On the premise that degradates resulting from hydrolysis of imipenem by DHP-I might be trapped in the epithelium and cause nephrotoxicity, inhibitors of DHP-I were coadministered with large nephrotoxic doses of imipenem. The result showed that nephrotoxicity was, in fact, prevented. Control studies revealed, however, that the prevention of nephrotoxicity results not from inhibition of DHP-I but from competitive exclusion of the antibiotic from the cell at the level of transport.

Imipenem Metabolites and Their Role in Nephrotoxicity

In experiments using radiolabeled imipenem, it was observed that good recovery of total radioactivity could be obtained in the rat and rabbit. The residual radioactivity remaining in kidneys of these animals was only a small fraction of the total recovered radioactivity. However, the difference between the residual label in the kidneys of the rat compared to the rabbit was striking. The rabbit, in which nerphrotoxicity can be induced by high levels of imipenem, had about ten-fold more residual label than did the kidneys of the rat, in which renal toxicity cannot be induced with imipenem. Analyses of the rabbit kidney cortex homogenates for intracellular degradates by liquid chromatography revealed four metabolites which retain the radioactivity from radiolabeled imipenem. Metabolite I was identified as the DHP-I hydrolysis products. Its accumulation was prevented by coadministration of DHP-I inhibitors with the radiolabeled imipenem.

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Single large doses of imipenem induce proximal tubular necrosis in the rabbit at doses over 90 mg/kg and in the Rhesus monkey at doses of 180 mg/kg. Cephaloridine (a beta-lactam molecule resembling imipenem) produces a histomorphologically similar tubular lesion in the same two species. The mechanism of renal toxicity must be quite different for the two compounds. In the case of cephaloridine, nephrotoxicity has been correlated with high intracortical concentrations of intact antibiotic. They result from active anionic pumping of this agent into the proximal tubular epithelium followed by slow egress. With imipenem, however, the intact antibiotic does not accumulate to an appreciable extent within the tubular epithelium since the fraction transported into tubule from the plasma appears to be almost completely metabolized by DHP-I. Further, upon addition of low levels of dehydropeptidase inhibitors, transported fraction appears to be free to pass through the tublar epithelium and enter the lumen of the nephron. Therefore, imipenem is subject to conventional, net secretion and does not accumulate when protected from metabolism. On the premise that degradates resulting from hydrolysis of imipenem by DHP-I might be trapped in the epithelium and cause nephrotoxicity, inhibitors of DHP-I were coadministered with large nephrotoxic doses of imipenem. The result showed that nephrotoxicity was, in fact, prevented Control studies revealed, however, that the prevention of nephrotoxicity results not from inhibition of DHP-I but from competitive exclusion of the antibiotic from the cell at the level of transport.

Imipenem Metabolites and Their Role in Nephrotoxicity

In experiments using radiolabeled imipenem, it was observed that good recovery of total radioactivity could be obtained in the rat and rabbit. The residual radioactivity remaining in kidneys of these animals was only a small fraction of the total recovered radioactivity. However, the difference between the residual label in the kidneys of the rat compared to the rabbit was striking. The rabbit, in which nerphrotoxicity can be induced by high levels of imipenem, had about ten-fold more residual label than did the kidneys of the rat, in which renal toxicity cannot be induced with imipenem. Analyses of the rabbit kidney cortex homogenates for intracellular degradates by liquid chromatography revealed four metabolites which retain the radioactivity from radiolabeled imipenem. Metabolite I was identified as the DHP-I hydrolysis products. Its accumulation was prevented by coadministration of DHP-I inhibitors with the radiolabeled imipenem.

Metabolite II, a minor component, arises during the the DHP-I activity or spontaneously from Degradate I.
Its identity remains unknown, but because of its very low concentration, it probably has no role in nephrotoxicity.
The role of Metabolites III and IV may be more important.
They were identified as cysteine adducts that are generated independent of DHP-I action and Degradate I. Degradate IV results from the conjugation of imipenem with L-cysteine of glutathione; IV gives rise to Degradate III spontaneously.
Upon intravenous injection, all four metabolites can gain entry into renal cortical tissue, but they do not induce nephrotoxicity at levels where imipenem causes renal damage. Thus, the metabolites per se are not nephrotoxic.
Since imipenem is secreted when its metabolism is blocked by DHP-I inhibitors, or is so rapidly metabolized in the tubular cell in the absence of inhibitor, it per se cannot be the nephrotoxic agent.

The agent responsible for the nephrotoxicity of imipenem when administered alone has yet to be identified.
What is clear at this point is that cilastatin sodium prevents the nephrotoxcity of imipenem in animal models by excluding the antibiotic competitively at the secretory site, thereby preventing its entry into the tubular cells, the site of nephrotoxicity.

Physiological Disposition of Radiolabeled Imipenem

The disposition of intact drug and radioactivity was studied in the Rhesus monkey, rabbit, rat, and man following intravenous dosing with radiolabeled imipenem administered separately or in combination with an equal dose of nonradioactive cilastatin sodium. Doses of 5, 10, 20, or 40 mg/kg of either drug entity were given to animals; in humans, the dose was 500 mg of radiolabeled imipenem alone or in combination with 500 mg of cilastatin sodium.

Renal excretion was the major mechanism for the elimination of drug-related material following radiolabeled imipenem (^{35}S or ^{14}C) dosing. Except for the rat, greater than 85% of the radioactive dose was recovered in the urine within six hours in all species.
Cilastatin sodium coadministered did not alter the excretion profiles of radioactivity. Negligible quantities of radioactivity were recovered in the feces.
In man, the urinary recovery of intact imipenem was 20% of the dose when given alone and increased to 70% when cilastatin sodium was coadministered.

The corresponding renal clearance estimates of imipenem were 74 and 182 ml/min.

High pressure liquid chromatographic analysis indicated that greater than 95% of the human urinary radioactivity was associated with intact imipenem and Metabolite I.

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spontaneously from Degradate I.
Its identity remains unknown, but because of its very low concentration, it
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The agent responsible for the nephrotoxicity of imipenem when administered
alone has yet to be identified.
What is clear at this point is that cilastatin sodium prevents the
nephrotoxcity of imipenem in animal models by excluding the antibiotic
competitively at the secretory site, thereby preventi j its entry into the
tubular cells, the site of nephrotoxicity.

Physiological Disposition of Radiolabeled Imipenem

The disposition of intact drug and radioactivity was studied in the Rhesus
monkey, rabbit, rat, and man following intravenous dosing with radiolabeled
imipenem administered separately or in combination with an equal dose of
nonradioactive cilastatin sodium. Doses of 5, 10, 20, or 40 mg/kg of either
drug entity were given to animals; in humans, the dose was 500 mg of
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High pressure liquid chromatographic analysis indicated that greater than 95%
of the human urinary radioactivity was associated with intact imipenem and
Metabolite I.

Combined radiometric and chromatographic analysis further established that greater than 80% of the human urinary radioactivity was Metabolite I when imipenem was given alone, while 70% of the dose was identified as intact imipenem when cilastatin sodium was coadministered.
In the case of the rat, rabbit, and Rhesus monkey, the majority of the urinary radioactivity chromatographed in the same region as imipenem and Metabolite I. Other minor radioactive fractions were observed at retention volumes corresponding to the cysteine adducts.

In all species, the plasma levels of radioactivity disappeared rapidly; in addition, AUCs of plasma radioactivity were similar for a given species when imipenem was given alone or in combination with cilastatin sodium. In man, it was shown that cilastatin sodium coadministration decreased the plasma clearance of intact imipenem by 20%.

In tissue distribution studies with rats, radioactivity derived from imipenem was distributed primarily in the kidneys and the liver. The rapid disappearance profile of radioactivity from these tissues was analogous to the plasma concentration vs time profiles. Analysis of selected tissues for intact imipenem and Metabolite I demonstrated that cilastatin sodium drastically increased the levels of intact imipenem and decreased the Metabolite I levels in these tissues. In general, the disappearance of imipenem and Metabolite I from the tissues paralleled the disappearance of these compounds from the plasma.

Physiological Disposition of Radiolabeled Cilastatin Sodium

The disposition of cilastatin sodium and radioactivity was studied in the Rhesus monkey, rabbit, rat, dog, and man following intravenous dosing with radiolabeled cilastatin sodium administered separately or in combination with an equal dose of nonradioactive imipenem. Doses of 5, 10, or 40 mg/kg of either drug entity were given to animals; in humans, the dose was 250 mg of radiolabeled cilastatin sodium alone or in combination with 250 or 1000 mg of imipenem.

In the monkey, rabbit, and man, renal excretion was the sole mechanism for the elimination of cilastatin sodium drug-related materials; negligible levels of radioactivity were detected in the feces.
Feces excretion of radioactivity was significant in the rat (>40%) and somewhat less in the dog.
Biliary excretion was significant in the rat, and evidence was obtained for enterohepatic recycling.

Imipenem did not alter the excretion of intact cilastatin sodium. The amount excreted into the urine was 15% for the rabbit, 45% for the monkey, and 77% for man, whether or not imipenem was coadministered. For a given species, renal clearances of intact cilastatin sodium are similar between treatments;

the values for the rabbit, monkey, and man are estimated to be 10,30, 180 ml/min, respectively. In man, N-acetyl-cilastatin sodium accounted for 10% of the dose in the presence or absence of imipenem.

Plasma radioactivity levels decreased rapidly in all species; greater than a 100-fold reduction occurred within six hours with or without the coadministration of imipenem.

There was no accumulation of radiolabeled material by rat tissues. Liver, kidney, and small intestine gave the highest tissue-to-plasma ratios. Although the levels were high in the early time periods, the tissue concentrations of radioactivity decreased rapidly, concomitant with the decrease in plasma radioactivity.
Parallel studies conducted following coadministration of unlabeled imipenem resulted in no significant change in the disposition profile of radioactivity.

Imipenem did not alter the renal excretion or plasma clearance of intact cilastatin sodium in any of the species studied. In man, no change was noted in the extent of the N-acetyl conjugate that formed.

HUMAN PHARMACOKINETICS

Human clinical studies have been conducted in healthy volunteers to define the disposition of imipenem and cilastatin when administered separately and when administered as a mixture.

Imipenem - Single-Dose Kinetics: The single-dose pharmacokinetics of imipenem administered alone has been investigated at intravenous doses ranging from 100 mg to 1000 mg in healthy male volunteers. The drug was administered as bolus intravenous injection or as a 20 minute constant rate infusion. These studies also provided the opportunity to evaluate the variability of imipenem urinary excretion between subjects and within subjects on different occasions, as well as the effect of probenecid on imipenem disposition.

The urinary recovery of imipenem varied between individuals from 6% to 38% of the administered dose but remained constant with a subject receiving imipenem on separate occasions. The renal clearance of the drug showed similar variance, ranging from 12.7 to 96.5 ml/min, although for a given individual incremental renal clearance was comparable day-to-day. Plasma clearance, however, was similar to all dosage levels and between subjects averaging between 211 and 238 ml/min. Total area under the plasma concentration time curve (AUC)increased proportionately with dose. Individual plasma clearance and total AUC were also consistent on a day-to-day basis.

It was also noted that human volunteers could be evenly divided between those that excreted less than 16% of an imipenem dose in urine (low excretors) and those that excreted more than 16% of the dose (high excretors).

Based on individual imipenem plasma concentration and urinary excretion data
gathered in these studies, it was shown that the disposition of imipenem was
adequately described by a two compartment open model with elimination
occurring from the central compartment only. On the average the plasma
half-life of imipenem is 1 hour at all dose levels, and the volume of
distribution of the drug is 11 liters.

When an oral 1.0 g dose of probenecid was administered 10 hr and again 1 hr
before an intravenous 250 mg dose of imipenem, the urinary recovery of the
antibiotic decreased from 18.5% to 13.7% of the dose while renal clearance
dropped from 42.5 to 27.8 ml/min. Total AUC increased slightly as plasma
clearance decreased from 226 to 200 ml/min. The plasma half-life remained at
1 hour.

Imipenem - Multiple Dose Kinetics
The multiple dose pharmacokinetics of imipenem were assessed in healthy
volunteers who received 250 mg of imipenem every 8 hours, or 500 mg every 8
hours. All doses were administered as 20-minute constant rate intravenous
infusions.

As noted in the single dose studies, renal clearance varied by as much as a
factor of 3 between individuals but was constant from dose-to-dose for a given
individual. Also, the AUC did not change dose-to-dose for a given individual,
showed little variability between individuals given the same imipenem dose,
and was proportional to the imipenem dose. The plasma clearance of imipenem
was similar from dose-to-dose among individuals and was independent of dose
size. The plasma half-life averaged 1 hour.

In summary, when imipenem is administered alone intavenously at doses ranging
from 100 to 1000 mg to healthy volunteers, plasma concentrations of drug are
proportional to dose. The plasma clearance of imipenem is approximately 220
ml/min and its plasma half-life is 1 hour. The urinary excretion and renal
clearance of imipenem vary considerably between individuals ranging from 6% to
38% of the dose and from 13 to 97 ml/min, respectively. The disposition of
imipenem is adequately described by a two-compartment, open model with
elimination occurring from the central compartment only. Repeated
administration of imipenem every 8 hours does not alter the disposition of the
drug and no accumulation is observed.

Cilastatin Sodium
Single and multiple intravenous doses of cilastatin sodium have been
administered to parallel panels of healthy volunteers. One panel received 25,
100 and 500 mg single intravenous doses and then three 500 mg doses given at 8
hour intervals. The second panel received 50, 250 and 1000 mg single
intravenous doses and then three 100 mg doses given at 8 hour intervals.
Blood and urine samples were collected for 8 hours after the 50, 100 and 250
mg single dose treatment only. Blood samples were collected for 8 hours after
the first and third dose of repeated administration while urine was collected
for 8 hours following the first and second doses, and for 24 hours following
the third dose.

Results showed that, on the average, approximately 70% of the cilastatin dose was recovered in urine within 8 hours of administration be it after a single dose or after repeated administration. Plasma levels appear to increase in proportion to dose, and there was no drug accumulation upon 8 hour administration. The plasma half-life of cilastatin was determined to be approximately 45 minutes.

Primaxin - Single Dose Kinetics

Several studies have been conducted in healthy volunteers to determine the effect of imipenem or cilastatin on the disposition of each other following single intravenous dose administration.

In one study, ^{14}C-imipenem, 500 mg, was administered alone and with an equal dose of cilastatin sodium. In another, ^{14}C-cilastatin sodium, 250 mg, was administered alone and with 250 mg and 1000 mg imipenem. All treatments were administered as 20-minute constant rate intravenous infusions. Study participants (4 subjects each) were evenly split amongst subjects who excrete less than 16% of an imipenem dose (low excretors) in urine when imipenem is administered alone and subjects who excrete more than 16% of an imipenem dose (high excretors) in urine.

As in previous studies, the intravenous administration of imipenem by itself resulted in low urinary recovery (a mean of 13% in low excretors and of 31% in high excretors) and variable urinary recovery (range of 12% to 42%). The individual renal clearance of the drug was also variable (range of 25 to 104 ml/min). Co-administration of an equal dose of cilastatin sodium brought urinary recovery of imipenem to a uniform 70-80% of the dose and renal clearance to approximately 160 ml/min. A slight increase in imipenem AUC, corresponding to about an 11% increase in plasma clearance, was also noted when cilastatin sodium was co-administered.

The disposition of imipenem when given intravenously with cilastatin sodium can also be adequately described by the same pharmacokinetic model previously described for imipenem administered alone.

Pharmacokinetic parameters for imipenem show no effect from the coadministration of cilastatin sodium except for the expected slight decrease in plasma clearance. The plasma half-life of the antibiotic remains 1 hour and the volume of distribution is 11 liters.

For cilastatin, coadministration of an equal or 4 times greater dose of imipenem had no effect on the disposition of cilastatin as observed after administration of cilastatin sodium alone. The urinary recovery of cilastatin averaged 77% of the dose while renal clearance average 148 ml/min. A two compartment open model also adequately describes cilastatin disposition following administration of cilastatin sodium alone or with imipenem. Regardless of the amount of imipenem coadministered, pharmacokinetic parameters for cilastatin remain unaffected. The plasma clearance of cilastatin was 195 ml/min, its plasma half-life was about 1 hour, and the volume of distribution was 9 liters. For all cilastatin parameters mentioned, little, if any, differences were noted between low and high imipenem excretors.

Two other studies have been conducted in healthy volunteers in which 250, 500 or 1000 mg doses of imipenem were administered alone or with various cilastatin doses ranging from 12.5 mg to 1000 mg. As noted in other studies, the urinary recovery of imipenem when administered alone was low averaging 13% of the dose in low imipenem excretors and 31% of the dose in high imipenem excretors. Variability in the renal clearance of the drug amongst subjects was also noted. However, once the imipenem/cilastatin dose ratio is 4:1 or less, the urinary recovery of imipenem stabilizes at approximately 70% of the dose for all subjects, and renal clearance of the drug is maintained at 130-140 ml/min. At imipenem/cilastatin dose ratios greater than 4:1, the urinary recovery and renal clearance of imipenem decrease, and the low and high excretor differences become apparent.

The plasma clearance of imipenem averaged approximately 220-240 ml/min when no cilastatin was coadministered and decreased slightly to approximately 190 ml/min at imipenem/cilastatin dose ratios of 4:1 or less. Total AUC for imipenem increased commensurately with this decrease in plasma clearance. The plasma half-life for imipenem was 1.0 hour regardless of the cilastatin dose.

At the higher cilastatin dose levels (250 mg and over), the plasma clearance of the inhibitor averaged 190-210 ml/min and appeared unaffected by coadministration of varying doses of imipenem. Total AUC increased in proportion to dose and the plasma half-life for cilastatin was generally about 1 hour. Varying the imipenem/cilastatin dose ratio from 4:1 to 1:4 had no effect on the disposition of cilastatin. The volume of distribution of cilastatin was 8-11 liters in all treatments.

In summary, the disposition of imipenem or cilastatin is independent of dose and is not affected by their coadministration. Cilastatin sodium inhibits the renal metabolism of the antibiotic. At the recommended ratio of 1:1, the plasma clearance of each drug is approximately 200 ml/min and the plasma half-life is nearly 1 hour. Renal clearance of imipenem is about 130 ml/min while that of cilastatin is about 150 ml/min.

Primaxin - Multiple Dose Kinetics

The multiple dose kinetics of imipenem and cilastatin have been studied in healthy volunteers following repeated administration of imipenem/cilastatin given every 6 hours.

At a dose of 1000 mg of each drug, the mean urinary recovery of imipenem was approximately 60% of the dose and renal clearance averaged 130 ml/min for 6 hours after the 1st, 17th, and 37th dose. The urinary excretion of cilastatin averaged 70% of the dose, and mean renal clearance was 143 ml/min after the 1st dose. Stabilized urine samples for cilastatin assay were not available after the 17th and 37th doses.

The plasma clearance of imipenem averaged approximately 210 ml/min in this study. The plasma half-life of imipenem throughout the study was approximately 1 hour. Little, if any, accumulation of imipenem was noted.

For cilastatin, plasma clearance averaged approximately 222 ml/min during all blood sampling periods. The plasma half-life of cilastatin was slightly less than 1 hour throughout the study. No accumulation of cilastatin was observed.

The results of two other studies, wherein 250/250 mg or 500/500 mg of imipenem/cilastatin was administered, confirmed the above findings.

In summary, repeated administration of 250/250 mg, 500/500 mg, or 1000/1000 mg of imipenem/cilastatin sodium every 6 hours does not affect the disposition of either drug. Little, if any, accumulation of either imipenem or cilastatin occurs, and pharmacokinetic parameters suggest that steady state is attained within the first day's dosing for either drug.

Special Studies

A. <u>Effect of Probenecid</u>: The effect of concomitant administration of probenecid on the plasma concentration and urinary excretion of imipenem and cilastatin was evaluated in healthy volunteers. Subjects received 500 mg imipenem alone (I.V. over 20 minutes), 500/500 mg imipenem/cilastatin (I.V. over 20 minutes), and 500/500 mg imipenem/cilastatin (I.V. over 20 minutes) preceded by two 1 gram oral doses of probenecid (1 gram 10 hours and 1 gram 1 hour prior to imipenem/cilastatin infusion). Inulin clearance was used to estimate the glomerular filtration rate (GFR).

The urinary excretion of imipenem averaged 12% and 32% of the dose in low and high imipenem excretors, respectively, when the antibiotic was administered alone. The renal clearance averaged 30 and 67 ml/min, respectively, in these two groups. The plasma clearance averaged approximately 230 ml/min, the volume of distribution averaged 10-11 liters, and the plasma half-life was 0.9 hour.

The coadministration of cilastatin increased the urinary recovery of imipenem to 66% of the dose and the renal clearance to 125 ml/min in all individuals. The plasma clearance decreased to 185 ml/min, and a concomitant increase in total AUC was observed. The volume of distribution and the plasma half-life of imipenem were not affected.

The concomitant administration of imipenem/cilastatin sodium and probenecid caused a decrease in the urinary recovery and renal clearance of imipenem to 55% of the dose and 88 ml/min, respectively. The plasma clearance of imipenem decreased to 159 ml/min resulting in a 16% increase in total AUC. The volume of distribution of imipenem remained 9 liters, and the plasma half-life was 1.1 hour.

The urinary recovery of cilastatin following I.V. administration of imipenem/cilastatin averaged 75% of the dose. Renal clearance was 173 ml/min. No difference was noted between low and high imipenem excretors. The plasma clearance averaged 218 ml/min, the volume of distribution was 9 liters, and the plasma half-life was 0.8 hour.

Addition of probenecid did not change the urinary recovery of cilastatin although the rate of excretion decreased as evidenced by a reduction in cilastatin renal clearance to 70 ml/min. Plasma clearance decreased to 89 ml/min resulting in a doubling of the total AUC and plasma half-life of cilastatin.

On the basis of individual determinations of GFR and that imipenem is 20% protein bound, it was shown that the net effect of renal tubular secretion and reabsorption of imipenem represents about 35% of imipenem renal clearance and that probenecid reduces this component to less than 10% of renal clearance.
Assuming that cilastatin completely inhibits the renal metabolism of imipenem, there still remains a non-renal component of imipenem elimination that represents 30-35% of imipenem plasma clearance. The contribution of this non-renal component increases to 45% of plasma clearance when probenecid is coadministered resulting in a decrease in the urinary recovery of imipenem. The effect of probenecid on the disposition of imipenem is minimal in comparison to the effect noted on other beta-lactam antibiotics.

The effect of probenecid on the disposition of cilastatin was more pronounced since renal clearance decreased from 173 to 70 ml/min. and plasma clearance decreased from 218 to 89 ml/min. As a result, the plasma AUC and the half-life of cilastatin doubled. Examination of the difference between plasma and renal clearance in both treatment situations revealed that the so-called "extra-renal" portion of cilastatin elimination decreased by a factor of 2.4 in the presence of probenecid. The parallel decrease in cilastatin plasma and renal clearance, as well as the 2.4 fold drop in the "extra renal" elimination of cilastatin indicate that not only is probenecid blocking the renal tubular secretion of cilastatin, but that this exclusion reduces the metabolic elimination of the drug. Hence, the "extra-renal" elimination of cilastatin appears to result from metabolism in the kidney and to be associated primarily with the secretory component of cilastatin excretion.

B. Effect of Renal Insufficiency: The effect of renal insufficiency has been studied in patients with varying degrees of renal insufficiency. Subjects received imipenem or cilastatin sodium (250 mg) alone and imipenem/cilastatin (250/250 mg). Only the results from the imipenem/cilastatin treatment will be discussed since these are data representative of the clinical dosage form.

In patients with mild renal impairment (31 ml/min/1.73 m^2 < GFR ≤ 99 ml/min/1.73 m^2), the urinary recovery of imipenem averaged 44% of the dose and the mean renal clearance of the drug was 62 ml/min. The plasma clearance of imipenem dicreased to 147 ml/min, and the plasma half-life increased to 1.8 hours.

Mean urinary recovery decreased to 17% of the dose, and renal clearance of imipenem decreased to 15 ml/min in patients with moderate renal insufficiently (10 ml/min/. ^{7n} m^{2} $\leq$ GFR $\leq$ 30 ml/min/1.73 m^{2}). The plasma clearance of the $^{\prime}$r ..ped to 83 ml/min, while the plasma half-life increased to 2   .

For patients requiring he..odialysis who received imipenem/cilastatin between dialysis sessions, 2.9% of the imipenem dose was excreted in urine and the renal clearance of the drug was 1.6 ml/min. The plasma clearance averaged 62 ml/min and its plasma half-life increased to 3.4 hours.

In comparison to healthy volunteers, total AUC increased by a factor of 1.7 in patients with mild renal impairment, by a factor of 2.8 in patients with moderate impairment, and by a factor of 3.6 in patients requiring hemodialysis.

Hemodialysis removes imirenem from plasma bringing the plasma half-life of the drug back to 1-2 hours and plasma clearance to 184 ml/min.

The effect of renal impairment on the plasma levels and urinary excretion of cilastatin is more dramatic than that observed for imipenem. In patients with mild renal impairment, 65% of the cilastatin dose was recovered in urine, and renal clearance averaged 62 ml/min. The plasma clearance of cilastatin in the.. patients was slightly less than 100 ml/min, and the plasma half-life of the drug was 1.5 hours.

In patients with moderate renal impairment, mean urinary recovery of cilastatin decreased to 48% of the dose, and renal clearance decreased to 18 ml/min. The plasma clearance of the drug decreased to 36 ml/min, while the plasma half-life increased to approximately 4 hours.

For patients requiring hemodialysis who received imipenem/cilastatin between dialysis sessions, the urinary recovery of cilastatin averaged 18% of the dose, and its renal clearance was 2 ml/min. The plasma clearance of cilastatin was low in these patients, averaging 13 ml/min, and the plasma half-life increased to 12 hours.

In comparison to healthy volunteers, total AUC increased by a factor of approximately 2 in patients with mild renal impairment, by a factor of 6.5 in patients with moderate renal impairment, and by a factor of 15-16 in patients requiring hemodialysis.

The 15-fold decrease in cilastatin plasma clearance and resultant similar increase in total AUC between healthy volunteers and patients requiring hemodialysis strongly suggests that the extra-renal elimination of cilastatin results from kidney metabolism. This portion of cilastatin total elimination decreases as kidney function declines.

Cilastatin is cleared from blood by hemodialysis producing an increase in plasma clearance to 75 ml/min and reducing the plasma half-life of the drug to 2-3 hours.

The results of these studies show that the elimination of imipenem and cilastatin decreases as the degree of renal impairment advances. Cilastatin is affected to a greater extent in this respect than is imipenem. The increased plasma levels of either entity noted in patients requiring hemodialysis would certainly be tempered by their undergoing periodic hemod lysis.

Based on the information derived from these studies, it is recommended that the daily dosage of Primaxin be cut in half either by reducing the dose of the drug given every 6 hours or by administering the drug every 12 hours. Monitoring of imipenem and cilastatin plasma levels is indicated to establish the proper regimen.

Conclusions:
1. Whether administered separately or together in man, imipenem and cilastatin are excreted exclusively in the urine.
2. When administered alone to man, imipenem urinary recovery and renal clearance are low and variable between subjects because of metabolism of the drug within the kidney primarily to the opened lactam.
3. At the recommended dosage ratio of 1:1, cilastatin inhibits the renal metabolism and alleviates the nephrotoxic potential of imipenem. The renal clearance of the antibiotic is 70% of the plasma clearance (195 ml/min).
4. Cilastatin is apparently metabolized by the kidneys, the principal metabolite being N-acetyl cilastatin. Seventy percent of an I.V. dose is recovered unchanged in urine. Imipenem has no effect on cilastatin disposition.
5. The disposition of either imipenem or cilastatin is not dose dependent. The plasma half-life of each drug is approximately 1 hour.
6. Probenecid coadministered with Primaxin has minimal effect on the disposition of imipenem.
7. Little, if any, accumulation of either drug is observed for Primaxin regimens given every 6 to 8 hours to patients with normal and mildly impaired renal function.
8. Decreasing renal function slows the elimination of imipenem and cilastatin. The effect is more notable for cilastatin. Primaxin dosage adjustment is indicated when creatinine clearance is $\leq$ 30 ml/min. Hemodialysis is relatively efficient in removing both imipenem and cilastatin from blood.

Imipenem Levels in Human Body Fluids and Tissues

Imipenem Levels in Aqueous Humor After 1 GM Dose

Investigator: Dr. Azelrod

No. of Patients: 13

Time after Dose	Serum	Aqueous Humor (mcg/ml)
25 minutes	95.2	3.60
30 minutes	73.5	1.44
30 minutes	73.2	4.00
30 minutes	68.3	1.83
1 hour	39.2	1.80
1.5 hours	36.0	5.88
2 hours	56.5	2.40
2 hours	13.5	3.90
2 hours 15 minutes	17.1	2.40
3 hours 45 minutes	20.8	1.92
4 hours	6.1	1.14
5 hours 30 minutes	9.6	2.92
6 hours 30 minutes	12.2	0.5

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30 minutes	73.5	1.44
30 minutes	73.2	4.00
30 minutes	68.3	1.83
1 hour	39.2	1.80
1.5 hours	36.0	5.88
2 hours	56.5	2.40
2 hours	13.5	3.90
2 hours 15 minutes	17.1	2.40
3 hours 45 minutes	20.8	1.92
4 hours	6.1	1.14
5 hours 30 minutes	9.6	2.92
6 hours 30 minutes	12.2	0.5

Tissue and Fluid Levels from Randomly Selected Patients
(Dr. McGregor's Phase III study)

Tissue or Fluid	No. of Patients	Dose	Time After Dose	Levels (mcg/ml)
Saliva	6	1 g	15 minutes	0.3
		500 mg	15 minutes	0.3
		1 g	15 minutes	0.6
		500 mg	20 minutes	0.3
		500 mg	1 hour	0.3
		1 g	20 minutes	< 0.3*
Sputum	5 (10 samples)	1 g	30 minutes	2.5
			60 minutes	2.1
			2 hours	0.88
			4 hours	0.96
			—	4.3
			—	2.6
			—	6.0
			—	3.4
			—	4.2
			—	10.4
Bile	1	1 g	30 minutes	2.5
Pleural Fluid	1	1 g	1 hour	22.0
Ileal Fluid	2	500 mg	6 hr collection	< 0.3*
Nasal Gastric Aspirate	3	1 g	30 minutes	< 0.3*
			15 minutes	< 0.3
			30 minutes	< 0.3
Gastric Aspirate	1 (2 samples)	500 mg	15 minutes	0.6
			1.5 hours	1.7
Abdominal Drain	1	500 mg	2 hours	9.8
Peritoneal Fluid	1	1 g	30 minutes	3.9

Tissue or Fluid	No. of Patients	Dose	Time After Dose	Levels (mcg/g)
Bone	6 (9 samples)	1 g 6 h	—	0.52
		1 g 6 h	—	4.05
		1 g 6 h	—	1.5
		1 g	10 minutes	0.42
		1 g	1.5 hours	2.5
		1 g	25 minutes	5.4
		1 g	20 minutes	3.9
		1 g	—	1.6
		1 g	—	1.3

*Undetectable

Imipenem Tissue Levels in Female Reproductive Organs

Investigator: Rudolph Galask, M.D.

This investigation is in progress.
Results obtained in three patients who completed the study were as follows:

Dose	Time after Dose	Tissue Level (mcg/g)	
500 mg	5 hours, 15 minutes	Ovary	- 5.1
		Fallopian tube	- 0.3
		Myometrium	- 0.2
		Endometrium	- 0.2
500 mg	3 hours, 45 minutes	Ovary	- 0.7
		Fallopian tube	- 0.9
		Myometrium	- 0.3
		Endometrium	- 0.9
1.0 g	2 hours, 30 minutes	Ovary	- 3.8
		Fallopian tube	- 5.1
		Myometrium	- 4.2
		Endometrium	- 4.2

Penetration of Primaxin (imipenen and cilastatin) Into Human Cerebrospinal Fluid

Investigator: R. J. Duma, M.D., Medical College of Virginia and McGuire Veteran Administration Hospital, Richmond, Virginia.

Cerebrospinal fluid penetration of Primaxin was studied in 33 adult patients; 22 had normal CSF, and 11 had inflamed meninges. Patients received a single intravenous infusion of 1 g over 30 minutes. Serum and CSF levels of imipenem and cilastatin were measured both by bioassay and by high pressure liquid chromatography. Data obtained at 1, 2, 4, 6, and 8 hours were pooled for ar lysis.

Results were as follows:

Part A: Uninflamed meninges (22 patients)

Mean Time After Dose (Hours)	Mean Serum Concentration (mcg/ml)		Mean CSF Concentration (mcg/ml)	
	Imipinem	Cilastatin	Imipinem	Cilastatin
1.2	28.7	28.2	0.62	< 0.25
2.2	23.7	25.7	0.73	0.32
4.2	4.8	3.7	0.90	0.37
6.2	2.0	< 2.0	0.88	1.70
8.1	2.7	2.4	0.78	0.59

Part B: Inflamed meninges (11 patients)

1.3	26.5	25.0	1.60	0.42
1.8	14.0	12.4	2.30	1.30
4.3	3.2	3.7	.39	0.61
6.6	1.6	< 2.0	1.10	0.83

In patients with uninflamed meninges, levels of imipenem in CSF peaked at 4 to 6 hours and appeared to plateau for at least 8 hours (despite 8 hour concentrations more than twice those of CSF, suggesting saturation kinetics). Calculated percent penetration by areas under the curve over 4 hours was 2.2. CSF levels of imipenim were higher in patients with inflamed meninges than in those with uninflamed meninges. In serum, cilastatin levels usually equaled imipenem levels, but in CSF cilastatin levels usually were lower than imipenem levels.

Penetration of Primaxin Into Interstitial Fluid
Investigator: Dr. Tan
No of Patients: 12
Dose: 1 g I.V. over 30 minutes

Hour	Serum	Skin Window Fluid (intermittent)	Skin Window Fluid (Continuous)
0.5	64.0	6.8	1.3*
1.0	37.8	16.1	7.1*
1.5	19.2	9.7	12.0
2.0	10.6	5.8	13.3
3.0	6.2	5.1	10.8
4.0	2.8	2.5	8.6
5.0	-	1.2	5.8
6.0	0.8	0.6	3.7
AUC	79.05	29.8	48

*Dr. Tan could not explain the discrepancy between continuous and intermittent during the 0.5 and 1 hour samples.

Imipenem Levels in CSF in Compassionate Treatment of Meningitis Cases (Assayed by MSDRL)

Patient	Treatment Day	Time of Dose / Dose	Sample Time	Imipenem (mcg/ml) CSF	Serum	Cilastin (mcg/ml) CSF	Serum
1	3	3:45 p.m. 500 mg q 8 h	3:15 p.m.	0.6	0.3	0.10	0.24
			4:30 p.m.	0.3	15.4	–	17.24
			5:30 p.m.	2.2	5.2	0.74	4.25
			6:30 p.m.	2.0	1.1	0.80	0.43
	5	10.00 a.m. 500 mg q 8 h	9:30 a.m.	0.9	0.3	0.80	0.34
			11.15 a.m.	0.8	26.6	0.92	27.3
			12.15 p.m.	0.6	7.5	0.53	7.43
			1.15 p.m.	0.6	3.4	–	2.54
	8 (day 1 of higher dose)	1 g q 8 h	trough	–	0.3	–	0.43
			1 hr post dose	2.6	21.7	0.22	32.31
			2 hr post dose	4.1	7.0	0.45	8.16
			3 hr post dose	–	2.4	–	1.37
	10	1 g q 8 h	trough	0.5	0.4	1.04	0.43
			1 hr post dose	1.0	16.7	–	27.03
			2 hr post dose	–	–		7.32
			3 hr post dose	–	14.6		15.53
	12	1 g q 8 h	trough	0.5	–	0.91	0.27
			1 hr post dose	1.2	25.4	0.98	–
			2 hr post dose	–	5.4	–	2.89
			3 hr post dose	–	3.1	0.35	1.14
	17	1 g q 8 h	trough	0.4	0.4	0.56	0.24
			1 hr post dose	3.3	28.8	1.14	35.04
			2 hr post dose	–	–	–	–
			3 hr post dose	1.8	1.9	1.12	0.91
2	7	1 g q 6 h	trough	–	0.8	–	0.93
			15 min p-dose	–	33.2	.	69.91
			5 h p-dose	3.7	16.9	3.	21.53
	14	1 g q 8 h	trough	–	0.3	–	0.22
			15 min p-dose	–	31.8		47.08
			2 h p-dose	2.6	15.5	2.26	25.41
3	–	1 g q 6 h	trough	–	0.9	–	0.51
			peak	–	27.8	–	29.11
			5 h p-dose	3.7	–	4.02	–

Clinical Studies (Domestic)

I. Controlled (3 studies)

    1. Protocol No. 001

        Title: "A Multicenter Study of the Comparative Efficacvy, Safety and
        Tolerance of Primaxin (imipenem/cilastatir sodium) and of Cefazolin in
        the Parenteral Therapy of Infections in Hospitalized Patients Caused
        by Susceptible Pathogenic Bacteria."

        Study Design: This was an open, randomized, controlled trial
        conducted in 11 medical centers across the United States.
        Hospitalized patients were considered for admission into the study if
        they exhibited strong presumptive evidence of bacterial infection. If
        the patient agreed to enter the study, an informed consent form was
        signed by the patient or by the patient's representative.

        Procedure: The study was conducted in the following manner: Each
        patient was assigned to the Primaxin or cefazolin treatment group
        based on a randomized schedule prepared by MSDRL.
        Each patient in the Primaxin group received 250 mg intravenously every
        6 hours, infused over a 5 to 15 minute period. Each patient in the
        cefazolin group received 1 g intravenously every 6 hours, infused over
        a 5 to 15 minute period.

        The patients were to be treated from 5 to 14 days based on the
        progress of their infection.
        Cultures from the site of the infection were collected from each
        patient pre, during, and post therapy to determine the efficacy of the
        treatment. Disk and MIC determinations were done for all isolated
        pathogens. Patients were carefully observed for any local or systemic
        adverse experiences.

        Laboratory tests including hematology, blood chemistries, and
        urinalysis were obtained prior to, during, and after the study drug
        therapy.

        At the conclusion of drug therapy, and after all clinical and
        laboratory data had been obtained, judgement was made by the
        investigator of the safety, tolerability, and clinical and
        bacteriologic efficacy of the study drug therapy for each patient.

        Response to treatment was assessed by both clinical and
        bacteriological outcomes.
        Favorable clinical outcomes included:

            -Cure (Investigators judgment that the signs and symptoms of the
            infection were resolved).
            -Improvement (Investigators judgment that the infection was
            brought under control, and the need for further intravenous
            therapy was not indicated).

Unfavorable clinical outcome included:

-No improvement
-Patients died of infection primarily (with or without a contributing background disease).

Favorable bacteriological outcome:

-Eradication of the etiologic pathogen(s)

Unfavorable bacteriological outcome:

-Suppression of the etiologic pathogen(s)
-Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse reactions. When an abnormal laboratory result or clinical event was noted, the investigator was required to render a judgment as to the intensity and seriousness of the occurrence and its relationship to the drug. They were also required to indicate the outcome and the type of action taken with regard to the adverse effect.

The following 11 investigators treated patients under Protocol No. 001:

	Number of Patients	
Investigators	Primaxin	Cefazolin
Richard E. Bryant, M.D. University of Oregon Health Science Center	3	2
Gordon M. Dickinson, M.D. University of Miami School of Medicine	28	27
Charles D. Ericsson, M.D. University of Texas Medical School	8	8
Robert J. Fass, M.D. Ohio State University Hospitals	14	16
Robert Fekety, M.D. University of Michigan Hospitals	1	-
Earl H. Freimer, M.D. Medical College of Ohio	12	12
John Leedom, M.D. University of Southern California School of Medicine	15	14
Robert L. Marier, M.D. L.S.U. Medical School	43	42
Richard V. McCloskey, M.D. Albert Einstein Medical Center Daroff Division	23	23

(Continued)

	Number of Patients	
Investigators	Primaxin	Cefazolin
John Mills, M.D.	7	8
San Francisco General Hospital		
Emmanuel Wolinsky, M.D.	7	6
Cleveland Metropolitan General Hospital		
TOTAL 11 STUDIES	161	158

Overall Summary of Studies Conducted Under Protocol No. 001

	Primaxin	Cefazolin
Total No. of Patients	161	158
Age Range (yrs)	17 - 83	16 - 84
Sex		
Male	99	90
Female	62	68

Evaluation

Efficacy

	Primaxin	Cefazolin
No. of Cases Evaluable	104	98
No. of Sites of Infection Evaluable	115	101
No. of Cases Unevaluable	57	60

Reasons Cases Unevaluable		
No pre-treatment pathogen	30	25
Effective concomitant antibiotic	0	5
Treatment course too short	17	16
Inadequate cultures	9	11
Patient lost to follow-up	1	0
Organism resistant to study drug	0	3

	Primaxin	Cefazolin
DOSE (Evaluable Cases)	250 mg q 6 h	1 g q 6 h
	(1 pt. received 2g/day)	

DURATION OF TREATMENT (days)
(Evaluable Cases)

	Primaxin	Cefazolin
5 14	93 patients	94 patients
14	11 patients	4 patients

(Continued)

	Number of Patients	
Investigators	Primaxin	Cefazolin
John Mills, M.D.	7	8
San Francisco General Hospital		
Emmanuel Wolinsky, M.D.	7	6
Cleveland Metropolitan General Hospital		
TOTAL 11 STUDIES	161	158

Overall Summary of Studies Conducted Under Protocol No. 001

	Primaxin	Cefazolin
Total No. of Patients	161	158
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Sex		
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Evaluation

Efficacy

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Reasons Cases Unevaluable		
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Effective concomitant antibiotic	0	5
Treatment course too short	17	16
Inadequate cultures	9	11
Patient lost to follow-up	1	0
Organism resistant to study drug	0	3

	Primaxin	Cefazolin
DOSE (Evaluable Cases)	250 mg q 6 h	1 g q 6 h
	(1 pt. received 2g/day)	

DURATION OF TREATMENT (days)
   (Evaluable Cases)

	Primaxin	Cefazolin
5 - 14	93 patients	94 patients
> 14	11 patients	4 patients

RESULTS

| | | PRIMAXIN | | | | CEFAZOLIN | | |
| | | CLINICAL RESPONSE | | | | CLINICAL RESPONSE | | |
INFECTION	NO.	CURE	IMP.	FAIL	NO.	CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, cell- ulitis, carbuncle/furuncle pyoderma, infected ulcers)	68	48(71%)	17(25%)	3(4%)	70	48(68%)	20(28%)	2(3%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5	2(40%)	3(60%)		4	2(50%)	2(50%)	
LOWER RESPIRATORY (Pneumonia, lung abscess, bronchiolitis)	14	9(64%)	4(29%)	1(7%)	15	11(73%)	4(27%)	
GYNECOLOGIC (Pelvic cellulitis)	1		1 (100%)		–			
SEPTICEMIA	16	14(88%)	2(12%)		5	4(80%)	1(20%)	
ENDOCARDITIS	1	1(100%)			–			
UTI (Uncomplicated) (Pyelonephritis)	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated)	3	2(67%)		1(33%)	2	2(100%)		

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CEFAZOLIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, cell- ulitis, carbuncle/furuncle pyoderma, infected ulcers)	68	48(71%)	17(25%)	3(4%)	70	48(68%)	20(28%)	2(3%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5	2(40%)	3(60%)		4	2(50%)	2(50%)	
LOWER RESPIRATORY (Pneumonia, lung abscess, bronchiolitis)	14	9(64%)	4(29%)	1(7%)	15	11(73%)	4(27%)	
GYNECOLOGIC (Pelvic cellulitis)	1		1 (100%)		-			
SEPTICEMIA	16	14(88%)	2(12%)		5	4(80%)	1(20%)	
ENDOCARDITIS	1	1(100%)			-			
UTI (Uncomplicated) (Pyelonephritis)	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated)	3	2(67%)		1(33%)	2	2(100%)		

INFECTION SKIN AND SKIN STRUCTURE	PRIMAXIN BACTERIOLOGICAL RESPONSE				CEFAZOLIN BACTERIOLOGIAL RESPONSE			
	NO.	ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	ERAD[1]	SUPP[2]	NOT ERAD
S. aureus(S)*	6	4(67%)	1(17%)	1(17%)	3	3(100%)		
S. aureus(R)**	34	31(91%)	1(3%)	2(6%)	39	34(87%)	3(8%)	2(5%)
S. epidermidis	7	6(86%)	1(14%)		2	2(100%)		
Beta-hem-Strep (Group A)	20	18(90%)	2(8%)		29	29(100%)		
Alpha-hem-Strep	3	3(100%)			1	1(100%)		
Other strepto- coccus species	10	8 (80%)		2 (20%)	11	11 (100%)		
Group B Strep.	5	4(80%)		1(20%)				
Group D Strep (enterococcus)	7	7(100%)			3	3(100%)		
Aeromonas hydrophilia	1	1(100%)			1	1(100%)		
Alcaligenes spp.	1	1(100%)			-			
C. freundii	2	2(100%)			1	1(100%)		
Eikenella corrodens	1	1(100%)			1	1(100%)		
E. aerogenes	1	1(100%)			-			
E. cloacae	2	2(100%)			1	1(100%)		
E. coli	6	5(83%)		1(17%)	3	2(67%)	1(33%)	
K. pneumoniae	2	2(100%)			1		1(100%)	
K. oxytoca	3	3(100%)			2	1(50%)		1(50%)
M. morganii	2	1(50%)		1(50%)	-			
P. multocida	1	1(100%)			-			
P. mirabilis	4	4(100%)			2	1(50%)	1(50%)	
P. rettgeri	2	2(100%)			-			
Providencia stuartii	1	1(100%)			-			
P. aeruginosa	2	2(100%)			-			
S. marcescens	1	1(100%)			-			
Vibrio parahemolyticus	1	1(100%)			1	1(100%)		
Lactobacillus spp	1	1(100%)			-			
B. fragilis	5	5(100%)			1	1(100%)		
B. melaninogenicus	3	3(100%)			3	3(100%)		
B. bivius	1	1(100%)			-			
Peptococcus spp	1	1(100%)			5	5(100%)		
Peptostreptococcus spp	1	1(100%)			-			
Fusobacterium spp	1	1(100%)			2	2(100%)		
A. eriksonii	1	1(100%)			-			
Clostridium spp	-				3	3(100%)		
Bacteroides spp	-				6	6(100%)		

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	CEFAZOLIN BACTERIOLOGICAL RESPONSE ERAD[1]	SUPP[2]	NOT ERAD[3]
BONE/JOINT								
S. aureus[(R)]	2	2(100%)			2	2(100%)		
Beta-hem-Strep								
(Group A)	2	2(100%)			1	1(100%)		
Streptococcus spp	1	1(100%)			1	1(100%)		
E. coli	1	1(100%)			--			
P. aeruginosa	1			1(100%)	-			
S. marcescens	1			1(100%)	-			
B. melaninogenicus					1	1(100%)		
Enterobacter								
cloacae	-				1	1(100%)		
P. mirabilis	-				1	1(100%)		
LOWER RESPIRATORY								
S. aureus [(S)]	1	1(100%)			-			
S. pneumoniae	8	8(100%)			11	11(100%)		
H. influenzae	4	3(75%)		1(25%)	6	5(83%)		1(17%)
H. parainfluenzae	1	1(100%)			-			
E. cloacae	1	1(100%)			-			
P. aeruginosa	1			1(100%)	-			
Klebsiella ozaenae	-				1		1 (100%)	
GYNECOLOGIC								
Streptococcus spp	1	1(100%)			-			
E. coli	1	1(100%)			-			
Peptostreptococcus								
spp	1	1(100%)			-			
Bacteroides spp	1	1(100%)			-			
SEPTICEMIA								
S. aureus [(R)]	3	3(100%)			-			
S. aureus [(S)]	1	1(100%)			-			
Streptococcus spp	1	1(100%)			-			
S. epidermidis	3	3(100%)			1	1(100%)		
S. pneumoniae	4	4(100%)			3	3(100%)		
Beta-hem-Strep								
(Group A)	1	1(100%)			-			
Group D Strep								
(enterococcus)	1	1(100%)			-			
Micrococcus	1	1(100%)			-			
C. diversus	1	1(100%)			-			
Bacillus subtilis	1	1(100%)			-			
E. coli	-				1	1(100%)		
ENDOCARDITIS								
S. aureus (R)	1	1(100%)			-			

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE				CEFAZOLIN BACTERIOLOGIAL RESPONSE		
		ERAD[1]	SUPP[2]	NOT ERAD[3]	NO.	ERAD[1]	SUPP[2]	NOT ERAD[3]
UTI (Uncomplicated)								
E. coli	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated)								
E. coli	2	2(100%)			2	2(100%)		
C. diversus	1			1(100%)	-			

   *(S) = Sensitive to penicillin
   **(R) = Resistant to penicillin
   1 = Eradicated
   2 = Suppressed
   3 = Not eradicated

In the Primaxin treatment group, one patient with pneumonia developed a superinfection with a resistant P. aeruginosa. In the cefazolin treatment group, 2 patients with pneumonia and 2 wtih urinary tract infection developed superinfections.

SAFETY

	Primaxin	Cefazolin
Total No. of Patients	161	158
No. of Patients with Systemic Side Effects	9(6%)	8(5%)
No. of Patients with Local Side Effects	10(6%)	5(3%)

LOCAL SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Pain at I.V.site	1(0.6%)		1(0.6%)		
Vein infection	1(0.6%)	1(0.6%)			
Phlebitis/thrombo- phlebitis	8(5.0%)	2(1.2%)	5(3.1%)	1(0.6%)	

CEFAZOLIN

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Pain at I.V. site	1(0.6%)	1(0.6%)			
Vein infection	1(0.6%)		1(0.6%)		
Phlebitis/thrombo- phlebitis	3(1.9%)	1(0.6%)	2(1.3%)		

(Continued)

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
SYSTEMIC SIDE EFFECTS			PRIMAXIN		
Vomiting	2(1.2%)		1(0.6%)		1(0.6%)
Diarrhea	1(0.6%)	1(0.6%)			
Pruritus	1(0.6%)			1(0.6%)	
Rash	1(0.6%)	1(0.6%)			
Dizziness	1(0.6%)				1(0.6%)
Apnea	1(0.6%)	1(0.6%)			
Chest pain/cough	1(0.6%)	1(0.6%)			
Hyperventilation	1(0.6%)				1(0.6%)
Paresthesia	1(0.6%)				1(0.6%)
Weakness	1(0.6%)				1(0.6%)
Thoracic spine pain	1(0.6%)				1(0.6%)
			CEFAZOLIN		
Diarrhea	1(0.6%)	1(0.6%)			
Pruritus	1(0.6%)				1(0.6%)
Rash	1(0.6%)		1(0.6%)		
Fever	1(0.6%)		1(0.6%)		
Asthenia	1(0.6%)		1(0.6%)		
Megacolon	1(0.6%)		1(0.6%)		
Vaginal candidiasis	2(1.3%)			2(1.3%)	

Deaths: There were two deaths in each treatment group. None was considered to be related to the study drug.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFAZOLIN
Hemoglobin	(D) 7	(D) 7
Hematocrit	(D) 5	(D) 7
WBC	(D) 3	(D) 2
Neutrophils	(D) 4	(D) 2
Eosinophils	(I) 2	(I) 4
Monocytes	(I) 3	0
Lymphocytes	(I) 2	(I) 1
Platelets	(I) 2	(D) 1 (I) 3
Positive Coombs' Test	1	1
Glucose	(I) 2	(I) 1
BUN	(I) 3	(I) 1
Creatinine	(I) 3	(I) 1
Uric acid	0	(I) 1
SGOT (AST)	(I) 13	(I) 4
SGPT (ALT)	(I) 14	(I) 3

(Continued)

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFAZOLIN
Bilirubin	(I) 3	(I) 2
Alk. phosphatase	(I) 9	(I) 1
LDH	(I) 5	(I) 1
Serum potassium	0	(I) 1
Urine protein	0	(I) 1
Urine uric acid	0	(I) 1
Urine WBC	(I) 1	(I) 2
Urine RBC	(I) 1	(I) 1
Urine epithelial cells	(I) 1	0

   (D) = Decreased
   (I) = Increased

Summary and Conclusions: This was an open, randomized, controlled multicenter
study comparing Primaxin and cefazolin in the treatment of infections caused
by susceptible bacterial. A total of 161 patients, 99 males and 62 females,
ranging in age from 17 to 83 years were enrolled in the Primaxin group. A
total of 158 patients, 90 males and 68 females, ranging in age from 16 to 84
years were enrolled in the cefazolin group. Demographic characteristics of
patients in each treatment group were similar. One hundred and four patients
with 115 sites of infection in the Primaxin treated group and 98 patients with
101 sites of infection in the cefazolin treated group were acceptable for
evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure of improvement occurred in 109/115 (95%) infections in the
patients in the Primaxin group and in 99/101 (98%) infections in the patients
in the cefazolin group.

A favorable bacteriological outcome (eradication) was achieved in 172 (90%) of
191 organisms isolated in the Primaxin group and in 146 (93%) of the 157
organisms isolated in the cefazolin group.

Systemic side effects were reported in 6% of the patients in the Primaxin
group and in 5% of the patients in the cefazolin group. Local side effects
were reported in 6% of the patients in the Primaxin group and in 3% of the
patients in the cefazolin group.

Laboratory test abnormalities were similar in each treatment group, except for
a higher incidence of abnormal SGOT and SGPT values in the Primaxin group.

The two deaths that occurred in each treatment group were not considered by
the investigators to be related to study drug.

This study demonstrates that Primaxin is as safe and effective as cefazolin in
the treatment of patients with serious infections caused by susceptible
bacteria.

2.   Protocol No. 003
      Title: "A Multiclinic Study of the Comparative Efficacy, Safety, and
      Tolerability of Primaxin (imipenem/cilastatin sodium) and of
      Moxalactam in the Parenteral Therapy of Infections in Hospitalized
      Patients Caused by Susceptible Pathogenic Bacteria."

      Study Design: This was an open, randomized, controlled trial
      conducted in 19 medical centers across the United States.
      Hospitalized patients were considered for admission into the study if
      they exhibited strong presumptive evidence of bacterial infection.
      If the patient agreed to enter the study, an informed consent form
      was signed by the patient or the patient's representative.

      Procedure: The study was conducted in the following manner:
      Each patient was assigned to the Primaxin or moxalactam treatment
      group based on a randomized schedule prepared by MSDRL. Neither the
      investigator nor the patient knew in advance which of the two
      treatments the patient would receive.

      Patients receiving Primaxin were treated with 2 g/day (500 mg every 6
      hours). Patients receiving moxalactam were treated with up to 6
      g/day. Both drugs were given by intravenous infusion. The patients
      were to be treated from 5-14 days based on the progress of their
      infections. The clinical and bacteriological courses of each
      patient's treatment were followed and documented. Culture from the
      site of infection and blood and urine samples were collected from
      each patient pre, during, and post therapy to determine the efficacy
      and safety of the treatment. Disk and/or MIC determinations were
      done for all isolated pathogens and compared to the patients'
      clinical outcome. Daily observations of the tolerability of
      intravenous therapy were made, and patients were carefully observed
      for any adverse clinical or laboratory experiences. At the
      conclusion of drug therapy, and after all clinical and laboratory
      data had been obtained, judgement was made by the investigator of the
      safety, tolerability, and clinical and bacteriologic efficacy of the
      study drug therapy for each patient.

      Response to treatment was assessed by both clinical and
      bacteriological outcomes.

      Favorable clinical outcome included:
            -Cure (Investigator's judgment that the signs and symptoms of
            the infection were resolved).
            -Improvement (Investigator's judgment that the infection was
            under control and that the need for further treatment was not
            indicated).

      Unfavorable clinical outcome included:
            -No improvement
            -Patient died of infection primarily

Favorable bacteriologic outcome:
    -Eradication of the etiologic pathogen(s)

Unfavorable bacteriologic outcome:
    -Suppression of the etiologic pathogen(s)
    -Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse
reactions.

When an abnormal laboratory result or clinical event was noted, the
investigators were required to render a judgment as to the intensity
and seriousness of the occurrence and its relationship to the study
drug. They were also required to indicate the outcome and the type
of action taken with regard to the adverse effect.

The following 19 investigators treated patients under Protocol 003:

| | Number of Patients | |
Investigators	Primaxin	Moxalactam
Alan S. Berkeley, M.D. Cornell Medical Center	18	16
Steven Berman, M.D. Internal Medicine & Infectious Diseases Honolulu, HI	20	20
Arnold W. Cohen, M.D. Albert Einstein Medical Center	5	4
Robert E. Condon, M.D. Medical College of Wisconsin	11	11
Lawrence J. Eron, M.D., F.A.C.P. Infectious Diseases Physicians, Inc. Fairfax, VA	20	20
David A. Eschenbach, M.D. University of Washington Seattle, WA	7	8
Robert J. Fass, M.D. Ohio State University Hospital	22	25
F. Robert Fekety, M.D. University of Michigan Hospital	2	2
Earl H. Freimer, M.D. Medical College of Ohio	11	10

(Continued)

Investigators	Number of Patients	
	Primaxin	Moxalactam
Charles A. Kallick, M.D. Cook County Hospital	4	6
Captain Walter W. Karney, MC, USN National Naval Medical Center	8	10
Richard D. Meyer, M.D. Cedars-Sinai Medical Center	15	16
Burt R. Meyers, M.D. The Mount Sinai Medical Center	3	3
James J. Rahal, Jr., M.D. V.A. Hospital New York, New York	13	12
William M. Rambo, M.D. Charleston Memorial Hospital Charleston, S.C.	21	19
Charles L. Rice, M.D. Michael Reese Hospital and Medical Center Chicago, IL	3	1
Gary L. Simon, M.D. George Washington University	12	13
Larry J. Strausbaugh, M.D. University of Missouri - Columbia Columbia, MD	5	6
Francis P. Tally, M.D. New England Medical Center Hospital Boston, MA	18	21
TOTAL	218	223

Three investigators, Berman, Eron and Freimer, decided to treat additional
patients with Primaxin after meeting the requirements of their segment of the
comparative trial. A total of 21 patients were entered into a noncomparative
Primaxin arm. These patients have been excluded from the analysis of efficacy
and safety of comparative patient and will be evaluated separately.

OVERALL SUMMARY OF STUDIES CONDUCTED UNDER PROTOCOL NO. 003

	Primaxin	Moxalactam
Total No. of Patients	218	223
Age Range (yrs)	14 - 91	14 - 96
Mean Age	48.9	48.4
Sex		
Male	109	99
Female	109	124

EVALUATION

EFFICACY

	Primaxin	Moxalactam
No. of Cases Evaluable	145	148
No. of Sites of Infection Evaluable	161	156
No. of Cases Unevaluable	73	75

REASONS CASES UNEVALUABLE

No pre-treatment pathogen	45	42
Organism resistant to study drug	1	4
Clinical diagnosis not clear	2	1
Inadequate bacteriological cultures	11	10
Treatment course too short	11	11
Effective concomitant treatment	3	4
Infection not included in claims	0	3

	Primaxin	Moxalactam
DOSE (Evaluable Cases)	500 mg q 6 h (2 g/day)	1-2 g q 8 h (3-6 g/day)

DURATION OF TREATMENT (days)
  (Evaluable Cases)

4 - 14	117 patients	138 patients
15 - 21	18 patients	7 patients
>21*	10 patients	3 patients

*Four patients were treated for 41 days.

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	MOXALACTAM CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess cellulitis, carbuncle/ furuncle, ulcers)	44	27(61%)	16(36%)	1(2%)	48	23(48%)	17(35%)	8(17%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5		5(100%)		1		1(100%)	
LOWER RESPIRATORY (Pneumonia, empyema)	28	20(71%)	7(25%)	1(4%)	28	17(61%)	7(25%)	4(14%)
GYNECOLOGIC (Endometritis, pelvic cellulitis, PID, tuboovarian abscess)	27	23(85%)	3(11%)	1(4%)	27	21(78%)	5(18%)	1(4%)
SEPTICEMIA	22	17(77%)	3(14%)	2(9%)	12	10(83%)	1(8%)	1(8%)
OTITIS MEDIA	1	1(100%)						
ENDOCARDITIS	1	1(100%)						
UTI (Uncomplicated) (Pyelonephritis)	6	6(100%)			13	11(85%)	2(15%)	
UTI (Complicated) (Pyelonephritis, renal abscess, cystitis)	5	2(40%)	1(20%)	2(40%)	6	4(67%)	1(16%)	1(16%)
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, liver abscess)	22	14(64%)	6(27%)	2(9%)	20	13(65%)	3(15%)	4(20%)
INFECTED VASCULAR GRAFT	-				1		1(100%)	

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE			NO.	MOXALACTAM BACTERIOLOGICAL RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
SKIN AND SKIN STRUCTURE								
Bacillus spp.	–				1	1(100%)		
S. aureus(S)	2	1(50%)		1(50%)	5	5(100%)		
S. aureus(R)	17	13(76%)	1(6%)	3(18%)	16	15(94%)		1(6%)
S. epidermidis	3	3(100%)			3	3(100%)		
Strep. (Group A)	5	5(100%)			4	4(100%)		
Strep. (Group B)	2	1(50%)	1(50%)		2	2(100%)		
Streptococcus spp.	8	7(88%)	1(12%)		4	4(100%)		
S. faecalis	7	7(100%)			2	1(50%)		1(50%)
Acinetobacter spp.	–				2	2(100%)		
Citrobacter spp.	2	2(100%)			1	1(100%)		
C. freundii	–				1	1(100%)		
E. aerogenes	2	2(100%)			–			
E. cloacae	2	2(100%)			3	3(100%)		
E. coli	5	4(80%)		1(20%)	8	6(75%)	1(12.5%)	1(12.5%)
Klebsiella spp	1	1(100%)			1	1(100%)		
K. oxytoca	1	1(100%)			5	5(100%)		
K. pneumoniae	3	3(100%)			2	2(100%)		
M. morganii	2	2(100%)			1	1(100%)		
P. mirabilis	5	1(20%)	1(20%)	3(60%)	12	11(92%)		1(8%)
P. vulgaris	2	2(100%)			2	1(50%)		1(50%)
P. stuartii	2	2(100%)			–			
Pseudomonas spp	–				1	1(100%)		
P. aeruginosa	11	6(55%)	1(9%)	4(36%)	8	5(62.5%)		3(37.5%)
Serratia spp.	1	1(100%)			2	2(100%)		
S. marcescens	2	2(100%)			2	1(50%)	1(50%)	
Eubacterium spp.	–				1	1(100%)		
Gaffkya anaerobia	–				1	1(100%)		
Peptococcus spp.	2	2(100%)			4	4(100%)		
Bacteroides spp.	7	7(100%)			4	4(100%)		
B. fragilis	1	1(100%)			1	1(100%)		
F. russii	1	1(100%)			1	1(100%)		
V. parvula	1	1(100%)			1	1(100%)		
BONE/JOINT								
S. aureus(R)	2	2(100%)			1	1(100%)		
S. faecalis	2	2(100%)			–			
E. coli	–				1	1(100%)		
P. mirabilis	2	2(100%)			1	1(100%)		
P. aeruginosa	1		1(100%)		–			
S. marcescens	1			1(100%)	–			
Bacteroides spp.	1	1(100%)			–			
B. fragilis	1	1(100%)			–			

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE			NO.	MOXALACTAM BACTERIOLOGICAL RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
LOWER RESPIRATORY								
S. aureus (S)	1	1(100%)			1	1(100%)		
S. intermedius	–				1	1(100%)		
S. pneumoniae	8	8(100%)			7	7(100%)		
Strep. (Group A)	1	1(100%)			–			
Strep. (Group B)	–				1	1(100%)		
S. viridans	1	1(100%)			1	1(100%)		
Beta-hem Strep.	2	2(100%)			–			
Acinetobacter spp	2	2(100%)			–			
A. hydrophilia	1	1(100%)			–			
Alcaligenes spp	1	1(100%)			–			
Citrobacter spp	1	1(100%)			–			
E. aerogenes	1			1(100%)				
E. cloacae	1	1(100%)			2	2(100%)		
E. coli	1	1(100%)			1	1(100%)		
H. influenzae	6	5(83%)	1(17%)		2	2(100%)		
H. parainfluenzae	1	1(100%)			1	1(100%)		
K. oxytoca	1	1(100%)			2	2(100%)		
K. pneumoniae	2	2(100%)			4	3(75%)		1(25%)
M. morganii	–				2	2(100%)		
P. mirabilis	1			1(100%)	4	2(50%)	1(25%)	1(25%)
Pseudomonas spp	1	1(100%)						
P. aeruginosa	3	3(100%)			5	1(20%)	2(40%)	2(40%)
S. marcescens	–				2	2(100%)		
B. catarrhalis	–				1	1(100%)		
Peptostreptococcus spp.	1	1(100%)						
Bacteroides spp.	3	3(100%)						
GYNECOLOGIC								
Corynebacterium spp	–				1	1(100%)		
S. aureus (R)	4	3(75%)	1(25%)		4	3(75%)		1(25%)
S. intermedius	–				1	1(100%)		
Strep. (Group A)	–				1	1(100%)		
Strep. (Group B)	7	7(100%)			7	7(100%)		
S. viridans	2	2(100%)			2	2(100%)		
Strep (non-hemolytic)	2	2(100%)			1	1(100%)		
S. faecalis	8	7(88%)	1(12%)		2			2(100%)
A. calcoaceticus	–				1			1(100%)
Enterobacter spp.	–				1	1(100%)		
E. cloacae	1	1(100%)			1	1(100%)		
E. coli	8	6(75%)	1(12.5%)	1(12.5%)	9	9(100%)		
Klebsiella spp.	1	1(100%)			1	1(100%)		
P. mirabilis	2	2(100%)			1	1(100%)		
P. aeruginosa	–				1			1(100%)
N. gonorroheae(-)*	2	2(100%)			–			
N. gonorroheae(+)**	–				1	1(100%)		

(Continued)

GYNECOLOGIC	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Bifidobacterium spp	1	1(100%)			-			
Propionibacterium spp	1	1(100%)			-			
Peptococcus spp	3	3(100%)			9	9(100%)		
Peptostreptococcus spp	1	1(100%)			-			
Bacteroides spp	5	5(100%)			4	4(100%)		
B. fragilis	1	1(100%)			-			
Fusobacterium spp	-				1	1(100%)		
G. vaginalis	4	4(100%)			2	2(100%)		
M. hominis	1	1(100%)			-			
Ureaplasma urealyticum	2	2(100%)			-			
Veillonella parvula	1	1(100%)			6	6(100%)		

(-)* = penicillinase negative
(+)** = penicillinase positive

SEPTICEMIA	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
S. aureus (S)	-				1	1(100%)		
S. aureus (R)	-				1	1(100%)		
S. pneumoniae	1	1(100%)			1	1(100%)		
Strep. (Group A)	1	1(100%)			1	1(100%)		
S. viridans	-				1	1(100%)		
s. sanguis	1	1(100)						
S. faecalis	1	1(100%)			-			
Acinetobacter spp	1	1(100%)			-			
E. cloacae	1	1(100%)			-			
E. coli	6	6(100%)			2	2(100%)		
K. pneumoniae	1	1(100%)			3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. stuartii	1	1(100%)			-			
P. aeruginosa	1	1(100%)			-			
S. marcescens	2	1(50%)		1(50%)	-			
Y. enterocolitica	1	1(100%)			-			
Clostridium spp.	1			1(100%)				
Peptostreptococcus spp	2	2(100%)			-			
Bacteroides spp	2	2(100%)			-			
Fusobacterium spp	2	2(100%)			-			
B. fragilis	-				1			1(100%)

OTITIS MEDIA								
S. pneumoniae	1	1(100%)			-			

(Continued)

INFECTION	NO.	PRIMAXIN BACTERIOLOGICAL RESPONSE ERAD	SUPP	NOT ERAD	NO.	MOXALACTAM BACTERIOLOGICAL RESPONSE ERAD	SUPP	NOT ERAD
OTITIS MEDIA								
S. pneumoniae	1	1(100%)			-			
ENDOCARDITIS								
S. sanguis	1	1(100%)			-			
INFECTED VASCULAR GRAFT								
S. aureus(R)	-				1	1(100%)		
UNCOMPLICATED UTI								
E. coli	3	3(100%)			8	7(87.5%)		1(12.5%)
E. cloacae	-				1	1(100%)		
P. mirabilis	1	1(100%)			2	2(100%)		
S. marcescens	-				1	1(100%)		
P. aeruginosa	-				1	1(100%)		
Klebsiella spp.	-				1	1(100%)		
K. pneumoniae	2	2(100%)			1	1(100%)		
COMPLICATED UTI								
E. coli	2	1(50%)		1(50%)	3	3(100%)		
P. mirabilis	-				1	1(100%)		
E. aerogenes	1	1(100%)			-			
K. pneumoniae	-				1	1(100%)		
P. aeruginosa	1			1(100%)	-			1(100%)
S. marcescens	1			1(100%)	-			
INTRA-ABDOMINAL								
S. aureus(R)	-				1			1(100%)
S. epidermidis	1	1(100%)			1			1(100%)
S. intermedius	4	4(100%)			1	1(100%)		
S. mitis	1	1(100%)			2	2(100%)		
S. morbillorum	2	2(100%)			-			
Strep. (Group A)	-				2	2(100%)		
Strep. (Group B)	-				1	1(100%)		
S. viridans	3	2(67%)		1(33%)	-			
S. faecalis	-				3	1(33%)		2(67%)
S. faecium	1	1(100%)			1	1(100%)		
S. bovis	1	1(100%)			-			
S. sanguis	1	1(100%)			-			
S. salivarus	-				-			
A. hydrophilia	-				1	1(100%)		
E. aerogenes	1	1(100%)			2	2(100%)		
E. cloacae	-				1	1(100%)		
E. coli	14	11(79%)		3(21%)	12	9(75%)		3(25%)

(Continued)

INTRAABDOMINAL	PRIMAXIN BACTERIOLOGICAL RESPONSE				MOXALACTAM BACTERIOLOGICAL RESPONSE			
	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD	
Klebsiella spp.	1	1(100%)		1		1(100%)		
K. pneumoniae	4	4(100%)		4		4(100%)		
P. multocida	1	1(100%)		-				
M. morganii	-			2		2(100%)		
P. mirabilis	1	1(100%)		3		2(67%)	1(33%)	
P. vulgaris	1	1(100%)						
P. aeruginosa	2	2(100%)		4		2(50%)	2(50%)	
Bifidobacterium spp.	-			1		1(100%)		
Clostridium spp	9	9(100%)						
C. perfringens	2	2(100%)		3		3(100%)		
Eubacterium spp	2	2(100%)		3		2(67%)	1(33%)	
Peptococcus spp	1	1(100%)						
Peptostreptococcus spp	4	4(100%)		3		3(100%)		
Bacteroides spp.	5	5(100%)		7		7(100%)		
B. fragilis	12	12(100%)		13		12(92%)	1(8%)	
Fusobacterium spp.	5	5(100%)		4		4(100%)		
V. parvula	1	1(100%)						

Bacterial superinfection occurred in 5 patients in the Primaxin group and in 8 patients in the Moxalactam group. However, none of the 5 patients in the Primaxin group who developed superinfections had resistant pathogens, whereas, 6 of the 8 patients who developed superinfections in the Moxalactam group had resistant pathogens.

Three patients in each treatment group developed candida superinfections.

SAFETY

	Primaxin	Moxalactam
Total No. of Patients	218	210
No. of Patients with Systemic Side Effects	24(11%)	19(9%)
No. of Patients with Local Side Effects	5(2%)	2(1%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	PRIMAXIN POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Diarrhea	6(2.8%)	2(0.9%)	3(1.4%)	1(0.5%)	
Nausea	1(0.5%)		1(0.5%)		
Vomiting	6(2.8%)	2(0.9%)	3(1.4%)	1(0.5%)	
Pruritus	1(0.5%)	1(0.5%)			

(Continued)

SYSTEMIC SIDE EFFECTS — PRIMAXIN

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Rash	3(1.4%)		1(0.5%)	1(0.5%)	1(0.5%)
Urticaria	1(0.5%)			1(0.5%)	
Fever	2(1.0%)	1(0.5%)	1(0.5%)		
Transient hearing loss	1(0.5%)		1(0.5%)		
Palpitation	1(0.5%)		1(0.5%)		
Tachycardia	1(0.5%)		1(0.5%)		
Respiratory distress syn.	1(0.5%)	1(0.5%)			
Pharyngeal pain	1(0.5%)			1(0.5%)	
Menorrhagia	1(0.5%)	1(0.5%)			
Hemorrhagic colitis	1(0.5%)			1(0.5%)	
Asthenia	1(0.5%)		1(0.5%)		
Hyperhydrosis	1(0.5%)		1(0.5%)		

SYSTEMIC SIDE EFFECTS — MOXALACTAM

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Diarrhea	9(4.3%)	4(1.9%)	4(1.9%)	1(0.5%)	
Nausea	1(0.5%)		1(0.5%)		
Vomiting	2(1.0%)		2(1.0%)		1(0.5%)
Serum Sickness	1(0.5%)		1(0.5%)		
Epistaxis	1(0.5%)			1(0.5%)	
Hemoperitoneum	1(0.5%)			1(0.5%)	
GI hemorrhage	1(0.5%)				
Dysuria	1(0.5%)	1(0.5%)			
Urinary frequency	1(0.5%)	1(0.5%)			
Abdominal pain	1(0.5%)	1(0.5%)			
Respiratory insufficiency	1(0.5%)	1(0.5%)			
Headache	1(0.5%)	1(0.5%)			
Convulsive disorder	1(0.5%)	1(0.5%)			
Alcohol intolerance	1(0.5%)		1(0.5%)		
Somnolence	1(0.5%)		1(0.5%)		
Vaginal discharge	1(0.5%)			1(0.5%)	
Myocardial infarction	1(0.5%)	1(0.5%)			

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	PRIMAXIN POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Phlebitis/ Thrombophlebitis	12(5.5%)		12(5.5%)		
Infused vein pain	1(0.5%)			1(0.5%)	
Infused vein infection	1(0.5%)		1(0.5%)		

	NO.	PROBABLY NOT RELATED	MOXALACTAM POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
I.V. site hemorrhage	1(0.5%)	1(0.5%)			
Infused vein pain	1(0.5%)			1(0.5%)	
Phlebitis/ Thrombophlebitis	4(1.9%)		4(1.9%)		

Deaths: There were eight deaths in the Primaxin treated group and eleven deaths in the Moxalactam treated group. None of these deaths was considered by the investigators to be related to the test drug.

Abnormal Laboratory Tests

TEST	PRIMAXIN	MOXALACTAM
Hemoglobin	(D) 1	(D) 8
Hematocrit	(D) 2	(D) 6
WBC	(D) 3	(D) 4
Neutrophils	(D) 1	(D) 1
Eosinophils	(I)17	(I)15
Platelets	(I) 2	(I) 2
	(D) 4	(D) 3
Positive Coombs' Test	7	5
Prothrombin time	(I) 9	(I) 9
Glucose	0	(I) 1
Creatinine	(I) 2	(I) 6
SGOT (AST)	(I) 7	(I)12
SGPT (ALT)	(I)10	(I)14
	(I) 2	(I) 1
phosphatase	(I) 6	(I) 6
	0	(D) 1
	0	(D) 1
	(I) 1	(D) 1
	(I) 3	(I) 2
	(I) 4	(I) 2
	3	(I) 3
		(I) 1
		0

Summary of 21 Patients Entered into the Non-Comparative Primaxin Arm Under
Protocol 003

	PRIMAXIN
TOTAL NO. OF PATIENTS	21

Age Range (years)   21 - 78

Sex
    Male   13
    Female   8

EVALUATION

EFFICACY

No. of Cases Evaluable   19
No. of Sites of Infection
    Evaluable   19
No. of Cases Unevaluable   2

REASONS CASES UNEVALUABLE
No pretreament pathogen   2

DOSE - 500 mg q 6 h (2g/day)
    (One patient received 3g/day)

DURATION (days) -- 5 - 14 days (13 patients)
              15 - 21 days (3 patients)
              34 - 37 days (3 patients)

RESULTS

		PRIMAXIN		
		CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMP	FAIL
SKIN & SKIN STRUCTURE	9	2(22%)	6(67%)	1(11%)
BONE/JOINT	1		1(100%)	
LOWER RESPIRATORY	2	1(50%)		1(50%)
UTI(Uncomplicated)	1		1(100%)	
INTRA-ABDOMINAL	6		5(83%)	1(17%)

		BACTERIOLOGIC RESPONSE		
ORGANISM	NO.	ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE				
S. aureus(R)	1	1(100%)		
Strep (Group A)	1	1(100%)		
Strep (Group B)	1	1(100%)		
S. faecalis	5	3(60%)	1(20%)	1(20%)
E. coli	3	2(67%)	1(33%)	

(Continued)

ORGANISM	NO.	BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE				
P. mirabilis	3	1(33%)		2(67%)
A. calcoaceticus	1	1(100%)		
P. aeruginosa	3	1(33%)		2(67%)
K. pneumoniae	1		1(100%)	
Peptostreptococcus spp	1	1(100%)		
Bacteroides spp	3	3(100%)		
B. fragilis	1	1(100%)		
BONE/JOINT				
S. faecalis	1	1(100%)		
P. mirabilis	1			1(100%)
P. stuartii	1			1(100%)
P. aeruginosa	1			1(100%)
LOWER RESPIRATORY				
K. pneumoniae	1	1(100%)		
E. hafniae	1			1(100%)
P. aeruginosa	1			1(100%)
UTI (Uncomplicated)				
E. coli	1			1(100%)
INTRA-ABDOMINAL				
S. faecalis	1	1(100%)		
E. coli	3	2(67%)		1(33%)
P. mirabilis	1			1(100%)
K. pneumoniae	2	1(50%)		1(50%)
P. aeruginosa	1	1(100%)		

The overall response rate for these non-randomized patients was significantly lower than in those in the comparative trial.

These patients were in general more severly ill and in almost all of the patients with unfavorable response there were medical reasons to explain the clinical failure or bacteriologic persistance.

Four patients had fungal superinfections. There were no bacterial superinfections.

SAFETY

	PRIMAXIN
Total No. of Patients	21
No. of Patients with Systemic Side Effects	2(9.5%)
No. of Patients with Local Side Effects	0

SYSTEMIC SIDE EFFECTS

	NO.	DEFINITELY RELATED
Candidiasis	1(4.8%)	1
Diarrhea*	1(4.8%)	1

*This patient's diarrhea was associated with a positive C. difficile toxin assay.

Two patients who had non drug-related adverse effects had drug discontinued. One had severe diarrhea that was probably related to previous piperacillin therapy. Another patient who had a brain tumor and seizures developed a grand mal seizure during therapy, and his primary physician decided not to continue the trial. The investigator called the seizure probably not related to study drug therapy.

Deaths: Two patients died of non-drug related causes.

Abnormal Laboratory Tests

Test	Abnormality	No
Platelets	I	2
Urine RBCs	I	1
BUN	I	1
SGOT	I	4
SGPT	I	3
Alk. phosphatase	I	4
Bilirubin	I	1

Summary and Conclusions (Comparative Arm of Protocol No. 003)
This was an open, randomized, controlled multicenter study comparing Primaxin and moxalactam in the treatment of infections caused by susceptible bacteria. A total of 218 patients, 109 males and 109 females, ranging in age from 14 to 91 years were enrolled in the Primaxin group. A total of 223 patients, 99 males and 124 females, ranging in age from 14 to 96 years were enrolled in the moxalactam group.
Demographic characteristics of patients in each treatment group were similar. One hundred and forty-five patients with 161 sites of infection in the Primaxin group and 148 patients with 156 sites of infection were acceptable for evaluation of drug efficacy. Safety was assessed in 218 patients in the Primaxin group and in 210 patients in the moxalactam group.

Clinical cure or improvement occurred in 152/161 (94%) infections in the Primaxin treated patients and in 137/156 (88%) infections in the moxalactam treated patients.

A favorable bacteriological outcome (eradication) was achieved in 288 (89%) of 323 organisms isolated in the Primaxin group and in 271 (88%) of 308 organisms isolated in the moxalactam group.

Systemic side effects were reported in 11% of the patients in the Primaxin group and in 9% of the patients in the moxalactam group. Local side effects were reported in 2% of the patients in the Primaxin group and in 1% of the patients in the moxalactam group.

Laboratory test abnormalities were similar in both treatment groups.

None of the deaths reported in each treatment group was considered by the investigator to be related to the study drug.

This study demonstrates that Primaxin and moxalactam are safe and effective in the treatment of patients with infections caused by susceptible bacteria.

3.   Protocol No. 11
     Title: "A Multicenter Randomized Study of the Comparative Efficacy, Safety and Tolerance of Primaxin Versus Clindamycin/Gentamicin in the Parenteral Therapy of Infections in Hospitalized Patients Caused by Susceptible Pathogenic Bacteria."

     Study Design: This was an open, controlled, randomized, multicenter study.

     Procedure: Patients with acute bacterial infections caused by organisms presumed or proven to be susceptible to both antibiotic regimens (Primaxin and clindamycin/gentamicin) were entered in the study according to a computer-generated randomized schedule. Evaluations were made concerning the bacteriologic and clinical efficacy, as well as the safety and tolerance of the two antimicrobial regimens. Laboratory data to assess safety were obtained before, during, and after therapy.
     Each patient in the Primaxin group received a total daily dose of 2.0 g administered in four equally divided doses every 6 hours by intravenous infusion.
     Each patient in the clindamycin/gentamicin group received 300-600 mg clindamycin every 6 to 8 hours and 1.0 to 1.7 mg/kg of gentamicin every 8 hours (gentamicin dosage was adjusted according to serum concentration assays).

     Two investigators enrolled patients under this protocol.   Joseph S. Solomkin, M.D., University of Cincinnati Medical Center, Cincinnati, Ohio.   Toni Hau, M.D., Case Western Reserve University, Cleveland, Ohio.

Overall Summary of Studies Conducted Under Protocol No. II

	Primaxin	Clindamycin/Gentamicin
Total No. of Patients	13	13
Age Range (yrs)	24 - 95	26 - 73
Mean Age	50.5	49.0
Sex		
Male	9	10
Female	4	3

EVALUATION

EFFICACY

	Primaxin	Clindamycin/Gentamicin
No. of Cases Evaluable	8	5
No. of Sites of Infection Evaluable	8	5
No. of Cases Unevaluable	5	8

REASONS CASES UNEVALUABLE

	Primaxin	Clindamycin/Gentamicin
No pre-treatment pathogen	3	4
Treatment course too short	1	2
Organism resistant to study drug	-	1
Inadequate bacteriological cultures	1	-
Concomitant effective antibiotic	-	1

	Primaxin	Clindamycin	Gentamicin
DOSE	500 mg q 6 h	300-600 mg q 6 h	1.0-1.7 mg/kg q 8 h

DURATION OF
TREATMENT (days)
5 - 14   8 patients   5 patients   5 patients

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CLINDAMYCIN/GENTAMICIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAI
SKIN & SKIN STRUCTURE (Wound Infection, abscess)	2	2(100%)			-			
LOWER RESPIRATORY (Pneumonia, bronchopneumonia)	2	1(50%)	1(50%)		2		1(50%)	1(50

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	CLINDAMYCIN/GENTAMICIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FA
UTI (Complicated) (Pyelonephritis)	1			1(100%)	-			
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE		NO.	CLINDAMYCIN/GENTAMICIN BACTERIOLOGIC RESPONSE	
		ERAD	NOT ERAD		ERAD	NOT ERA
SKIN & SKIN STRUCTURE						
S. viridans group	1	1(100%)				
Streptococcus spp	1	1(100%)				
S. faecalis	1	1(100%)				
E. coli	1	1(100%)				
Peptococcus spp	1	1(100%)				
Bacteroides spp	2	2(100%)				
LOWER RESPIRATORY						
H. influenzae	1		1(100%)	-		
E. coli	1	1(100%)		1	1(100%)	
Enterobacter spp	-			1	1(100%)	
P. aeruginosa	-			1		1(100%)
INTRA-ABDOMINAL						
S. aureus(S)	-			1	1(100%)	
Strep (Group A)	1	1(100%)		-		
Strep (Group D enterococci)	1	1(100%)		-		
S. viridans group	1	1(100%)		-		
Beta-hemolytic Strep	1	1(100%)		-		
E. coli	2	2(100%)		1	1(100%)	
E. cloacae	1	1(100%)		-		
K. pneumoniae	1	1(100%)		-		
P. aeruginosa	1	1(100%)		-		
Peptococcus spp.	1	1(100%)		-		
Peptostreptococcus spp	1	1(100%)		-		
B. fragilis	-			2	2(100%)	
Bacteroides spp.	4	4(100%)		1	1(100%)	
Fusobacterium spp.	2	2(100%)		-		
UTI (Complicated)						
Providencia spp.	1		1(100%)	-		

SAFETY

SIDE EFFECTS
There were no local or systemic side effects reported in these studies.

Deaths: Two patients in the Primaxin-treated group and one patient in the
clindamycin/gentamicin-treated group died during or shortly after
discontinuation of treatment. These deaths were considered by the
investigators definitely not drug related.

Abnormal Laboratory Tests
The only abnormality reported was an increase in serum creatinine in 2
patients in the clindamycin/gentamicin group.

Summary and Conclusions: This was an open, randomized, controlled study
comparing Primaxin and clindamycin plus gentamicin in the treatment of
infections caused by susceptible bacteria.

A total of 13 patients, 9 males and 4 females, ranging in age from 24 to 95
years were enrolled in the Primaxin group. A total of 13 patients, 10 males
and 3 females, ranging in age from 20 to 73 years were enrolled in the
clindamycin/gentamicin group.

Eight patients in the Primaxin group and 5 patients in the
clindamycin/gentamicin group were acceptable for evaluation of drug efficacy.
Safety was assessed in all 13 patients in each treatment group.

Clinical cure or improvement occurred in 7/8 (87.5%) patients in the Primaxin
group and in 4/5 (80.0%) of the patients in the clindamycin/gentamicin group.

A favorable bacteriological outcome (eradication) was achieved in 25 (93%) of
27 organisms isolated in the Primaxin group and in 7 (87.5%) of 8 organisms
isolated in the clindamycin/gentamicin group.

No systemic or local side effects were reported in this study. The only
laboratory test abnormality reported was an increase in serum creatinine in 2
patients in the clindamycin/gentamicin group.

Although the number of patients in this study was rather small, results tend
to indicate that Primaxin compares favorably with clindamycin plus gentamicin
in the treatment of patients with infections caused by susceptible bacteria.

CLINICAL STUDIES (Domestic)
II. Uncontrolled

   1.   Protocol No. 016
        Title: "A Multicenter Open Study of the Efficacy, Safety, and
        Tolerance of Primaxin (imipenem/cliastatin) in the Parenteral Therapy
        of Infections Caused by Pathogenic Bacteria in Hospitalized Patients."

Study Design: This was an open, dose ranging, bacteriologically controlled study of the efficacy, safety, and tolerance of Primaxin in hospitalized patients with presumed or proven bacterial infection.

Procedure: Patients accepted for entry into the study were required to provide a signed written informed consent form. A clinical history was obtained, and a complete physical examination was performed.
Once the clinical diagnosis was established and the proper bacteriologic cultures and susceptibility studies, and laboratory tests were obtained, treatment was started with Primaxin at a dose ranging from 1.0 to 4.0 g/day depending on the type and severity of the infection. Each dose was administered by intravenous infusion over a period of 15 to 30 minutes.
During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded. A daily infusion tolerance record was also kept.

Any abnormal physical sign or symptom which occurred during the course of drug treatment was recorded in the case report form. Patients were observed with particular attention to any evidence of allergic phenomenon including rashes, itching, or anaphylactic manifestations.

Follow-up cultures were obtained during and after completion of therapy, except in the obvious cases in which cultures were impossible to obtain by virtue of a healed site such as in cases of cellulitis, abscesses, etc.

Laboratory tests of hematologic, renal, and hepatic function were repeated at various times during therapy and following completion of therapy.

At the conclusion of drug therapy and after all clinical and laboratory data had been obtained. Judgment was made by the investigator of the safety, tolerability, and clinical and bacteriological efficacy of the study drug for each patient.

Response to treatment was assessed by both clinical and bacteriological outcomes
Favorable clinical outcomes included:
     -Cure (Investigators judgment that the signs and symptoms of the infection were resolved).
     -Improvement (Investigators judgment that the infection was brought under control, and the need for further intravenous therapy was not indicated).

Unfavorable clinical outcome included:
     -No improvement.
     --Patient died of infection primarily (with or without a contributing background disease).

Favorable bacteriologic outcome:
   -Eradication of the etiologic pathogen(s)

Unfavorable bacteriologic outcome:
   -Suppression of the etiologic pathogen(s)
   -Persistance of the etiologic pathogen(s)

Drug safety was assessed by both clinical and laboratory adverse
reactions. When an abnormal laboratory result or clinical event was
noted, the investigator was required to render a judgment as to the
intensity and seriousness of the occurrence and its relationship to
the drug. They were also required to indicate the outcome and the
type of action taken with regard to the adverse effect.

Investigators: Fifty-two well-qualified investigators in the USA
participated in this multiclinic study.

Overall Summary of Studies Conducted Under Protocol No. 016

Total No. of Patients: 717
Age Range (years): 12-101
Mean Age (years): 50.7
Sex
    Male: 437
    Female: 280

EVALUATION

EFFICACY
No. of Cases Evaluable: 506
No. of Sites of Infection Evaluable: 573
No. of Cases Unevaluable: 211

REASONS CASES UNEVALUABLE
No pretreatment pathogen: 97
Organism resistant to study drug: 3
Clinical diagnosis not clear: 5
Inadequate bacteriologic culture: 30
Treatment course too short: 35
Effective therapy prestudy: 1
Effectiv concomitant therapy: 14
No post-treatment culture: 20
No follow-up: 6

DURATION OF TREATMENT
   (Evaluable Cases)

Days	No. Patients
4-14	366
15-29	98
30-49	41
61	1

RESULTS

INFECTION	NO.	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/furuncle decubitus and other skin ulcers)	129	67(51.9%)	56(43.4%)	6(4.7%)
BONE/JOINT (Osteomyelitis, pyogenic arthritis)	53	27(50.9%)	21(39.6%)	5(9.4%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess, bronchitis)	108	45(41.7%)	48(44.4%)	15(13.9%)
UPPER RESPIRATORY (Peritonsillar abscess, tracheitis)	2		1(50%)	1(50%)
OTITIS	3	1(33.3%)	1(33.3%)	1(33.3%)
GYNECOLOGIC (PID, endometritis, tubo-ovarian abscess, pelvic abscess)	49	36(73.5%)	10(20.4%)	3(6.1%)
INTRA-ABDOMINAL (Peritonitis, abscess, liver abscess, cholangitis, cholecystitis)	44	30(68.2%)	12(27.3%)	2(4.5%)
UTI (Uncomplicated) (Cystitis, pyelonephritis)	12	11(91.7%)	1(8.3%)	
UTI (Complicated) (Cyst'`is, pyelonephritis, renal abscess)	73	55(75.3%)	16(21.9%)	2(2.7%)

BACTERIAL SEPTICEMIA	66	50(75.8%)	14(21.2%)	2(3.0%)
BACTEREMIA	24	15(62.5%)	8(33.3%)	1(4.2%)
ENDOCARDITIS	9	9(100%)		
BRAIN ABSCESS	1	1(100%)		

	BACTERIOLOGIC RESPONSE	
ORGANISM	NO.	ERADICATED
SKIN & SKIN STRUCTURE		
Corynebacterium spp.	4	4(100%)
S. aureus[S]	9	8(88.9%)
S. aureus[R]	43	36(83.7%)
S. epidermidis	7	4(57.1%)
Alpha-hemolytic streptococci	7	7(100%)
Beta-hemolytic streptococci	1	1(100%)
Group A Streptococci	15	14(93.3%)
Group B Streptococci	5	5(100%)
Group D Streptococci		
(enterococci)	16	12(75%)
S. faecalis	6	6(100%)
Other Streptococcus species	17	17(100%)
Acinetobacter spp.	1	1(100%)
Acinetobacter calcoaceticus	4	4(100%)
Aeromonas hydrophilia	3	2(66.7%)
Citrobacter diversus	2	2(100%)
Citrobacter freundii	2	2(100%)

(Continued)	No.	Eradicated
Enterobacter spp.	1	1(100%)
Enterobacter aerogenes	4	4(100%)
Enterobacter cloacae	9	9(100%)
Escherichia coli	17	17(100%)
Klebsiella oxytoca	7	7(100%)
Klebsiella pneumoniae	4	3(75%)
Morganella morganii	7	7(100%)
Proteus spp.	1	1(100%)
Proteus rettgeri	1	1(100%)
Proteus vulgaris	4	3(75%)
Proteus mirabilis	20	12(60%)
Pseudomonas aeruginosa	37	26(70.3%)
Serratia spp.	1	1(100%)
Serratia marcescens	5	4(80%)
Eikenella spp.	1	1(100%)
Eubacterium spp.	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus spp.	13	13(100%)
Peptostreptococcus spp.	5	5(100%)
Bacteroides spp.	19	19(100%)
Bacteroides fragilis	12	12(100%)
Fusobacterium spp.	3	3(100%)
Veillonella parvula	1	1(100%)

BONE/JOINT

	No.	Eradicated
S. aureus(S)	8	8(100%)
S. aureus(R)	16	15(93.8%)
S. epidermidis	5	5(100%)
Streptococcus spp.	10	10(100%)
Group D Streptococci (enterococci)	5	5(100%)

(Continued)	No.	Eradicated
Enterobacter spp.	1	1(100%)
Enterobacter aerogenes	4	4(100%)
Enterobacter cloacae	9	9(100%)
Escherichia coli	17	17(100%)
Klebsiella oxytoca	7	7(100%)
Klebsiella pneumoniae	4	3(75%)
Morganella morganii	7	7(100%)
Proteus spp.	1	1(100%)
Proteus rettgeri	1	1(100%)
Proteus vulgaris	4	3(75%)
Proteus mirabilis	20	12(60%)
Pseudomonas aeruginosa	37	26(70.3%)
Serratia spp.	1	1(100%)
Serratia marcescens	5	4(80%)
Eikenella spp.	1	1(100%)
Eubacterium spp.	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus spp.	13	13(100%)
Peptostreptococcus spp.	5	5(100%)
Bacteroides spp.	19	19(100%)
Bacteroides fragilis	12	12(100%)
Fusobacterium spp.	3	3(100%)
Veillonella parvula	1	1(100%)

BONE/JOINT

S. aureus(S)	8	8(100%)
S. aureus(R)	16	15(93.8%)
S. epidermidis	5	5(100%)
Streptococcus spp.	10	10(100%)
Group D Streptococci		
(enterococci)	5	5(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
S. facecalis	2	2(100%)
Aceinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	1	1(100%)
Enterobacter aerogenes	3	3(100%)
Enterobacter cloacae	6	6(100%)
Escherichia coli	2	1(50%)
Morganella morganii	2	2(100%)
Proteus species	1	0
Proteus vulgaris	2	1(50%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	21	19(90.5%)
Serratia marcescens	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus species	3	3(100%)
Peptostreptococcus spp.	1	1(100%)
Bacteroides species	2	1(50%)
Bacteroides fragilis	3	2(66.7%)
Fusobacterium spp.	1	1(100%)
LOWER RESPIRATORY		
S. aureus(S)	2	2(100%)
S. aureus(R)	6	6(100%)
S. epidermidis	1	0
S. pneumoniae	20	20(100%)
Group A Streptococci	1	1(100%)
Group D Streptococci (enterococci)	4	2(50%)
Other Streptococcus species	8	8(100%)
Acinetobacter calcoaceticus	4	4(100%)
Citrobacter freundii	1	0
Enterobacter aerogenes	2	2(100%)
Enterobacter agglomerans	1	1(100%)
Enterobacter cloacae	8	7(87.5%)
Escherichia coli	8	7(87.5%)
H. influenzae	24	22(91.7%)
H. parainfluenzae	2	2(100%)
Klebsiella pneumoniae	17	14(82.3%)
Proteus mirabilis	12	4(33.3%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	38	9(23.7%)
Serratia marcescens	5	3(60%)
Branhamella catarrhalis	1	1(100%)
Eikenella corrodens	1	1(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
UPPER RESPIRATORY		
S. aureus[R]	1	0
Streptococcus spp.	1	1(100%)
Enterobacter aerogenes	1	1(100%)
Klebsiella pneumoniae	1	1(100%)
Peptostreptococcus spp.	1	1(100%)
Bacteroides (not fragilis)	1	1(100%)
Fusobacterium spp.	1	1(100%)
GYNECOLOGIC		
S. aureus[S]	3	3(100%)
S. aureus[R]	4	4(100%)
S. epidermidis	16	16(100%)
Alpha-hemolytic Streptococci	3	3(100%)
Group B Streptococci	13	13(100%)
Group D Streptococci		
(Enterococci)	13	11(84.6%)
S. faecalis	3	3(100%)
Other Streptococcus species	6	6(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	2	2(100%)
Citrobacter freundii	1	1(100%)
Enterobacter aerogenes	2	2(100%)
Escherichia coli	16	15(93.8%)
Klebsiella pneumoniae	5	5(100%)
Morganella morganii	1	1(100%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	1	0
Bifidobacterium spp	2	2(100%)
Clostridium perfringens	1	1(100%)
Gaffkya anaerobia	1	1(100%)
Peptococcus spp	1	1(100%)
Peptostreptococcus spp	6	6(100%)
Bacteroides spp	22	20(90.9%)
Bacteroides fragilis	7	6(85.7%)
Gardnerella vaginalis	3	3(100%)
Veillonella parvula	1	1(100%)
INTRA-ABDOMINAL		
S. aureus[R]	1	1(100%)
Group D Streptococci		
(Enterococci)	7	5(71.4%)
S. faecalis	1	0
Streptococcus viridans group	6	6(100%)
Other Streptococcus species	8	8(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter species	2	2(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
Citrobacter freundii	1	1(100%)
Enterobacter aerogenes	2	2(100%)
Enterobacter cloacae	3	1(33.3%)
Escherichia coli	25	20(80%)
Klebsiella oxytoca	3	3(100%)
Klebsiella pneumoniae	6	6(100%)
Morganella morganii	2	2(100%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	5	4(80%)
Pseudomonas alcaligenes	1	1(100%)
Bifidobacterium adolescentis	1	1(100%)
Clostridium spp	12	12(100%)
Propionibacterium acnes	3	3(100%)
Peptococcus spp	2	2(100%)
Peptostreptococcus spp	2	1(50%)
Bacteroides spp	4	4(100%)
Bacteroides fragilis	19	18(94.7%)
Fusobacterium spp	2	2(100%)
UNCOMPLICATED UTI		
Escherichia coli	8	8(100%)
Proteus mirabilis	2	2(100%)
Proteus vulgaris	1	1(100%)
Enterobacter cloacae	1	1(100%)
Pseudomonas aeruginosa	1	1(100%)
COMPLICATED UTI		
S. aureus (R)	1	0
Group D Streptococcus		
(Enterococci)	4	3(75%)
Escherichia coli	15	11(73.3%)
Proteus mirabilis	6	4(66.7%)
Morganella morganii	3	3(100%)
Providencia stuartii	3	1(33.3%)
Proteus rettgeri	3	2(66.7%)
Enterobacter cloacae	7	6(85.7%)
Klebsiella pneumoniae	5	5(100%)
Klebsiella oxytoca	1	1(100%)
Pseudomonas aeruginosa	35	31(88.6%)
Serratia species	1	1(100%)
Serratia marcescens	1	1(100%)
Bifidobacterium spp	1	1(100%)
Peptococcus spp	1	1(100%)

(Continued)

ORGANISM	BACTERIOLOGIC RESPONSE	
	NO.	ERADICATED
BACTERIAL SEPTICEMIA		
S. aureus(S)	2	2(100%)
S. aureus(R)	9	8(88.9%)
S. epidermidis	1	1(100%)
S. pneumoniae	7	7(100%)
Group D Streptococci		
(enterococci)	2	2(100%)
S. faecalis	1	1(100%)
Other Streptococcus species	9	9(100%)
H. influenzae	1	1(100%)
Escherichia coli	17	17(100%)
Proteus mirabilis	1	1(100%)
Klebsiella pneumoniae	3	3(100%)
Klebsiella oxytoca	1	1(100%)
Citrobacter freundii	1	1(100%)
Acinetobacter calcoaceticus	1	1(100%)
Pseudomonas aeruginosa	1	1(100%)
Serratia marcescens	4	4(100%)
Flavobacterium spp	1	1(100%)
Salmonella (Group D)	1	1(100%)
N. gonorrhoeae	1	1(100%)
Corynebacterium acnes	1	1(100%)
Clostridium bifermentans	1	1(100%)
Bacteroides fragilis	3	2(66.7%)
BACTEREMIA		
S. aureus(S)	1	1(100%)
S. aureus(R)	2	2(100%)
S. epidermidis	1	1(100%)
S. pneumoniae	1	1(100%)
Group D Streptococci		
(Enterococci)	1	1(100%)
H. influenzae	1	1(100%)
Escherichia coli	7	7(100%)
Enterobacter cloacae	3	3(100%)
Citrobacter diversus	1	1(100%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	4	4(100%)
Bacteroides bivius	1	1(100%)
ENDOCARDITIS		
S. aureus(S)	1	1(100%)
S. aureus(R)	5	5(100%)
Streptococcus spp	1	1(100%)
S. pneumoniae	1	1(100%)
Streptococcus viridans group	1	1(100%)
BRAIN ABSCESS		
S. aureus(R)	1	1(100%)

The incidence of superinfections due to bacteria was approximately 2%, and that due to yeast or fungi was approximately 1%. The bacteria most frequently involved in superinfections were resistant strains of P. aeruginosa, P. maltophilia, and S. epidermidis.

Resistance to Primaxin developed in 27 of 143 (19%) Pseudomonas aeruginosa isolates. Many of these were isolated from sputum or endotracheal tubes or from chronic wounds. One strain each of Proteus mirabilis and enterococcus also developed resistance to Primaxin.

SAFETY

Total No. of Patients: 717
No. of Patients with Systemic Side Effects: 81(11.3%)
No. of Patients with Local Side Effects: 18(2.5%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY ...LATED	DEFINITELY RELATED
Nausea	16(2.2%)	2(0.3%)	6(0.8%)	7(0.9%)	1(0.1%)
Vomiting	12(1.8%)	4(0.6%)	4(0.6%)	2(0.3%)	2(0.3%)
Diarrhea	16(2.2%)	5(0.7%)	8(1.7%)	1(0.1%)	2(0.3%)
Pseudomem-branous colitis*	3(0.4%)			3(0.4%)	
Heartburn	1(0.1%)		1(0.1%)		
Pruritus	2(0.3%)		1(0.1%)	~(0.1%)	
Facial edema	1(0.1%)			1(0.1%)	
Rash	7(0.9%)		3(0.4%)	3(0.4%)	1(0.1%)
Urticaria	2(0.3%)			1(0.1%)	1(0.1%)
Erythema multiforme	1(0.1%)				1(0.1%)
Pruritus vulvae	1(0.1%)		1(0.1%)		
Fever	4(0.5%)		3(0.4%)		1(0.1%)
Septic shock	2(0.3%)	2(0.3%)			
Tinnitus	1(0.1%)		1(0.1%)		
Vertigo	2(0.3%)		2(0.3%)		
Headache	3(0.4%)	1(0.1%)	2(0.3%)		
Confusion	3(0.4%)	2(0.3%)		1(0.1%)	
Dizziness	2(0.3%)	1(0.1%)	1(0.1%)		
Encephalopathy	1(0.1%)			1(0.1%)	
Seizures	9(1.3%)	3(0.4%)	3(0.4%)	3(0.4%)	
Myoclonus	2(0.3%)			2(0.3%)	
Palpitations	1(0.1%)		1(0.1%)		
Hypotension	7(0.9%)	4(0.5%)	3(0.4%)		
Chest pain	2(0.3%	1(0.1%)	1(0.1%)		
Dyspnea	1(0.1%)	1(01.%)			

The incidence of superinfections due to bacteria was approximately
2%, and that due to yeast or fungi was approximately 1%.
The bacteria most frequently involved in superinfections were
resistant strains of P. aeruginosa, P. maltophilia, and S.
epidermidis.

Resistance to Primaxin developed in 27 of 143 (19%) Pseudomonas
aeruginosa isolates. Many of these were isolated from sputum or
endotracheal tubes or from chronic wounds. One strain each of
Proteus mirabilis and enterococcus also developed resistance to
Primaxin.

SAFETY

Total No. of Patients: 717
No. of Patients with Systemic Side Effects: 81(11.3%)
No. of Patients with Local Side Effects: 18(2.5%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Nausea	16(2.2%)	2(0.3%)	6(0.8%)	7(0.9%)	1(0.1%)
Vomiting	12(1.8%)	4(0.6%)	4(0.6%)	2(0.3%)	2(0.3%)
Diarrhea	16(2.2%)	5(0.7%)	8(1.7%)	1(0.1%)	2(0.3%)
Pseudomem-branous colitis*	3(0.4%)			3(0.4%)	
Heartburn	1(0.1%)		1(0.1%)		
Pruritus	2(0.3%)		1(0.1%)	1(0.1%)	
Facial edema	1(0.1%)			1(0.1%)	
Rash	7(0.9%)		3(0.4%)	3(0.4%)	1(0.1%)
Urticaria	2(0.3%)			1(0.1%)	1(0.1%)
Erythema multiforme	1(0.1%)				1(0.1%)
Pruritus vulvae	1(0.1%)		1(0.1%)		
Fever	4(0.5%)		3(0.4%)		1(0.1%)
Septic shock	2(0.3%)	2(0.3%)			
Tinnitus	1(0.1%)		1(0.1%)		
Vertigo	2(0.3%)		2(0.3%)		
Headache	3(0.4%)	1(0.1%)	2(0.3%)		
Confusion	3(0.4%)	2(0.3%)		1(0.1%)	
Dizziness	2(0.3%)	1(0.1%)	1(0.1%)		
Encephalopathy	1(0.1%)			1(0.1%)	
Seizures	9(1.3%)	3(0.4%)	3(0.4%)	3(0.4%)	
Myoclonus	2(0.3%)			2(0.3%)	
Palpitations	1(0.1%)		1(0.1%)		
Hypotension	7(0.9%)	4(0.5%)	3(0.4%)		
Chest pain	2(0.3%	1(0.1%)	1(0.1%)		
Dyspnea	1(0.1%)	1(01.%)			

(Continued)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Syncope	1(0.1%)	1(0.1%)			
Cyanosis	1(0.1%)		1(0.1%)		
Polyarthropathy	1(0.1%)		1(0.1%)		

LOCAL SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Phlebitis/thrombo- phlebitis	16(2.2%)		2(0.3%)	12(1.7%)	2(0.3%)
Infused vein pain	2(0.3%)			1(0.1%)	1(0.1%)

*Five other patients had abnormal intestinal mucosa on colonoscopy
or sigmoidoscopy or had C. difficile toxin in their stools.

A brief description of the events surrounding the development of
seizures in nine patients follows:

Patients with seizures considered 'probably not drug related' by the investigator

A 44 year-old male with osteomyelitis developed a single episode of
tonic-clonic seizure activity on day 26 of Primaxin therapy. No
cause for his seizure could be found with the possible exception that
he was also being treated with hyperbaric oxygen. The patient was
medicated with phenytoin, and Primaxin therapy was continued for a
total of 6 weeks without further seizures.

A 63 year-old male with a history of COPD, CHF, alcoholism, liver
disease, esophogeal varices, and a left lung mass developed
respiratory distress after aspiration. He was intubated and started
on Primaxin therapy. The patient became hypotensive and developed
renal failure and acidosis. On the fifth day of Primaxin treatment
he developed status epilepticus as an agonal event.
At autopsy he was found to have carcinomatous pneumonia with
metastases to lymph nodes, adrenal glands, liver, brain, and bones.

A 30 year-old female with history of multiple sclerosis and seizure
disorder developed a septicemia and was placed on Primaxin therapy.
After 14 days of treatment she had one seizure without obvious cause
except for her underlying seizure disorder. An extensive work-up,
including LP, EEG, CT scan, was unrewarding. Phenytoin treatment was
started, and she was treated with Primaxin for 6 more days without
any more seizures.

Patients with seizures considered 'possibly drug related' by the
Investigator

A 69 year-old female with a history of seizure disorder (on Dilantin
maintenance) was started on Primaxin treatment, but Dilantin was not
administered. On the 3rd day of treatment she started having
multiple seizures. Primaxin was discontinued on the 6th day partly
because no organism was cultured and partly because of the seizures.
After reinstitution of Dilantin and institution of phenobarbital her
seizures were controlled.
During her hospitalization this patient had received metoclopramide
which is contraindicated in patients with history of seizures,
because it can increase the frequency and severity of seizures.

A 71 year-old female with a history of COPD, respiratory
insufficiency (respirator-dependent), and arrythmias developed
quadriparesis possibly due to a brainstem infarct. One day after
Primaxin was started for the treatment of pneumonia, she developed
supra-ventricular tachycardia with marked hypotension. On the 3rd
and 4th days of Primaxin therapy she had brief (1-2 min) tonic/clonic
seizures, and the Primaxin dose was lowered. From the 6th to the 9th
day of therapy she had intermittent seizures (treated with Dilantin
and phenobarbital) and episodes of bradycardia and marked
hypotension. Because a resistant Pseudomonas was isolated from the
sputum, Primaxin was discontinued, and clindamycin and amikacin were
started. She continued to have seizures while on these antibiotics,
along with severe episodes of hypotension. She finally died six days
after therapy had been discontinued.

A 68 year-old male had a past history of ASCVD, poorly-controlled
insulin dependent diabetes, chronic renal insufficiency, and organic
CNS disease (chronic organic brain syndrome secondary to multiple
cerebrovascular accidents). Two weeks following amputation of a
gangrenous foot, a new episode of CVA occurred. The patient's
impaired level of consciousness continued to deteriorate, and he
developed CHF and acute respiratory failure probably secondary to
aspiration. He had to be intubated and required mechanical
ventilation and subsequently developed a gram-negative pneumonia.
Treatment with cefamandole was instituted, but when the patient
failed to improve and cefamandole-resistant organisms were isolated,
Primaxin therapy was initiated. On the 5th day of treatment, 10
minutes after he had both jugular and subclavian catheters removed,
he experienced a 30-60 second grand mal seizure Laboratory
evaluation at that time revealed a blood sugar greater than 300 and a
serum calcium of 3.6. An additional decreased dose of Primaxin was
given and tolerated without incident. The patient subsequently
recovered.

Patients with seizures considered 'possibly drug related' by the
investigator

A 69 year-old female with a history of seizure disorder (on Dilantin
maintenance) was started on Primaxin treatment, but Dilantin was not
administered. On the 3rd day of treatment she started having
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serum calcium of 3.6. An additional decreased dose of Primaxin was
given and tolerated without incident. The patient subsequently
recovered.

Patients with seizures considered 'probably drug related' by the
investigator

A 90 year-old female was treated with Primaxin for a bacterial
septicemia. On the 14th day of treatment she developed a grand mal
seizure which lasted approximately 2 minutes. Laboratory values at
that time were normal. A CT head scan with contrast showed diffuse
cortical atrophy.

A 70 year-old female with a past history of grand mal seizures (3
occurrences over a 48 hour interval) was treated with Primaxin for an
osteomyelitis. On the 4th day of treatment the patient experienced
myoclonic activity, and on the 6th day she had a grand mal seizure.
This event and the ensuing post-ictal state lasted for approximately
24 hours during which time neurologic evaluation demonstrated a
normal CT scan of the head, EEG, and LP (except for an increased CSF
protein). Primaxin therapy was discontinued, and the patient was
started on Dilantin and recovered without any focal neurological
deficit.

A 77 year-old female with endocarditis was placed on Primaxin
treatment. On the 6th day of therapy she developed grand mal
seizures. A CAT scan showed possible cerebral emboli. She was
started on Dilantin therapy and had seizures again on day 15 and 16
of therapy. Primaxin was discontinued on day 18, and she had no
further seizures.

Deaths: Forty-five deaths were reported in this study. None was
considered by the investigator to be related to Primaxin therapy.

Abnormal Laboratory Tests

Test	
Hemoglobin	(D) 4
Hematocrit	(D) 4
WBC	(D)11
Neutrophils	(D) 3
Monocytes	(I) 2
Eosinophils	(I)27
Platelets	(I)12
	(D) 6
Positive Coombs' test	16
Prothrombin time	(I) 2
BUN	(I) 2
Creatinine	(I) 1
Bilirubin	(I) 3
SGOT (AST)	(I)26

(Continued)

Abnormal Laboratory Tests

Test
SGPT (ALT)	(I)25
Alkaline phosphatase	(I)23
Serum chloride	(I) 3
Urine protein	(I) 1
WBCs in urine	(I) 1
Urine bilirubin	(I) 3
Urine urobilinogen	(I) 4

Summary and Conclusions

This was an open, multiclinic, non-comparative study of the efficacy and safety of Primaxin in the treatment of patients with serious infections caused by susceptible pathogenic bacteria.
A total of 717 patients, 437 males and 280 females, ranging in age from 12 to 101 years were enrolled in this protocol.
Five hundred and six patients with 573 sites of infection were acceptable for evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure or improvement occurred in 123/129 (95%) skin and skin structure infections, in 48/53 (91%) bone and/or joint infections, in 93/108 (86%) lower respiratory tract infections, in 46/49 (94%) gynecologic infections, in 42/44 (95%) intra-abdominal infections, in 12/12 (100%) uncomplicated urinary tract infections, in 71/73 (97%) complicated urinary tract infections, in 64/66 (97%) bacterial septicemia, and in 9/9 (100%) patients with endocarditis.

As shown in the table depicting the bacteriologic response to Primaxin treatment, the eradication rate for most infections was, in general, very good considering the nature of the infections treated. Regarding the low eradication rate of P. aeruginosa in lower respiratory tract infections, it should be noted that many of these patients had severe infections superimposed on some chronic lung disease (COPD, cystic fibrosis, bronchiectasis) where complete eradication of the infecting organism is hardly ever achieved. In addition, many of these patients had previously failed treatment with other antibiotic regimens to which the organism had developed resistance.

Systemic side effects were reported in 11.3% of the patients. The most common side effects were nausea, vomiting, diarrhea, and allergic skin rashes. Seizures and/or myoclonus occurred in 1.5% of the patients.

Local side effects were reported in 2.5% of the patients.

The most commonly reported abnormal laboratory values were eosinophilia and abnormal liver function tests.

(Continued)

Abnormal Laboratory Tests

Test
SGPT (ALT)   (I)25
Alkaline phosphatase   (I)23
Serum chloride   (I) 3
Urine protein   (I) 1
WBCs in urine   (I) 1
Urine bilirubin   (I) 3
Urine urobilinogen   (I) 4

Summary and Conclusions

This was an open, multiclinic, non-comparative study of the efficacy and
safety of Primaxin in the treatment of patients with serious infections caused
by susceptible pathogenic bacteria.
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side effects were nausea, vomiting, diarrhea, and allergic skin rashes.
Seizures and/or myoclonus occurred in 1.5% of the patients.

Local side effects were reported in 2.5% of the patients.

The most commonly reported abnormal laboratory values were eosinophilia and
abnormal liver function tests.

2.   Protocol No. 009
      Title: "An Open, Multiple-Dose Clinical Pharmacology and Therapeutic
      Study of the Safety, Tolerance, and Eff cacy of Primaxin
      (imipenem/cilastatin) in the Parenteral Therapy of Bacterial
      Infections in Hospitalized Patients."

      Study Design and Procedure: This was an open multiple-dose study
      conducted in 20 hospitalized patients with proven or suspected
      bacterial infections caused ry pathogens presumed or known to be
      susceptible to Primaxin.

      Upon admission to the hospital each patient had a complete history
      and physical examination, and all abnormal signs and symptoms
      relating to both the acute infection and to background diseases were
      noted and recorded.
      Following appropriate diagnostic studies, patients were treated with
      Primaxin, 500 mg every 6 hours, by constant intravenous infusion of
      approximately 20 minutes duration.
      During the study period, daily measurements of temperature, pulse,
      blood pressure, and respiratory rate were recorded.

      The clinical and bacteriological course of the patient was followed
      and documented with serial observations including safety studies of
      blood and urine obtained before, during, and after therapy.
      Patients were observed with particular attention to any evidence of
      allergic reactions including rash, itching, or anaphylactic
      manifestations. Daily observations of the tolerance of intravenous
      therapy were made.

      Multiple blood samples for drug assay were obtained following the
      first dose and again following a dose given within the last 3 days of
      drug therapy. The total urine voided during the 6 hour dosing
      interval on each of these occasions was collected at 0-1, 1-2, 2-4,
      and 4-6 hours.

      At the conclusion of drug therapy, and after all clinical and
      laboratory data were obtained, judgment was made on the clinical and
      bacteriological efficacy of study drug therapy, its safety and
      tolerability.

Summary of Study Conducted Under Protocol No. 009

Investigator: W. Lance George, M.D., V.A. Wadsworth Medical Center, Los
Angeles, California

TOTAL NO. OF PATIENTS: 20

AGE RANGE (Years): 39-76

MEAN AGE (Years): 56.1

SEX:
    Male: 20

EVALUA,ION

EFFICACY
NO. OF CASES EVALUABLE: 15
NO. OF SITES OF INFECTION EVALUABLE: 16
NO. OF CASES UNEVALUABLE: 5

REASONS CASES UNEVALUABLE
No pre-treatment pathogen: 2
Inadequate bacteriologic culture: 2
No post-treatment follow-up: 1

DURATION OF TREATMENT
   (Evaluable Cases)

DAYS	NO. OF PATIENTS
4-14	7
15-29	3
30-41	5

RESULTS

		CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE (cellulitis)	1	1(100%)		
BONE/JOINT (Osteomyelitis, pyogenic arthritis)	6	1(16.7%)	5(83.3%)	
LOWER RESPIRATORY (Pneumonia, bronchitis)	2	1(50%)	1(50%)	
UTI (Uncomplicated) (Cystitis)	1	1(100%)		
UTI (Complicated) (Cystitis)	6	3(50%)	3(50%)	

ORGANISM	NO.	BACTERIOLOGIC RESPONSE ERADICATED	NOT ERADICATED
SKIN & SKIN STRUCTURE			
Corynebacterium spp	1	1(100%)	
S. aureus(R)	1	1(100%)	
E. coli	1	1(100%)	
BONE/JOINT			
S. aureus(R)	2	2(100%)	
Streptococcus spp	1	1(100%)	
E. coli	2	2(100%)	
M. morganii	1	1(100%)	
P. mirabilis	2	1(50%)	1(50%)
P. aeruginosa	4	3(75%)	1(25%)
B. fragilis	1	1(100%)	
B. vulgatus	1	1(100%)	
LOWER RESPIRATORY			
E. coli	1	1(100%)	
P. mirabilis	1		1(100%)
P. aeruginosa	2	1(50%)	1*(50%)
S. marcescens	1	1(100%)	
UTI (Uncomplicated)			
E. coli	1	1(100%)	
UTI (Complicated)			
Strep. (Group B)	2	2(100%)	
Strep. (Group D enterococci)	1	1(100%)	
E. coli	4	2(50%)	2(50%)
C. diversus	1		1(100%)
Citrobacter spp	1	1(100%)	

*P. aeruginosa persisted in one patient with pneumonia and underlying bronchiectasis. Organisms are usually difficult to eradicate in this chronic condition.

SAFETY

TOTAL NO. OF PATIENTS: 20
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 2(10%)
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 1(5%)

SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Fever	1(5%)	1(5%)			
Abdominal pain	1(5%)	1(5%)			
Diarrhea	1(5%)		1(5%)		

ORGANISM	NO.	BACTERIOLOGIC RESPONSE	
		ERADICATED	NOT ERADICATED
SKIN & SKIN STRUCTURE			
Corynebacterium spp	1	1(100%)	
S. aureus(R)	1	1(100%)	
E. coli	1	1(100%)	
BONE/JOINT			
S. aureus(R)	2	2(100%)	
Streptococcus spp	1	1(100%)	
E. coli	2	2(100%)	
M. morganii	1	1(100%)	
P. mirabilis	2	1(50%)	1(50%)
P. aeruginosa	4	3(75%)	1(25%)
B. fragilis	1	1(100%)	
B. vulgatus	1	1(100%)	
LOWER RESPIRATORY			
E. coli	1	1(100%)	
P. mirabilis	1		1(100%)
P. aeruginosa	2	1(50%)	1*(50%)
S. marcescens	1	1(100%)	
UTI (Uncomplicated)			
E. coli	1	1(100%)	
UTI (Complicated)			
Strep. (Group B)	2	2(100%)	
Strep. (Group D enterococci)	1	1(100%)	
E. coli	4	2(50%)	2(50%)
C. diversus	1		1(100%)
Citrobacter spp	1	1(100%)	

*P. aeruginosa persisted in one patient with pneumonia and underlying bronchiectasis. Organisms are usually difficult to eradicate in this chronic condition.

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SYSTEMIC SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Fever	1(5%)	1(5%)			
Abdominal pain	1(5%)	1(5%)			
Diarrhea	1(5%)		1(5%)		

(Continued)

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL					
Phlebitis	1(5%)		1(5%)		

Abnormal Laboratory Tests

Hemoglobin	(D)1
Hematocrit	(D)1
WBC	(D)1
Eosinophils	(I)1
Platelets	(D)1
SGPT	(I)1
Positive Coombs' test	1

PHARMACOKINETICS

Based on creatinine clearance (GFR) information, the majority of the patient population enrolled in this study could be divided into two groups: those with apparently normal renal function and those with mild renal impairment. In patients with GFR $>$ 100 ml/min, the urinary recovery of imipenem during each dose interval averaged 50-57% of the dose, and mean renal clearance was between 105 and 128 ml/min.

In patients with GFR $<$ 100 ml/min, the urinary recovery of imipenem averaged 37-46% of the dose, and mean renal clearance was 69-88 ml/min. In the same comparison, the urinary excretion of cilastatin was 52% to 68% of the dose, and renal clearance averaged between 101 and 123 ml/min (GFR $>$ 100) while in patients with mild renal impairment, urinary excretion of cilastatin averaged 41-45% of the dose, and mean renal clearance was between 50 and 72 ml/min.

In this study the urinary excretion of either imipenem or cilastatin in patients with apparent normal renal function was somewhat lower than expected. The reason for this occurrence is not obvious, although most subjects were noted as having neurologic disorders leading to a neurogenic bladder, difficulty in voiding, and/or urine reduction.

The plasma clearance of imipenem averaged 201-223 ml/min during each dosing interval studied in patients with GFR $>$ 100 ml/min and 167-176 ml/min in patients with GFR $<$ 100 ml/min.

The mean area-under-the serum curve (AUC) was 25% greater in patients with mild renal impairment, but the AUC did not change from the first to the 9th dose for either group. Similarly, cilastatin plasma clearance averaged 215-223 ml/min in patients with GFR $>$ 100 ml/min during each dosing interval and 142-159 ml/min in patients with GFR $<$ 100 ml/min. The AUC was 50% greater in patients with mild renal impairment but did not change between dosing intervals for either group.

The plasma half-life of imipenem and cilastatin did not change throughout the study for either group but was slightly longer in patients with mild renal impairment.

These results indicate that repeated administration of 500 mg each of imipenem/cilast in every 6 hours does not alter the disposition of either drug in patients with normal renal function or patients with mild renal impairment from that observed after a single dose. Little if any accumulation of either drug occurs in either patient group indicating that steady state conditions prevail by the end of the first day's dosing.

3. Compassionate Protocol No. 002
Early in the Primaxin program a special protocol was designed which would allow the entry of patients who would need the antibiotic on a compassionate basis.
As a rule, most patients treated under this protocol were seriously ill and had already been treated with several courses of other antibiotics. With rare exceptions, Primaxin was not made available unless it was the only antibiotic (or at least the only beta-lactam) to which the primary pathogen(s) was (were) susceptible. In addition, because early in these studies the rate of development of resistance to Primaxin was unknown, Merck insisted upon the adjunctive use of a second antibiotic, usually an aminoglycoside. However, although virtually every patient received two antibiotics, many had organisms susceptible only to Primaxin; therefore, these cases were eligible for evaluation of drug efficacy.

Forty patients were treated with Primaxin under the compassionte protocol. They ranged in age from 16 to 81 years with a mean age of 43.9 years. There were 17 females and 23 males. Primaxin was administered at the following daily doses:

        1G - 2 patients
        2G - 13 patients
        3G - 10 patients
        4G - 15 patients

Duration of treatment was as follows:

        3 - 5 days   6 patients
        6 - 10   7 patients
        11 - 15   11 patients
         ≥ 16   16 patients

The results obtained in 13 patients considered eligible for efficacy evaluation were as follows:

INFECTION	NO.	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
LOWER RESPIRATORY	8	1(12.5%)	5(62.5%)	2(25.0%)
INTRA-ABDOMINAL	2		2(100%)	
BACTERIAL SEPTICEMIA	1		1(100%)	
SKIN & SKIN STRUCTURE	2		1(50%)	1(50%)

ORGANISM	NO.	BACTERIOLOGIC RESPONSE	
		ERADICATED	NOT ERADICATED
LOWER RESPIRATORY			
Acinetobacter calcoaceticus	3	2(66.7%)	1(33.3%)
P. aeruginosa	6		6(100%)
P. maltophilia	1		1(100%)
S. marcescens	1		1(100%)
INTRA-ABDOMINAL			
P. aeruginosa	2	2(100%)	
P. fluorescens	1		1(100%)
BACTERIAL SEPTICEMIA			
P. aeruginosa	1	1(100%)	
SKIN & SKIN STRUCTURE			
Strep (Group D enterococci)	2	1(50%)	1(50%)
Enterobacter cloacae	1		1(100%)
P. aeruginosa	2		2(100%)

SAFETY

NO. OF PATIENTS: 40
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 2(5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 8(20%)

SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL					
Erythema I.V. site	1(2.5%)	1(2.5%)			
Phlebitis/thrombo- phlebitis	1(2.5%)			1(2.5%)	

The results obtained in 13 patients considered eligible for efficacy
evaluation were as follows:

INFECTION	NO.	CLINICAL RESPONSE		
		CURE	IMPROVE	FAIL
LOWER RESPIRATORY	8	1(12.5%)	5(62.5%)	2(25.0%)
INTRA-ABDOMINAL	2		2(100%)	
BACTERIAL SEPTICEMIA	1		1(100%)	
SKIN & SKIN STRUCTURE	2		1(50%)	1(50%)

ORGANISM	NO.	BACTERIOLOGIC RESPONSE	
		ERADICATED	NOT ERADICATED
LOWER RESPIRATORY			
Acinetobacter calcoaceticus	3	2(66.7%)	1(33.3%)
P. aeruginosa	6		6(100%)
P. maltophilia	1		1(100%)
S. marcescens	1		1(100%)
INTRA-ABDOMINAL			
P. aeruginosa	2	2(100%)	
P. fluorescens	1		1(100%)
BACTERIAL SEPTICEMIA			
P. aeruginosa	1	1(100%)	
SKIN & SKIN STRUCTURE			
Strep (Group D enterococci)	2	1(50%)	1(50%)
Enterobacter cloacae	1		1(100%)
P. aeruginosa	2		2(100%)

SAFETY

NO. OF PATIENTS: 40
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 2(5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 8(20%)

SIDE EFFECTS

	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL					
Erythema I.V. site	1(2.5%)	1(2.5%)			
Phlebitis/thrombo-phlebitis	1(2.5%)			1(2.5%)	

(Continued)

SIDE EFFECTS

SYSTEMIC	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Chills	1(2.5%)	1(2.5%)			
Nausea	2(5%)	1(2.5%)	1(2.5%)		
Dysuria	1(2.5%)	1(2.5%)			
Nystagmus	1(2.5%)	1(2.5%)			
Hyperhydrosis	1(2.5%)	1(2.5%)			
Confusion	1(2.5%)	1(2.5%)			
Hearing loss	2(5%)	2(5%)			
Apnea	1(2.5%)	1(2.5%)			
Intracerebral hemorrhage	1(2.5%)	1(2.5%)			
Oliguria and anuric	1(2.5%)	1(2.5%)			
Convulsive disorder	2(5%)	1(2.5%)		1(2.5%)	

Both patients who developed hearing loss were also receiving an aminoglycoside antibiotic which could have contribued to this adverse effect.

Of the two patients who developed convulsions, one had recurrent seizures while on tobramycin and cefoperazone, 2 weeks after Primaxin therapy had been discontinued. The other patient was found to have a cerebellar abscess at autopsy.

Deaths: Twelve patients died during or shortly after Primaxin treatment. All were considered by the investigators "definitely not drug related".

Abnormal Laboratory Tests
Leukopenia	2 cases
Neutropenia	2 cases
Eosinophilia	3 cases
Increased SGOT	1 case
Increased alkaline phosphatase	2 cases
Increased serum creatinine	1 case

CLINICAL STUDIES (Foreign)

I. Controlled (3 Studies)

    1. Protocol No. 514
        Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety and Tolerance of I.V. Administered Primaxin and Cephalothin in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

Study Design: This was an open, controlled, randomized, multiclinic study to compare the efficacy, safety and tolerability of Primaxin versus cephalothin in the treatment of hospitalized patients with infections caused by susceptible bacteria.

Procedure: Patients were assigned to receive either Primaxin or cephalothin according with a computer-generated, randomized allocation schedule.
Each patient in the Primaxin group received 250 mg every 6 hours, and those in the cephalothin group received 2 grams every 6 hours. Both antibiotics were administered by intravenous infusion over 15 to 30 minutes.
Patients were to be treated for a minimum of 5 days.

After signing an informed consent form, all patients provided a complete clinical history and underwent a physical examination.
During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded.
A daily infusion tolerance record of the study drug was kept.
Tolerance was evaluated on the basis of pain, erythema, induration of the vein, and ulceration of the infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function were carried out in all patients before study drug therapy, four to seven days after initiation of therapy, and one to three days after termination of therapy. Additional diagnostic test (e.g., X-ray, sonography) were performed as indicated.

Blood cultures and cultures of other suspected sites were obtained prior to, during, and after study drug therapy. Gram stains and standard bacteriologic susceptibility tests were performed on all cultures. Standard susceptibility tests were performed by either disc or broth dilution method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

The five investigators who conducted studies under this protocol and their affiliations are listed below:

   Y. Benard, Centre Hospitalier Universitaire Co'te de Nacre, Caen, France.
   M. Des Roseaux, Centre Hospitalier Universi aire, Co'te de Nacre, Caen, France.
   J. Modal, Hopital Claude Bernard, Paris, France.
   F. Vachon, Hopital Claude Bernard, Paris, France.
   D. L. Tyrell, University of Alberta, Edmonton, Alberta, Canada.

Study Design: This was an open, controlled, randomized, multiclinic study to compare the efficacy, safety and tolerability of Primaxin versus cephalothin in the treatment of hospitalized patients with infections caused by susceptible bacteria.

Procedure: Patients were assigned to receive either Primaxin or cephalothin according with a computer-generated, randomized allocation schedule.
Each patient in the Primaxin group received 250 mg every 6 hours, and those in the cephalothin group received 2 grams every 6 hours. Both antibiotics were administered by intravenous infusion over 15 to 30 minutes.
Patients were to be treated for a minimum of 5 days.

After signing an informed consent form, all patients provided a complete clinical history and underwent a physical examination.
During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded.
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Blood cultures and cultures of other suspected sites were obtained prior to, during, and after study drug therapy. Gram stains and standard bacteriologic susceptibility tests were performed on all cultures. Standard susceptibility tests were performed by either disc or broth dilution method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

The five investigators who conducted studies under this protocol and their affiliations are listed below:

    Y. Benard, Centre Hospitalier Universitaire Co'te de Nacre, Caen, France.
    M. Des Roseaux, Centre Hospitalier Universitaire, Co'te de Nacre, Caen, France.
    J. Mod i, Hopital Claude Bernard, Paris, France.
    F. Vacnon, Hopital Claude Bernard, Paris, France.
    D. L. Tyrell, University of Alberta, Edmonton, Alberta, Canada.

Summary of Studies Conducted Under Protocol No. 514

	PRIMAXIN	CEPHALOTHIN
TOTAL NO. OF PATIENTS	47	38
AGE RANGE (Years)	19-68	20-75
MEAN AGE (Years)	50.9	52.5
SEX		
Male	28	20
Female	19	18

EVALUATION

EFFICACY

	PRIMAXIN	CEPHALOTHIN
NO. OF CASES EVALUABLE	15	11
NO. OF SITES OF INFECTION EVALUABLE	16	11
NO. OF CASES UNEVALUABLE	32	27

REASONS CASES UNEVALUABLE

No pre-treatment pathogen	17	15
Clinical diagnosis not clear	2	1
Effective concomitant antibiotic	1	0
Treatment course too short	3	2
Inadequate cultures	9	9

DOSE (Evaluable Cases)   250 mg q 6 h   2g q 6 h

DURATION OF TREATMENT (Days)   6-15   5-14
    (Evaluable Cases)

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	CEPHALOTHIN CLINICAL RESPONSE CURE	IMP.	FA
SKIN & SKIN STRUCTURE (Abscess)	1	1(100%)			-			
LOWER RESPIRATORY (Bronchitis, pneumonia, empyema)	7	5(71%)		2(29%)	5	4(80%)	1(20%)	
SEPTICEMIA	3	3(100%)			4	3(75%)	1(25%)	
UTI (Uncomp) (cystitis, pyelonephritis)	4	4(100%)			1	1(100%)		
UTI (Complicated) (pyelonephritis)	1	1(100%)			1	1(100%)		

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEPHALOTHIN BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE								
S. aureus(S)*	1	1(100%)			-			
LOWER RESPIRATORY								
K. pnuemoniae	-				1	1(100%)		
P. multocida	1	1(100%)			-			
K. ozaenae	1	1(100%)			-			
E. coli	1	1(100%)			-			
S. pneumoniae	2	2(100%)			1	1(100%)		
P. aeruginosa	1	1(100%)			-			
H. influenzae	2	2(100%)			3	3(100%)		
SEPTICEMIA								
E. coli	1	1(100%)			2	2(100%)		
B. fragilis	1	1(100%)			-			
S. pneumoniae	1	1(100%)			1	1(100%)		
P. mirabilis	-				1	1(100%)		
UTI (Uncomp.)								
E. coli	4	4(100%)			1	1(100%)		
UTI (Complicated)								
K. pneumoniae	1	1(100%)			-			
E. coli	-				1	1(100%)		

*(S) = Sensitive

In the Primaxin treated group, 1 patient with an empyema developed a reinfection with a resistant P. aeruginosa strain. In the Cephalothin treated group, 1 patient with urinary tract infection developed a reinfection.

SAFETY

	PRIMAXIN	CEPHALOTHIN
TOTAL NO. OF PATIENTS	47	38
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	2(4%)	4(10.5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	1(2%)	1(3%)

LOCAL SIDE EFFECTS

		PRIMAXIN
		PROBABLY
	NO.	RELATED
Pain on infusion	1(2.1%)	1(2.1%)
Phlebitis/thrombo- phlebitis	1(2.1%)	1(2.1%)

	NO.	CEPHALOTHIN PROBABLY RELATED
Pain on infusion	1(2.6%)	1(2.6%)
Phlebitis/thrombo-phlebitis	1(2.6%)	1(2.6%)
Venous intolerance	1(2.6%)	1(2.6%)
Erythema, IV Site	1(2.6%)	1(2.6%)

SYSTEMIC SIDE EFFECTS

	PRIMAXIN	DEFINITELY RELATED
Pruritus	1	1(2.1%)

		CEPHALOTHIN
STEVENS-JOHNSON SYNDROME	1	1(2.6%)

Deaths

Two patients in the cephalothin group died during treatment. They were judged by the investigators to be definitely not drug-related.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEPHALOTHIN
Eosinophils	1/6	1/1
SGOT (AST)	1/4	1/1
SGPT (ALT)	1/1	0
Bilirubin	1/1	
Alk. phosphatase	1/1	1/1
LDH	1/1	0

Summary and Conclusions

This was an open, randomized, controlled multicenter study comparing Primaxin and cephalothin in the treatment of infections caused by susceptible bacteria.

A total of 47 patients, 28 males and 29 females, ranging in age from 19 to 68 years were enrolled in the Primaxin group. A total of 38 patients, 20 males and 18 females, ranging in age from 20 to 75 years were enrolled in the cephalothin group. Demographic characteristics of patients in each treatment group were similar.

Fifteen patients with 16 sites of infection in the Primaxin group and 11 patients in the cephalothin group were acceptable for evaluation of drug efficacy. All patients were considered in assessing safety.

Clinical cure or improvement occurred in 14/16 (87.5%) infections in the Primaxin treated patients and in 11/11 (100%) in the cephalothin treated patients.

One of the treatment failures in the Primaxin group occurred in a patient with empyema who developed a reinfection with a <u>Pseudomonas</u> strain resistant to Primaxin.

A favorable bacteriological outcome (eradication) was achieved in 17 (100%) of 17 organisms isolated in the Primaxin group and in 11 (100%) of 11 organisms isolated in the cephalothin group.

Systemic side effects were reported in 2% of the patients in the Primaxin group and in 3% of the patients in the cephalothin group. Local side effects were reported in 4% of the patients in the Primaxin group and in 10.5% of the patients in the cephalothin group.

The laboratory test abnormalities reported in the Primaxin group were eosinophilia (6 patients), increased SGOT values (4 patients), and an instance each of elevated SGPT, bilirubin, alkaline phosphatase, and LDH values. In the cephalothin group, one instance each of eosinophilia, and elevated SGOT and alkaline phosphatase values.

No deaths occurred in the Primaxin group, and two occurred in the cephalothin group. They were judged by the investigators as "definitely not drug related".

Results of this study demonstrate Primaxin and cephalothin are relatively safe and effective in the treatment of patients with serious infections caused by susceptible bacteria.

2.   Protocol No. 513
      Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety, and Tolerance of Intravenously Administered Primaxin and Cefotaxime in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

      Study Design: This was an open, active, drug-controlled, randomized, multiclinic study to compare the efficacy, safety, and tolerance of Primaxin and Cefotaxime in the intravenous treatment of hospitalized patients with infections caused by bacteria persumed susceptible to both agents.

      Procedure: Treatment group assignment was made using a computer-generated randomization allocation schedule. Having completed the informed consent procedure and screening for study eligibility, patients were allocated either to the Primaxin or the Cefotaxime group.
      Each patient in the Primaxin group received a total daily dose of 1.5 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.
      Patients in the Cefotaxime group received a total daily dose of 6 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.

One of the treatment failures in the Primaxin group occurred in a patient with empyema who developed a reirfection with a Pseudomonas strain resistant to Primaxin.

A favorable bacteriological outcome (eradication) was achieved in 17 (100%) of 17 organisms isolated in the Primaxin group and in 11 (100%) of 11 organisms isolated in the cephalothin group.

Systemic side effects were reported in 2% of the patients in the Primaxin group and in 3% of the patients in the cephalothin group. Local side effects were reported in 4% of the patients in the Primaxin group and in 10.5% of the patients in the cephalothin group.

The laboratory test abnormalities reported in the Primaxin group were eosinophilia (6 patients), increased SGOT values (4 patients), and an instance each of elevated SGPT, bilirubin, alkaline phosphatase, and LDH values. In the cephalothin group, one instance each of eosinophilia, and elevated SGOT and alkaline phosphatase values.

No deaths occurred in the Primaxin group, and two occurred in the cephalothin group. They were judged by the investigators as "definitely not drug related".

Results of this study demonstrate Primaxin and cephalothin are relatively safe and effective in the treatment of patients with serious infections caused by susceptible bacteria.

2.   Protocol No. 513
      Title: "A Multiclinic, Randomized Study of the Comparative Efficacy, Safety, and Tolerance of Intravenously Administered Primaxin and Cefotaxime in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

      Study Design: This was an open, active, drug-controlled, randomized, multiclinic study to compare the efficacy, safety, and tolerance of Primaxin and Cefotaxime in the intravenous treatment of hospitalized patients with infections caused by bacteria persumed susceptible to both agents.

      Procedure: Treatment group assignment was made using a computer-generated randomization allocation schedule. Having completed the informed consent procedure and screening for study eligibility, patients were allocated either to the Primaxin or the Cefotaxime group.
      Each patient in the Primaxin group received a total daily dose of 1.5 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.
      Patients in the Cefotaxime group received a total daily dose of 6 g administered in three equal doses as an intravenous infusion over 30 minutes every 8 hours.

Before entry into the study, all patients provided a complete
clinical history and underwent a physical examination. During the
study drug period, daily measurements of temperature, pulse, blood
pressure, and respiratory rate were recorded. A daily infusion
tolerance record of the study drug was kept. Tolerance was evaluated
on the basis of pain, erythema, induration of the vein, and
ulceration of the infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function
were carried out in all patients before, during, and after
termination of therapy. Additional diagnostic tests (e.g., x-ray,
sonography) were performed as indicated.

Blood cultures and cultures of other suspected sites were obtained
prior to, during, and after study drug therapy. Gram stains and
standard bacteriologic susceptibility tests (by either disc or broth
dilution method) were performed in all cultures.

Response to treatment was assessed by both clinical and
bacteriological outcomes.

Thirteen investigators conducted studies under Protocol No. 513.
Their names and affiliations are listed below:

Achong, M., St. Joseph's Hospital, Hamilton, Ontario
Bowie, W., Vancouver General Hospital, Shaughnessy Hospital,
   Vancouver, Canada
Daikas, G., "King Paul" Hospital, University of Athens Medical
   School, Athens, Greece
Glauser, M., Clinique Medicale Universitaire, Lausanne,
   Switzerland
Hell, K., Chirurgische Abteilung, Liestal, Switzerland
Opperkuch, W., Ruhr-University of Bochum, Bochum, West Germany
Ronald, A., Basic Sciences Center, St. Boniface General Hosptial
   Winnipeg, Canada
Stamboulian, D., British Hospital of Buenos Aires, Buenos Aires,
   Argentina
Stille, W., Klinixum A. J. W. Gocthe-Universitaet, Frankfurt,
   West Germany
Ten Napel, C., Hospital 'Ziekenzorg', Enschede, Holland
Veriava, Y., Coronation Hosp.al, Johannesburg, South Africa
Wittmann, D., Allgemeines Krankenhaus Altona, Hamburg, West
   Germany
Yourassowsky, E., Hospital Brugmann, Brussels, Belgium

Overall Summary of Studies Conducted Under Protocol 513

	PRIMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS	123	111
AGE RANGE (Years)	16-80	18-81
MEAN AGE (Years)	52.6	54.9
SEX		
Male	78	65
Female	45	46

EVALUATION

EFFICACY

	PRIMAXIN	CEFOTAXIME
NO. OF CASES EVALUABLE	69	69
NO. OF SITES OF INFECTION EVALUABLE	88	84
NO. OF CASES UNEVALUABLE	54	42

REASONS CASES UNEVALUABLE

No pretreatment pathogen	24	19
Organism resistant to study drug	1	0
Clinical diagnosis not clear	2	1
Inadequate bacteriologic cultures	8	13
Effective concomitant antibiotic	4	2
Treatment course too short	15	6
Infection not included in claims	-	1

DOSE	PRIMAXIN	CEFOTAXIME
	500 mg q 8 h	2 g q 8 h

DURATION OF TREATMENT (Days)
(Evaluable Cases)

5-14	65 patients	63 patients
15-17	4 patients	5 patients
33		1 patient

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	CEFOTAXIME CLINICAL RESPONSE CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, erysipelas)	16	13(81%)	2(13%)	1(6%)	15	10(67%)	3(20%)	2(13%)
LOWER RESPIRATORY (Bronchitis, pneumonia, bronchopneumonia, empyema, lung abscess)	19	11(58%)	3(16%)	5(26%)	24	18(75%)	3(12.5%)	3(12.5%)

Overall Summary of Studies Conducted Under Protocol 513

	PRIMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS	123	111
AGE RANGE (Years)	16-80	18-81
MEAN AGE (Years)	52.6	54.9
SEX		
Male	78	65
Female	45	46

EVALUATION

EFFICACY

	PRIMAXIN	CEFOTAXIME
NO. OF CASES EVALUABLE	69	69
NO. OF SITES OF INFECTION		
EVALUABLE	88	84
NO. OF CASES UNEVALUABLE	54	42

REASONS CASES UNEVALUABLE

No pretreatment pathogen	24	19
Organism resistant to study drug	1	0
Clinical diagnosis not clear	2	1
Inadequate bacteriologic cultures	8	13
Effective concomitant antibiotic	4	2
Treatment course too short	15	6
Infection not included in claims	-	1

DOSE	PRIMAXIN	CEFOTAXIME
	500 mg q 8 h	2 g q 8 h

DURATION OF TREATMENT (Days)
   (Evaluable Cases)

	PRIMAXIN	CEFOTAXIME
5-14	65 patients	63 patients
15-17	4 patients	5 patients
33		1 patient

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	CEFOTAXIME CLINICAL RESPONSE CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, erysipelas)	16	13(81%)	2(13%)	1(6%)	15	10(67%)	3(20%)	2(13%)
LOWER RESPIRATORY (Bronchitis, pneumonia, bronchopneumonia, empyema, lung abscess)	19	11(58%)	3(16%)	5(26%)	24	18(75%)	3(12.5%)	3(12.5%)

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	CEFOTAXIME CLINICAL RESPONSE CURE	IMP.	FAIL
MEDIASTINITIS	1	1(100%)			1	1(100%)		
SEPTICEMIA	28	26(93%)		2(7%)	27	23(85%)	2(7.4%)	2(7.4%)
UTI (Complicated) (cystitis, pyelonephritis)	7	3(43%)	3(43%)	1(14%)	4	3(75%)	1(25%)	
UTI (Uncomplicated) (cystitis, pyelonephritis. perinephric abscess)	2	2(100%)			2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, cholecystitis)	15	6(40%)	5(33%)	4(27%)	11	10(91%)	1(9%)	

ORGANISM SKIN & SKIN STRUCTURE	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERAD	NO.	CEFOTAXIME BACTERIOLOGIC RESPONSE ERAD	SUPP	NOT ERAD
S. aureus$^{(S)}$	1	1(100%)			1	1(100%)		
S. aureus$^{(R)}$	6	5(83%)		1(17%)	4	4(100%)		
Strep (Group A)	2	2(100%)			2	2(100%)		
Strep (Group D)	1	1(100%)						
Alpha-hem strep	1	1(100%)						
S. intermedius	1	1(100%)						
S. faecalis	-				1			1(100%)
E. cloacae	-				3	3(100%)		
A. calcoaceticus	1	1(100%)						
A. odorans	1	1(100%)						
E. coli	6	6(100%)			2			2(100%)
K. pneumoniae	1	1(100%)			1	1(100%)		
M. morganii	2	1(50%)		1(50%)	1	1(100%)		
P. mirabilis	1			1(100%)				
P. vulgaris	-				1			1(100%)
P. aeruginosa	1	1(100%)			1	1(100%)		
S. marcescens	1	1(100%)			2	2(100%)		
Peptococcus sp.	2	2(100%)			1	1(100%)		
Peptostrep sp.	3	3(100%)						
B. fragilis	4	4(100%)			1			1(100%

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEFOTAXIME BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
LOWER RESPIRATORY								
S. aureus(R)	-				1	1(100%)		
S. bovis	1	1(100%)			--			
S. pneumoniae	4	4(100%)			9	9(100%)		
Beta-hem-strep	-				1	1(100%)		
Non-hem-strep	-				1	1(100%)		
E. cloacae	-				1	1(100%)		
F. coli	3	3(100%)			4	2(50%)		2(50%)
H. influenzae	5	4(80%)		1(20%)	6	6(100%)		
H. parainfluenzae	1	1(100%)			1	1(100%)		
K. pneumoniae	1	1(100%)			2	2(100%)		
P. mirabilis	3	1(33%)		2(67%)	1	1(100%)		
P. aeruginosa	2			2(100%)				
MEDIASTINITIS								
S. aureus(R)	1	1(100%)						
S. marcescens	-				1			1(100%)
SEPTICEMIA								
S. aureus(S)	-							
S. aureus(R)	5	4(80%)		1(20%)	4	1(100%)		
S. pneumoniae	3	3(100%)			1	1(100%)		
E. cloacae	2	2(100%)			-			
A. calcoaceticus	-				1	1(100%)		
C. diversus	-				1	1(100%)		
E. coli	11	10(91%)		1(9%)	15	13(87%)		2(13%)
H. influenzae	1	1(100%)						
K. pneumoniae	3	3(100%)			1	1(100%)		
K. oxytoca	-				1	1(100%)		
M. morganii	1	1(100%)			3	3(100%)		
P. mirabilis	-				1	1(100%)		
P. vulgaris	-				2	2(100%)		
S. marcescens	-				2	2(100%)		
Serratia spp.	1	1(100%)						
Meningococcus (Group B)	1	1(100%)						
B. fragilis	1	1(100%)						
UTI (Uncomp.)								
E. coli	1	1(100%)			2	2(100%)		
S. faecalis	1	1(100%)			-			
E. cloacae	1	1(100%)			-			

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEFOTAXIME BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
LOWER RESPIRATORY								
S. aureus[R]	-				1	1(100%)		
S. bovis	1	1(100%)			-			
S. pneumoniae	4	4(100%)			9	9(100%)		
Beta-hem-strep	-				1	1(100%)		
Non-hem-strep	-				1	1(100%)		
E. cloacae	-				1	1(100%)		
E. coli	3	3(100%)			4	2(50%)		2(50%)
H. influenzae	5	4(80%)		1(20%)	6	6(100%)		
H. parainfluenzae	1	1(100%)			1	1(100%)		
K. pneumoniae	1	1(100%)			2	2(100%)		
P. mirabilis	3	1(33%)		2(67%)	1	1(100%)		
P. aeruginosa	2			2(100%)				
MEDIASTINITIS								
S. aureus[R]	1	1(100%)						
S. marcescens	-				1			1(100%)
SEPTICEMIA								
S. aureus[S]	-							
S. aureus[R]	5	4(80%)		1(20%)	4	1(100%)		
S. pneumoniae	3	3(100%)			1	1(100%)		
E. cloacae	2	2(100%)			-			
A. calcoaceticus	-				1	1(100%)		
C. diversus	-				1	1(100%)		
E. coli	11	10(91%)		1(9%)	15	13(87%)		2(13%)
H. influenzae	1	1(100%)						
K. pneumoniae	3	3(100%)			1	1(100%)		
K. oxytoca	-				1	1(100%)		
M. morganii	1	1(100%)			3	3(100%)		
P. mirabilis	-				1	1(100%)		
P. vulgaris	-				2	2(100%)		
S. marcescens	-				2	2(100%)		
Serratia spp.	1	1(100%)						
Meningococcus (Group B)	1	1(100%)						
B. fragilis	1	1(100%)						
UTI (Uncomp.)								
E. coli	1	1(100%)			2	2(100%)		
S. faecalis	1	1(100%)			-			
E. cloacae	1	1(100%)			-			

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEFOTAXIME BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAI
UTI (Complicated)								
S. aureus[R]	-				1	1(100%)		
E. coli	4	2(50%)		2(50%)	3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. vulgaris	1			1(100%)	-			
S. faecalis	1	1(100%)			-			
K. pneumoniae	1	1(100%)			-			
C. freundii	1			1(100%)	-			
C. diversus	-				1	1(100%)		
P. aeruginosa	3	2(67%)		1(33%)	1			1(100%
INTRA-ABDOMINAL								
S. epidermidis	1	1(100%)			-			
S. mitis	-				1	1(100%)		
Strep (Group D)	2	2(100%)			-			
S. faecalis	7	5(71%)		2(29%)	2	2(100%)		
E. cloacae	1	1(100%)			1			1(100%
E. coli	8	5(62.5%)		3(37.5%)	7	7(100%)		
K. pneumoniae	3	2(67%)		1(33%)	1	1(100%)		
M. morganii	-				4	3(75%)		1(25%)
P. mirabilis	2	1(50%)		1(50%)	2	2(100%)		
P. aeruginosa	6	2(33%)		4(67%)	1			1(100%
Bifidobacterium	1	1(100%)			-			
Lactobacillus	1	1(100%)			-			
Peptostreptococcus	-				1	1(100%)		
B. fragilis	-				3	3(100%)		
B. melaninogenicus	1	1(100%)			-			
B. ruminicola	1	1(100%)			-			
Veillonella	1	1(100%)			-			

In the Primaxin group, one patient with a chronic pyelonephritis due to P. aeruginosa, E. coli and S. faecalis improved, and all organisms were eradicated. However, 14 days post-treatment the same E. coli and S. faecalis were isolated from the urine together with a M. morganii (designated as a reinfection).
Another patient with acute pyelonephritis due to E. coli developed a reinfection with a different E. coli strain.

Three patients in the cefotaxime group, one with an infected ulcer due to M. morganii, and two with complicated urinary tract infections due to E. coli relapsed during the follow-up period.

Superinfection developed in 3 patients in the Primaxin group and in 4 patients in the cefotaxime group.

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				CEFOTAXIME BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
UTI (Complicated)								
S. aureus(R)	–				1	1(100%)		
E. coli	4	2(50%)		2(50%)	3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. vulgaris	1			1(100%)	–			
S. faecalis	1	1(100%)			–			
K. pneumoniae	1	1(100%)			–			
C. freundii	1			1(100%)	–			
C. diversus	–				1	1(100%)		
P. aeruginosa	3	2(67%)		1(33%)	1			1(100%)
INTRA-ABDOMINAL								
S. epidermidis	1	1(100%)			–			
S. mitis	–				1	1(100%)		
Strep (Group D)	2	2(100%)			–			
S. faecalis	7	5(71%)		2(29%)	2	2(100%)		
E. cloacae	1	1(100%)			1			1(100%)
E. coli	8	5(62.5%)		3(37.5%)	7	7(100%)		
K. pneumoniae	3	2(67%)		1(33%)	1	1(100%)		
M. morganii	–				4	3(75%)		1(25%)
P. mirabilis	2	1(50%)		1(50%)	2	2(100%)		
P. aeruginosa	6	2(33%)		4(67%)	1			1(100%)
Bifidobacterium	1	1(100%)			–			
Lactobacillus	1	1(100%)			–			
Peptostreptococcus	–				1	1(100%)		
B. fragilis	–				3	3(100%)		
B. melaninogenicus	1	1(100%)			–			
B. ruminicola	1	1(100%)			–			
Veillonella	1	1(100%)			–			

In the Primaxin group, one patient with a chronic pyelonephritis due to P. aeruginosa, E. coli and S. faecalis improved, and all organisms were eradicated. However, 14 days post-treatment the same E. coli and S. faecalis were isolated from the urine together with a M. morganii (designated as a reinfection).
Another patient with acute pyelonephritis due to E. coli developed a reinfection with a different E. coli strain.

Three patients in the cefotaxime group, one with an infected ulcer due to M. morganii, and two with complicated urinary tract infections due to E. coli relapsed during the follow-up period.

Superinfection developed in 3 patients in the Primaxin group and in 4 patients in the cefotaxime group.

SAFETY

	PRIMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS	123	111
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	8(6.5%)	3(3%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	13(10.5%)	9(8%)

LOCAL SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Infused vein infection	1(0.8%)	1(0.8%)			
Infused vein pain	3(2.4%)	1(0.8%)		1(0.8%)	1(0.8%)
Phlebitis/thrombo-phlebitis	6(4.8%)			3(2.4%)	3(2.4%)

CEFOTAXIME

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Phlebitis/thrombo-phlebitis	3(2.7%)		1(0.9%)	1(0.9%)	1(0.9%)

SYSTEMIC SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	2(1.6%)			1(0.8%)	1(0.8%)
Vomiting	2(1.6%)				2(1.6%)
Glossitis	1(0.8%)				1(0.8%)
Fever	2(1.6%)			1(0.8%)	1(0.8%)
Flushing	1(0.8%)				1(0.8%)
Rash	1(0.8%)		1(0.8%)		
Somnolence	3(2.4%)		1(0.8%)	2(1.6%)	
Headache	1(0.8%)	1(0.8%)			
Hypotension	1(0.8%)			1(0.8%)	
Oliguria/anuria	1(0.8%)			1(0.8%)	
Polyuria	1(0.8%)			1(0.8%)	
Meningitis	1(0.8%)		1(0.8%)		
Fullness in ears	1(0.8%)	1(0.8%)			

CEFOTAXIME

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Vomiting	1(0.9%)			1(0.9%)	
Diarrhea	3(2.7%)		2(1.8%)		1(0.9%)
Mucous in feces (C. difficile positive)	1(0.9%)		1(0.9%)		
Constipation	1(0.9%)				1(0.9%)
Fever	2(1.8%)		1(0.9%)	1(0.9%)	
Pruritus	1(0.9%)		1(0.9%)		
Rash	1(0.9%)		1(0.9%)		
Septic shock	1(0.9%)			1(0.9%)	

Deaths

Ten patients in the Primaxin group died during the study or within two weeks after therapy was discontinued. Six of these deaths were considered by the investigator as definitely not drug related, three as probably not drug related, and one as probably drug related. This patient died of septic shock with blood cultures positive for Primaxin resistant <u>Pseudomonas</u> which emerged during therapy. Although this was not a toxic effect of the drug, the investigator rated this adverse experience probably drug related (failure of therapy).

Seven patients in the cefotaxime group died during or shortly after therapy was discontinued. Six of these were considered by the investigator as definitely not drug related and one as possibly drug related. This patient received cefotaxime for six days for complicated cystitis with bacteremia and died of septic shock.

Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFOTAXIME
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
RBC	—	(D) 1
WBC	—	(D) 2
Eosinophils	(I) 5	(I) 3
Platelets	(I) 5	(I) 1
	(D) 1	
Blood Urea	(I) 3	(I) 2
BUN	(I) 3	(I) 2
Creatinine	(I) 1	(I) 1
SGOT (AST)	(I) 6	(I) 4
SGPT (ALT)	(I) 6	(I) 5
Bilirubin	(I) 2	(I) 1
Alk. phosphatase	(I) 5	(I) 6
Serum potassium	—	(D) 1
Positive Coombs' test	4	—
Urine protein	(I) 2	(I) 1
Urine casts	—	(D) 1
Prothrombin time	—	(I) 1

Summary and Conclusions

This was an open, randomized, controlled multicenter study comparing Primaxin and cefotaxime in the treatment of infections caused by susceptible bacteria. A total of 123 patients, 78 males and 45 females, ranging in age from 16 to 80 years were enrolled in the Primaxin group. A total 111 patients, 65 males and 46 females, ranging in age from 18 to 81 years were enrolled in the cefotaxime group. Demographic characteristics of patients in each treatment group were similar.

Sixty nine patients with 88 sites of infection in the Primaxin group and 69 patients with 84 sites of infection in the cefotaxime group were acceptable for evaluation for drug efficacy. All patients were considered in assessing safety.

Clinical cure or improvement occurred in 75/88 (85%) infections in the
Primaxin treated patients and in 77/84 (92%) infections in the cefotaxime
treated patients.

A favorable bacteriological outcome (eradication) was achieved in 109 (81%) of
135 organisms isolated in the Primaxin group and in 100 (85%) of 114 organisms
isolated in the cefotaxime treated group.
The main reason for the difference in cure rate between the two antibiotics
was the unusually high failure rate of Primaxin in infections caused by P.
mirabilis.

Systemic side effects were reported in 10.5% of the patients in the Primaxin
group and in 8% of the patients in the cefotaxime group. Local side effects
were reported in 6.5% of the patients in the Primaxin group and in 3% of the
patients in the cefotaxime group.

The laboratory test abnormalities reported were similar in both treatment
groups, except for Coombs' test which was positive in 4 patients in the
Primaxin group. None was reported in the cefotaxime group.

There were 10 deaths in the Primaxin group. One of these was considered by
the investigator "probably drug related" not because of a toxic effect but
because of failure of therapy. Seven patients died in the cefotaxime group.
One of these was considered "possibly drug related" because of treatment
failure.

Results of this study demonstrate that both Primaxin and cefotaxime are
relatively safe and effective in the treatment of patients with serious
infections caused by susceptible bacteria. A difference, however, was evident
in infections caused by P. mirabilis where Primaxin was not quite as effective
as cefotaxime.

3.   Protocol No. 5004
      Title: "A Multiclinic, Randomized Study of the Comparative Efficacy,
      Safety and Tolerance of Intravenously Administered Primaxin and
      Gentamicin/Clindamycin in the Treatment of Hospitalized Patients with
      Infections Caused by Susceptible Bacteria."

      Study Design: This was an open, controlled, randomized, multiclinic
      study.

      Procedure: Treatment group assignment was made using a
      computer-generated, randomized allocation schedule. Having completed
      the informed consent procedure, patients were allocated either to the
      Primaxin or the Gentamicin/Clindamycin group.
      Each patient in the Primaxin group received a total daily dose of 2.0
      g administered in four equally divided doses every 6 hours as an
      intravenous infusion over 15 to 30 minutes. Each patient in the
      Gentamicin/Clindamycin group received 600 mg clindamycin every 6
      hours and gentamicin (1.5 mg/kg/dose t.i.d.) adjusted according to
      serum concentration assays.

Before entry into the study, all patients provided a complete clinical history and underwent a physical exam. During the study period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded. A daily infusion tolerance record of the study drug was kept. Tolerance was evaluated on the basis of pain, erythema, induration of the vein, and ulceration of the infusion site.

Standard diagnostic tests of hematologic, renal, and hepatic function were carried out before, during and after completion of therapy. In addition to the serum creatinine analyses that were part of the routine blood chemistry studies, renal function in terms of creatinine clearance was also estimated. Additional diagnostic test (e.g., x-ray, sonography) were performed as indicated. Serum concentrations of gentamicin were determined at least twice weekly for adjustment in gentamicin dosage. Blood cultures and cultures of other suspected sites were obtained prior to, during, and after study drug therapy. Gram stains and standard bacteriologic susceptibility tests were performed by either disc or broth dilution method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

Eight investigators conducted studies under this protocol. Their names and affiliations are listed below:

Alestig, K., Ostra Hospital, Goteborg, Sweden
Cronberg, S., Malmo General Hospital, Malmo, Sweden
Kager, L., Huddinge Hospital, Huddinge, Sweden
Philipson, A.E.L., Danderyd Hospital, Danderyd, Sweden
Schreiner, A., Haukeland Hospital, Bergen, Norway
Trollfore, B., Umea Regional Hospital, Umea, Sweden
Weich, D.J.V., University of the Orange Tree State,
    Bloemfontein, South Africa
Guerra, J., Instituto de Enfermedades Tropicales Alexander Von
Humbolt, Lima, Peru

Overall Summary of Studies Conducted Under Protocol 5004

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
TOTAL NO. OF PATIENTS	102	112
AGE RANGE (Years)	15-79	16-84
MEAN AGE (Years)	48.9	50.4
SEX		
Male	64	57
Female	38	55

EVALUATION

EFFICACY

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
NO. OF CASES EVALUABLE	70	80
NO. OF SITES OF INFECTION EVALUABLE	77	85
NO. OF CASES UNEVALUABLE	32	32

REASONS CASES UNEVALUABLE

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
No pretreatment pathogen	19	24
Treatmen. course too short	10	4
Organism resistant to study drug	1	1
Inadequate bacteriologic cultures	2	3

	PRIMAXIN	GENTAMICIN	CLINDAMYCIN
DOSE	500 mg q 6 h	1.5 mg/kg q 8 h	600 mg q 6 h

DURATION OF TREATMENT (days) (Evaluable Cases)	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
4-14	65 patients	77 patients
15-20	5 patients	3 patients

RESULTS

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE CURE	IMP.	FAIL	NO.	GENTAMICIN/CLINDAMYCIN CLINICAL RESPONSE CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/ furuncle, ulcers)	14	9(64.3%)	5(37.7%)		17	11(64.7%)	4(23.5%)	2(11.8%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess)	12	11(91.7%)	1(8.3%)		21	16(76.2%)	4(19.0%)	1(4.8%)
SEPTICEMIA	10	10(100%)			11	8(72.7%)	1(9.1%)	2(18.2%)
UTI (Uncomplicated) (Cystitis, pyelo- nephritis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	
UTI (Complicated) (Cystitis, pyelonephritis)	8	5(62.5%)	3(37.5%)		2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis, cholecystitis)	20	16(80%)	2(10%)	2(10%)	24	14(58.3%)	8(33.3%)	2(8.3%)

EVALUATION

EFFICACY

	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
NO. OF CASES EVALUABLE	70	80
NO. OF SITES OF INFECTION		
EVALUABLE	77	85
NO. OF CASES UNEVALUABLE	32	32

REASONS CASES UNEVALUABLE

No pretreatment pathogen	19	24
Treatment course too short	10	4
Organism resistant to study drug	1	1
Inadequate bacteriologic cultures	2	3

	PRIMAXIN	GENTAMICIN	CLINDAMYCIN
DOSE	500 mg q 6 h	1.5 mg/kg q 8 h	600 mg q 6 h

DURATION OF TREATMENT (days)	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
(Evaluable Cases)		
4-14	65 patients	77 patients
15-20	5 patients	patients

RESULTS

		PRIMAXIN				GENTAMICIN/CLINDAMYCIN		
		CLINICAL RESPONSE				CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMP.	FAIL	NO.	CURE	IMP.	FAIL
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/ furuncle, ulcers)	14	9(64.3%)	5(37.7%)		17	11(64.7%)	4(23.5%)	2(11.8%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess)	12	11(91.7%)	1(8.3%)		21	16(76.2%)	4(19.0%)	1(4.8%)
SEPTICEMIA	10	10(100%)			11	8(72.7%)	1(9.1%)	2(18.2%)
UTI (Uncomplicated) (Cystitis, pyelo- nephritis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	
UTI (Complicated) (Cystitis, pyelonephritis)	8	5(62.5%)	3(37.5%)		2	2(100%)		
INTRA-ABDOMINAL (Peritonitis. abscess, cholangitis, cholecystitis)	20	16(80%)	2(10%)	2(10%)	24	14(58.3%)	8(33.3%)	2(8.3%)

(Continued)

INFECTION	NO.	PRIMAXIN CLINICAL RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN CLINICAL RESPONSE		
		CURE	IMP.	FAIL		CURE	IMP.	FAIL
GYNECOLOGIC (Endometritis, PID. tubo-ovarian abscess)	8	6(75%)	2(25%)		5	5(100%)		
BONE/JOINT (Infectious arthritis, osteomyelitis)	1	1(100%)			1			1(100%)
ENTERITIS	1	1(100%)			1	1(100%)		

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE								
S. aureus(S)	1	1(100%)			2	2(100%)		
S. aureus(R)	5	3(60%)		2(40%)	10	9(90%)		1(10%)
S. epidermidis	2	2(100%)			-			
Strep (Group A)	2	1(50%)		1(50%)	5	5(100%)		
S. pyogenes	-				1	1(100%)		
Beta-hem-strep	-				1	1(100%)		
S. faecalis	1			1(100%)	4	2(50%)		2(50%)
E. coli	1	1(100%)			2	1(50%)		1(50%)
P. mirabilis	1	1(100%)			2	1(50%)		1(50%)
Klebsiella spp.	1	1(100%)			-			
E. agglomerans	1	1(100%)			-			
Pseudomonas spp.	1	1(100%)			-			
P. aeruginosa	1			1(100%)	1			1(100%)
Bacteroides spp.	1	1(100%)			-			
B. fragilis	1	1(100%)			1	1(100%)		
Peptostreptococcus	1	1(100%)			-			
Anaerobes, mixed	2	2(100%)			-			
LOWER RESPIRATORY								
S. aureus(R)	-				1	1(100%)		
S. pneumoniae	5	5(100%)			11	10(90.9%)		1(9.1%)
Alpha-hem-strep	-				2	2(100%)		
Streptococcus spp	-				1	1(100%)		
H. influenzae	6	6(100%)			6	4(66.7%)	1(16.6%)	1(16.6%)
H. parainfluenzae	-				1	1(100%)		
E. coli	-				1			1(100%)
Gram-neg-rods	1	1(100%)			-			
P. mirabilis	-				1	1(100%)		
Enterobacter spp.	-				1	1(100%)		

(Continued)

ORGANISM	\multicolumn{4}{c}{PRIMAXIN BACTERIOLOGIC RESPONSE}	\multicolumn{4}{c}{GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE}
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
Klebsiella spp.	1	1(100%)			–			
B. catarrhalis	1	1(100%)			–			
S. marcescens	–				1	1(100%)		
M. meningitidis	1	1(100%)			1	1(100%)		
B. fragilis	–				1	1(100%)		
Fusobacterium	–				1	1(100%)		

SEPTICEMIA

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
S. aureus(S)	1	1(100%)			1	1(100%)		
S. aureus(R)	2	2(100%)			–			
S. epidermidis	–				1	1(100%)		
Alpha-hem-strep	1	1(100%)			1	1(100%)		
S. pneumoniae	1	1(100%)			1	1(100%)		
S. bovis	1	1(100%)			–			
E. coli	4	4(100%)			6	4(66.7%)		2(33.3%
Klebsiella spp	–				1	1(100%)		
P. mirabilis	–				1	1(100%)		
Salmonella (Group B)	1	1(100%)			–			
Bacteroides spp	1	1(100%)			1	1(100%)		
B. fragilis	1	1(100%)			–			
B. melaninogenicus	1	1(100%)			–			
B. corrodens	1	1(100%)			–			

UTI (Uncomp.)

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
E. coli	3	2(66.7%)		1(33.3%)	3	2(66.7%)		1(33.3%

UTI (Complicated)

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
E. coli	3	2(66.7%)		1(33.3%)	2	2(100%)		
P. mirabilis	1			1(100%)	–			
P. stuartii	1			1(100%)	–			
Pseudomonas spp	2	2(100%)			–			
P. aeruginosa	1	1(100%)			–			

INTRA-ABDOMINAL

ORGANISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
S. aureus(S)	–				1	1(100%)		
S. aureus(R)	2	1(50%)		1(50%)	2	2(100%)		
S. epidermidis	–				4	2(50%)		2(50%)
Streptococcus spp	–				1	1(100%)		
Alpha-hem-Strep	1	1(100%)			–			
Beta-hem-Strep	1	1(100%)			1		1(100%)	
S. faecalis	–				4	3(75%)		1(25%)
A. calcoaceticus	1	1(100%)			–			
K. pneumoniae	2	2(100%)			2	1(50%)		1(50%)

(Continued)

ORGANISM	PRIMAXIN BACTERIOLOGIC RESPONSE				GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE			
	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA
Klebsiella spp.	1	1(100%)			-			
B. catarrhalis	1	1(100%)			-			
S. marcescens	-				1	1(100%)		
M. meningitidis	1	1(100%)			1	1(100%)		
B. fragilis	-				1	1(100%)		
Fusobacterium	-				1	1(100%)		

SEPTICEMIA

S. aureus(S)	1	1(100%)			1	1(100%)		
S. aureus(R)	2	2(100%)			-			
S. epidermidis	-				1	1(100%)		
Alpha-hem-strep	1	1(100%)			1	1(100%)		
S pneumoniae	1	1(100%)			1	1(100%)		
S. bovis	1	1(100%)			-			
E. coli	4	4(100%)			6	4(66.7%)		2(33.3%
Klebsiella spp	-				1	1(100%)		
P. mirabilis	-				1	1(100%)		
Salmonella (Group B)	1	1(100%)			-			
Bacteroides spp	1	1(100%)			1	1(100%)		
B. fragilis	1	1(100%)			..			
B. melaninogenicus	1	1(100%)			-			
B. corrodens	1	1(100%)			-			

UTI (Uncomp.)

E. coli	3	2(66.7%)		1(33.3%)	3	2(66.7%)		1(33.3%

UTI (Complicated)

E. coli	3	2(66.7%)		1(33.3%)	2	2(100%)		
P. mirabilis	1			1(100%)	-			
P. stuartii	1			1(100%)	-			
Pseudomonas spp	2	2(100%)			-			
P. aeruginosa	1	1(100%)			-			

INTRA-ABDOMINAL

S. aureus(S)	-				1	1(100%)		
S. aureus(R)	2	1(50%)		1(50%)	2	2(100%)		
S. epidermidis	-				4	2(50%)		2(50%)
Streptococcus spp	..				1	1(100%)		
Alpha-hem-Strep	1	1(100%)			-			
Beta-hem-Strep	1	1(100%)			1		1(100%)	
S. faecalis	-				4	3(75%)		1(25%)
A. calcoaceticus	1	1(100%)			-			
K. pneumoniae	2	2(100%)			2	1(50%)		1(50%)

(Continued)

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
Haemophilus spp	1	1(100%)			-			
Citrobacter spp	1	1(100%)			-			
C. diversus	1	1(100%)			-			
Gram-neg-rods	-				1	1(100%)		
E. cloacae	-				1			1(100%)
E. agglomerans	2	2(100%)			2	1(50%)		1(50%)
E. hafniae	1	1(100%)			1	1(100%)		
E. coli	10	10(100%)			14	12(85.7%)		2(14.3%)
P. mirabilis	-				1			1(100%)
P. rettgeri	-				1	1(100%)		
M. morganii	-				1			1(100%)
Pseudomonas spp	-				1			1(100%)
P. aeruginosa	.	1(100%)			1			1(100%)
Serratia spp	-				1	1(100%)		
C. perfringens	1	1(100%)			1	1(100%)		
C. butyricum	-				1	1(100%)		
C. histolyticum	-				1	1(100%)		
S. typhi	1	1(100%)			-			
S. choleraesuis	1	1(100%)			-			
Peptococcus spp	2	2(100%)			1	1(100%)		
Peptostreptococcus spp	1	1(100%)			-			
P. granulosum	-				1	1(100%)		
E. lentum	1	1(100%)			-			
Lactobacillus	1	1(100%)			-			
Bacteroides spp	2	2(100%)			2	2(100%)		
B. fragilis	3	3(100%)			7	4(57.1%)	1(14.3%)	2(28.6%)
B. bivius	1	1(100%)			-			
B. melaninogenicus	-				1	1(100%)		
B. ruminicola	-				1	1(100%)		

GYNECOLOGIC

S. aureus[R]	-				1			1(100%)
S. epidermidis	1	1(100%)			-			
Strep (non-hem)	1	1(100%)			-			
Alpha-hem-strep	-				1	1(100%)		
Beta-hem-strep	-				1	1(100%)		
E. coli	1	1(100%)			1			1(100%)
E. agglomerans	1	1(100%)			-			
H. influenzae	1	1(100%)			-			
K. pneumoniae	1	1(100%)			-			
P. mirabilis	1	1(100%)			-			
P. aeruginosa	-				1	1(100%)		
N. gonorrhoeae	-				1	1(100%)		
E. lentum	-				1	1(100%)		

(Continued)

ORGANISM	NO.	PRIMAXIN BACTERIOLOGIC RESPONSE			NO.	GENTAMICIN/CLINDAMYCIN BACTERIOLOGIC RESPONSE		
		ERAD	SUPP	NOT ERAD		ERAD	SUPP	NOT ERAD
P. granulosum	1	1(100%)			−			
Peptococcus spp	1	1(100%)			1	1(100%)		
Peptostreptococcus spp	−				1	1(100%)		
Bacteroides spp	1	1(100%)			−			
B. fragilis	1	1(100%)			1	1(100%)		
BONE/JOINT								
S. pyogenes	1	1(100%)			−			
B. fragilis	−				1			1(100%)
ENTERITIS								
Campylobacter	1	1(100%)			1	1(100%)		
Salmonella Type B	1			1(100%)				

Two patients in the Primaxin group and seven in the Gentamicin/Clindamycin group developed superinfections.

Reinfections occurred in eight patients in the Primaxin group (seven with urinary tract infections and one with a severe intraabdominal infection) and in one patient with urinary tract infection in the Gentamicin/Clindamycin group.

SAFETY

	PRIMAXIN	CLINDAMYCIN/GENTAMICIN
TOTAL NO. OF PATIENTS	102	112
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS	6(5.9%)	5(4.5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS	17(16.7%)	25(22.3%)

LOCAL SIDE EFFECTS

		PRIMAXIN			
	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Phlebitis/thrombo-phlebitis	6(5.9%)	1(1.0%)		3(3.0%)	2(1.9%)

		GENTAMICIN/CLINDAMYCIN			
Infused vein pain	2(1.8%)			2(1.8%)	
Vein induration	1(0.9%)			1(0.9%)	
Phlebitis/thrombo-phlebitis	2(1.8%)			1(0.9%)	1(0.9%)

SYSTEMIC SIDE EFFECTS

PRIMAXIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	7(7.0%)		4(4%)	3(3%)	
Vomiting	3(3.0%)		2(2%)	1(1%)	
Diarrhea*	9(9.0%)	7(7%)		2(2%)	
Abdominal pain	1(1.0%)			1(1%)	
Hiccups	1(1.0%)	1(1%)			
Increased salivation	1(1.0%)			1(1%)	
Fever	1(1.0%)		1(1%)		
Chills	1(1.0%)	1(1%)			
Rash	3(3.0%)		3(3%)		
Headache	1(1.0%)	1(1%)			
Chest discomfort	1(1.0%)	1(1%)			
Hypotension	1(1.0%)			1(1%)	
Vaginal candidiasis	1(1.0%)		1(1%)		
Hemoptysis	1(1.0%)	1(1%)			
Anxiety	1(1.0%)	1(1%)			

GENTAMICIN/CLINDAMYCIN

	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEFINITELY
Nausea	1(0.9%)	1(0.9%)			
Vomiting	1(0.9%)	1(0.9%)			
Diarrhea	10(8.9%)	6(5.3%)	1(0.9%)	2(1.8%)	1(0.9%)
Hiccups	2(1.8%)	2(1.8%)			
Increased salivation	1(0.9%)	1(0.9%)			
Fever	2(1.8%)		2(1.8%)		
Chills	1(0.9%)	1(0.9%)			
Rash	8(7.1%)	1(0.9%)	2(1.8%)	3(2.6%)	2(1.8%)
Urticaria	1(0.9%)	1(0.9%)			
Headache	2(1.8%)	2(1.8%)			
Dizziness	1(0.9%)			1(0.9%)	
Dyspnea	1(0.9%)	1(0.9%)			
Hearing loss	2(1.8%)			2(1.8%)	
Oral candidiasis	1(0.9%)			1(0.9%)	

*One patient with diarrhea had positive C. difficile toxin in the stools.

Deaths: Two patients in the Primaxin group died during the study. Both deaths were considered by the investigators definitely not drug related.

Three patients in the Gentamicin/Clindamycin group died during the study or within 14 days after termination of therapy. Two of these deaths were considered definitely not drug related and one probably not drug related.

Abnormal Laboratory Tests

TEST	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
RBC	(D) 1	(D) 3
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
WBC	(D) 1	-
Eosinophils	(I) 2	(I) 1
Platelet count	-	(I) 2
Platelet estimate	(I) 4	(D) 1
Positive Coombs' Test	2	2
BUN	(I) 1	(I) 2
Blood urea	(I) 1	(I) 2
Creatinine	(I) 4	(I) 22
Serum uric acid	-	(I) 6
SGOT (ASAT)	(I) 9	(I) 10
SGPT (ALAT)	(I) 12	(I) 11
Bilirubin	(I) 1	(I) 1
Alk. phosphatase	(I) 7	(I) 6
Serum potassium	(I) 1	(I) 2
	(D) 1	(D) 1
Serum chloride	(D) 1	(D) 4
Urine protein	(I) 1	(I) 5
Urine WBCs	(I) 3	(I) 8
Urine RBCs	(I) 1	(I) 2
Urine casts	(I) 3	(I) 13

Summary and Conclusions: This was an open, randomized, controlled multicenter
study comparing Primaxin and gentamicin plus clindamycin in the treatment of
infections caused by susceptible bacteria.
A total of 102 patients, 64 males and 38 females, ranging in age from 15 to 79
years were enrolled in the Primaxin group. A total of 112 patients, 57 males,
and 55 females, ranging in age from 16 to 84 years were enrolled in the
Gentamicin/Clindamycin group.
Seventy patients with 77 sites of infection in the Primaxin group and 80
patients with 85 sites of infection in the gentamicin/clindamycin group were
acceptable for evaluation of drug efficacy.
All patients were considered in assessing safety.

Clinical cure or improvement occurred in 75/77 (97%) infections in the
Primaxin treated patients and in 77/85 (91%) infections in the
gentamicin/clindamycin treated patients.

A favorable bacteriological outcome (eradication) was achieved in 104 (90%) of
115 organisms isolated in the Primaxin treated patients and in 112 (78%) of
144 organisms isolated in the gentamicin/clindamycin treated patients.

Systemic side effects were reported in 16.7% of the patients in the Primaxin
group and in 22.3% of the patients in the gentamicin/clindamycin group. Local
side effects were reported in 5.9% of the patients in the Primaxin group and
in 4.5% of the patients in the gentamicin/clindamycin group.

The laboratory test abnormalities reported were similar in both treatment groups; however, there were more patients with elevated serum creatinine, serum uric acid, and urine casts in the gentamicin/clindamycin group than in the Primaxin group.

There were two deaths in the Primaxin group; both were considered definitely not drug related. There were three deaths in the gentamicin/clindamycin group; two were considered definitely not drug related and one probably not drug related.

Results of this study demonstrate that Primaxin was safe and effective in the treatment of infections caused by susceptible bacteria. The combination of gentamicin plus clindamycin was somewhat less effective particularly in infections caused by E. coli, H. influenzae, and Enterobacter species.

Clinical Studies (Foreign)

II. Uncontrolled

Protocol No. 536
Title: "A Multiclinic Open Study of the Efficacy, Safety, and Tolerance of Primaxin (imipenem/cilastatin) in the Treatment of Hospitalized Patients with Infections Caused by Susceptible Bacteria."

Study Design
This was a noncomparative, variable dosage, bacteriologically controlled evaluation of Primaxin in the intravenous therapy of hospitalized patients with infections casued by susceptible bacteria.

Procedure
All patients accepted for entry into this study were required to sign an informed consent form.
Each patient provided a complete clinical history and underwent a physical examination. Primaxin was administered at a total daily dosage of 1.5 grams (500 mg q 8 h) or 2.0 grams (500 mg q 6 h), depending on the severity of the infection. Each dose was given by intravenous infusion over a 15-minute period.

During the study drug period, daily measurements of temperature, pulse, blood pressure, and respiratory rate were recorded. A daily infusion tolerance record of the study drug was kept.
Standard diagnostic tests of hematology, renal, and hepatic function were carried out before study drug therapy and were repeated during and after completion of therapy. Additional diagnostic tests (e.g. x-ray, sonography) were performed as indicated.
Bacteriologic cultures were obtained prior to, during, and after completion of therapy, except in cases in which cultures were impossible to obtain by virtue of a healed site. Gram stain and standard bacteriologic susceptibility tests were performed in all cultures by either disc or MIC method.

Response to treatment was assessed by both clinical and bacteriological outcomes.

Investigators
Twenty-five investigators (23 from Germany and 2 from Austria) participated in this multiclinic study.

Overall Summary of Studies Conducted Under Protocol No. 5?o

TOTAL NO. OF PATIENTS: 234

AGE RANGE (years):   16-87

MEAN AGE (years):   51.7

SEX
    Male: 137

    Female: 97
EVALUATION

EFFICACY
NO. OF CASES EVALUABLE: 165
NO. OF SITES OF INFECTION EVALUABLE: 180
NO. OF CASES UNEVALUABLE: 69

REASONS CASES UNEVALUABLE
No pretreatment pathogen   41
Treatment course too short   13
Inadequate bacteriologic cultures   10
Effective concomitant antimicrobial therapy   4
Diagnosis not clear   1

DURATION OF TREATMENT
    (Evaluable cases)

DAYS	NO. OF PATIENTS
5-14	159
15-30	6

RESULTS

| | | CLINICAL RESPONSE | | |
INFECTION	NO.	CURE	IMPROVE	FAIL
SKIN & SKIN STRUCTURE	44	34 (77.3%)	8 (18.2%)	2 (4.5%)
(Wound infection, abscess, cellulitis, carbuncle/furuncle, decubitus & other skin ulcers				

(Continued)

BONE/JOINT	1	1 (100%)		
(Pyogenic arthritis)				
LOWER RESPIRATORY	20	11 (55.0%)	7 (35.0%)	2 (10.0%)
(Pneumonia, empyema, bronchitis)				
GYNECOLOGIC	10	10 (100%)		
(PID, endometritis, tubo-ovarian abscess)				
INTRA-ABDOMINAL	46	44 (95.6%)	1 (2.2%)	1 (2.2%)
(Peritonitis, abscess, liver abscess, cholangitis, gall bladder empyema				

RESULTS

		CLINICAL RESPONSE		
UTI (Uncomplicated)	NO.	CURE	IMPROVE	FAIL
(Cystitis, pyelonephritis)	5	5 (100%)		
UTI (Complicated)	35	19 (54.3%)	16 (45.7%)	
(Cystitis, pyelonephritis renal abscess)				
INFECTION				
BACTERIAL SEPTICEMIA	19	18 (94.7%)	1 (5.3%)	

ORGANISM		BACTERIOLOGIC RESPONSE
SKIN & SKIN STRUCTURE	NO.	ERADICATED
Gemella	1	1 (100%)
S. aureus^S	5	5 (100%)
S. aureus^R	9	8 (89.9%)
S. epidermidis	4	3 (75%)
Streptococcus spp.	2	2 (100%)
Streptococcus (Group A)	3	3 (100%)
Streptococcus (Group C)	1	1 (100%)
Streptococcus (Group D) Enterococci)	6	4 (66.7%)
Streptococcus faecalis	2	2 (100%)
Streptococcus viridans	2	2 (100%)
Beta-hemolytic streptococci	3	3 (100%)

(Continued)	NO.	ERADICATED
Acinetobacter spp.	1	0
Enterobacter spp.	4	3 (75%)
Enterobacter aerogenes	1	0
Escherichia coli	19	12 (63.2%)
Klebsiella oxytoca	1	0
Morganella morganii	1	1 (100%)
Proteus mirabilis	3	1 (33.3%)
Proteus vulgaris	1	1 (100%)
Pseudomonas aeruginosa	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	3	3 (100%)
Fusobacterium spp.	1	1 (100%)
Acidaminococcus fermentans	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
BONE/JOINT	NO.	ERADICATED
S. aureus^R	1	1 (100%)

INTRA-ABDOMINAL

S. aureus^S	3	3 (100%)
S. aureus^R	3	3 (100%)
S. epidermidis	4	4 (100%)
Streptococcus spp.	1	1 (100%)
Streptococcus (Group D) Enterococci)	3	3 (100%)
Streptococcus faecalis	1	1 (100%)
Streptococcus viridans	5	5 (100%)
Non-hemolytic streptococci	2	2 (100%)
Citrobacter freundii	2	1 (50%)
Enterobacter spp.	1	1 (100%)
Enterobacter cloacae	1	1 (100%)
Escherichia coli	27	24 (88.9%)
Klebsiella pneumoniae	2	2 (100%)
Lactobacillus	1	1 (100%)
Morganella morganii	3	2 (66.7%)
Proteus mirabilis	2	2 (100%)
Proteus vulgaris	3	2 (66.7%)
Providencia rettgeri	1	1 (100%)
Pseudomonas spp.	1	1 (100%)
Pseudomonas aeruginosa	2	1 (50%)
Serratia liquefaciens	1	1 (100%)
Clostridium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	6	5 (83.3%)
Bacteroides fragilis	1	1 (100%)

(Continued)	NO.	ERADICATED
Acinetobacter spp.	1	0
Enterobacter spp.	4	3 (75%)
Enterobacter aerogenes	1	0
Escherichia coli	19	12 (63.2%)
Klebsiella oxytoca	1	0
Morganella morganii	1	1 (100%)
Proteus mirabilis	3	1 (33.3%)
Proteus vulgaris	1	1 (100%)
Pseudomonas aeruginosa	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	3	3 (100%)
Fusobacterium spp.	1	1 (100%)
Acidaminococcus fermentans	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
BONE/JOINT	NO.	ERADICATED
S. aureus^R	1	1 (100%)

INTRA-ABDOMINAL

S. aureus^S	3	3 (100%)
S. aureus^R	3	3 (100%)
S. epidermidis	4	4 (100%)
Streptococcus spp.	1	1 (100%)
Streptococcus (Group D) Enterococci)	3	3 (100%)
Streptococcus faecalis	1	1 (100%)
Streptococcus viridans	5	5 (100%)
Non-hemolytic streptococci	2	2 (100%)
Citrobacter freundii	2	1 (50%)
Enterobacter spp.	1	1 (100%)
Enterobacter cloacae	1	1 (100%)
Escherichia coli	27	24 88.9%)
Klebsiella pneumoniae	2	2 (100%)
Lactobacillus	1	1 (100%)
Morganella morganii	3	2 (66.7%)
Proteus mirabilis	2	2 (100%)
Proteus vulgaris	3	2 (66.7%)
Providencia rettgeri	1	1 (100%)
Pseudomonas spp.	1	1 (100%)
Pseudomonas aeruginosa	2	1 (50%)
Serratia liquefaciens	1	1 (100%)
Clostridium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	6	5 (83.3%)
Bacteroides fragilis	1	1 (100%)

LOWER RESPIRATORY	NO.	ERADICATED
S. aureus[S]	4	4 (100%)
S. aureus[R]	2	2 (100%)
S. epidermidis	1	0
Streptococcus spp.	1	1 (100%)
S. pneumoniae	2	2 (100%)
Streptococcus (Group D) Enterococci)	3	2 (66.7%)
Escherichia coli	3	2 (66.7%)
Haemophilus influenzae	4	3 (75%)
Klebsiella pneumoniae	2	1 (50%)
Pasteurella multocida	1	1 (100%)
Proteus vulgaris	1	0
Pseudomonas aeruginosa	6	4* (66.7%)
Corynebacterium (acnes)	1	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Fusobacterium spp.	1	1 (100%)

*Two patients with pneumonia in whom P. aeruginosa persisted in the sputum were considered clinically cured by the investigator. Both these patients were in the same intensive care unit where P. aeurginosa was frequently isolated.

ORGANISM		BACTERIOLOGIC RESPONSE
GYNECOLOGIC	NO.	ERADICATED
Streptococcus (Group D) Enterococci)	1	1 (100%)
Escherichia coli	7	5 (71.4%)
Proteus vulgaris	1	1 (100%)
Neisseria gonorrhoeae	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	2	2 (100%)

UTI (Uncomplicated)

S. aureus[R]	1	1 (100%)
Streptococcus (Group D Enterococci)	1	1 (100%)
Escherichia coli	4	4 (100%)
Proteus vulgaris	1	1 (100%)
Enterobacter spp.	1	1 (100%)
Klebsiella oxytoca	1	1 (100%)

UTI (complicated)	NO.	ERADICATED
S. aureus^R	5	5 (100%)
S. epidermidis	4	4 (100%)
Streptococcus (Group D Enterococci)	5	5 (100%)
Streptococcus faecalis	1	0 —
Escherichia coli	13	6 (46.2%)
Proteus mirabilis	4	1 (25%)
Enterobacter spp.	1	1 (100%)
Citrobacter freundii	1	0 —
Klebsiella pneumoniae	1	0 —
Pseudomonas aeruginosa	3	2 (66.7%)

BACTERIAL SEPTICEMIA

	NO.	ERADICATED
S. aureus^S	3	3 (100%)
S. aureus^R	2	2 (100%)
S. epidermidis	2	2 (100%)
Streptococcus pneumoniae	1	1 (100%)
Streptococcus (Group D Enterococci)	1	1 (100%)
Streptococcus faecalis	1	1 (100%)
Acinetobacter spp.	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Escherichia coli	6	6 (100%)
Klebsiella pneumoniae	1	1 (100%)
Salmonella (Group A)	1	1 (100%)
Bacteroides spp.	1	1 (100%)

Six patients were designated by the investigators as developing superinfections. Four of these occurred at the site of the primary infection and two at a different site.
Four patients healed spontaneously, and two required additional antibiotic therapy. Only one patient with a bronchopneumonia developed a superinfection with a Primaxin-resistant P. aeruginosa. The organism was successfully eradicated with a combination of tobramycin and piperacillin.

SAFETY

TOTAL NO. OF PATIENTS: ----------------------- 234

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS ----- 24 (10.3%)

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS -------- 27 (11.5%)

UTI (complicated)	NO.	ERADICATED
S. aureus^R	5	5 (100%)
S. epidermidis	4	4 (100%)
Streptococcus (Group D Enterococci)	5	5 (100%)
Streptococcus faecalis	1	0 -
Escherichia coli	13	6 (46.2%)
Proteus mirabilis	4	1 (25%)
Enterobacter spp.	1	1 (100%)
Citrobacter freundii	1	0 -
Klebsiella pneumoniae	1	0 -
Pseudomonas aeruginosa	3	2 (66.7%)

BACTERIAL SEPTICEMIA

S. aureus^S	3	3 (100%)
S. aureus^R	2	2 (100%)
S. epidermidis	2	2 (100%)
Streptococcus pneumoniae	1	1 (100%)
Streptococcus (Group D Enterococci)	1	1 (100%)
Streptococcus faecalis	1	1 (100%)
Acinetobacter spp.	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Escherichia coli	6	6 (100%)
Klebsiella pneumoniae	1	1 (100%)
Salmonella (Group A)	1	1 (100%)
Bacteroides spp.	1	1 (100%)

Six patients were designated by the investigators as developing
superinfections. Four of these occurred at the site of the primary infection
and two at a different site.
Four patients healed spontaneously, and two required additional antibiotic
therapy. Only one patient with a bronchopneumonia developed a superinfection
with a Primaxin-resistant P. aeruginosa. The organism was successfully
eradicated with a combination of tobramycin and piperacillin.

SAFETY

TOTAL NO. OF PATIENTS: ------------- ---------- 234

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS ----- 24   (10.3%)

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS -------- 27   (11.5%)

SIDE EFFECTS
SYSTEMIC

	No.	Probably Not Related	Possible Related	Probably Related	Definitely Related
Diarrhea	11 (4.7%)		2 (0.8%)	6 (2.6%)	3 (1.3%)
Nausea	10 (4.3%)		2 (0.8%)	5 (2.1%)	3 (1.3%)
Vomiting	6 (2.6%)		1 (0.4%)	2 (0.8%)	3 (1.3%)
Heartburn	1 (0.4%)			1 (0.4%)	
Abdominal pain	1 (0.4%)		1 (0.4%)		
Brown tongue	3 (1.3%)			3 (1.3%)	
Allergic dermatitis	1 (0.4%)			1 (0.4%)	
Pruritus	1 (0.4%)			1 (0.4%)	
Rash	1 (0.4%)				1 (0.4%)
Dizziness	3 (1.3%)			1 (0.4%)	2 (0.8%)
Hypotension	1 (0.4%)			1 (0.4%)	
Dyspnea	1 (0.4%)		1 (0.4%)		

LOCAL

	No.	Probably Not Related	Possible Related	Probably Related	Definitely Related
Pain	9 (3.8%)	4 (1.7%)	3 (1.3%)	1 (0.4%)	1 (0.4%)
Induration	11 (4.7%)	7 (3%)	4 (1.7%)		
Erythema	12 (5.1%)	6 (2.5%)	6 (2.5%)		
Phlebitis/ thrombo- phlebitis	5 (2.1%)		4 (1.7%)	1 (0.4%)	

Deaths
Three deaths were reported in this study. Two were considered by the investigator as definitely not related and one as probably not drug related.

Abnormal Laboratory Tests

Test		
WBC	(D)	1
Monocytes	(I)	8
Eosinophils	(I)	6
Basophils	(I)	3
Prothrombin time	(I)	2
Positive Coombs' test		2
Creatinine	(I)	1
SGOT (AST)	(I	6
SGPT (ALT)	(I)	11
Alkaline phosphatase	(I)	4

Overall Summary of the Efficacy and Safety of Primaxin in Controlled and Uncontrolled Studies (Compassionate Protocol Excluded)

	CONTROLLED	UNCONTROLLED
NO. OF STUDIES	6	3
NO. OF INVESTIGATORS	58	78

DEMOGRAPHIC SUMMARY OF PATIENTS

TOTAL NO. OF PATIENTS	1,656
AGE RANGE (years)	12 - 101

SEX

Male	994
Female	662

EVALUATION

EFFICACY

TOTAL NO. OF PATIENTS	1,656
NO. OF PATIENTS EVALUABLE	1,116
NO. OF SITES OF INFECTION EVALUABLE	1,253

RESULTS

		CLINICAL RESPONSE		
INFECTION	NO.	CURE	IMPROVE	FAIL
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess)	214	115 (53.7%)	72 (33.6%)	27 (12.6%)
URINARY TRACT – UNCOMPLICATED (Cystitis, pyelonephritis)	41	38 (92.7%)	2 (4.9%)	1 (2.4%)
URINARY TRACT – COMPLICATED (Cystitis, pyelonephritis) renal or perinephric abscess)	139	90 (64.7%)	42 (30.2%)	7 (5.1%)

	NO.	CURE	IMPROVE	FAIL
INTRA-ABDOMINAL (Abscess, peritonitis, cholecystitis, cholangitis, liver abscess, perirectal abscess)	156	112 (71.8%)	32 (20.5%)	12 (7.7%)
ENTERITIS	1	1 (100%)		
GYNECOLOGIC (Endometritis, pelvic cellulitis, pelvic inflammatory disease, tubo-ovarian abscess, pelvic abscess	95	75 (78.9%)	16 (16.8%)	4 (4.2%)
BACTERIAL SEPTICEMIA	164	138 (84.1%)	20 (12.2%)	6 (3.7%)
BACTEREMIA	24	15 (62.5%)	8 (33.3%)	1 (4.2%)
ENDOCARDITIS	11	11 (100%)		
BONE/JOINT Infectious arthritis, osteomyelitis)	72	32 (44.4%)	35 (48.6%)	5 (6.9%)
SKIN & SKIN STRUCTURE (Wound infection, abscess, cellulitis, carbuncle/furuncle, infected decubitus and other skin ulcers)	328	204 (62.2%)	110 (33.5%)	14 (4.3%)
OTITIS	4	2 (50%)	1 (25%)	1 (25%)
UPPER RESPIRATORY	2		1 (50%)	1 (50%)
MEDIASTINITIS	1	1 (100%)		
BRAIN ABSCESS	1	1 (100%)		

INTRA-ABDOMINAL	NO.	CURE	IMPROVE	FAIL
(Abscess, peritonitis, cholecystitis, cholangitis, liver abscess, perirectal abscess)	156	112 (71.8%)	32 (20.5%)	12 (7.7%)
ENTERITIS	1	1 (100%)		
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OTITIS	4	2 (50%)	1 (25%)	1 (25%)
UPPER RESPIRATORY	2		1 (50%)	1 (50%)
MEDIASTINITIS	1	1 (100%)		
BRAIN ABSCESS	1	1 (100%)		

| ORGANISM | | BACTERIOLOGIC RESPONSE |
LOWER RESPIRATORY	NO.	ERADICATED
S. aureus^{S*}	7	7 (100%)
S. aureus^{R**}	9	9 (100%)
S. epidermidis	2	0
S. pneumoniae	49	49 (100%)
Streptococcus (Group A)	2	2 (100%)
S. viridans group	1	1 (100%)
Beta-hemolytic streptococcus not Group A	2	2 (100%)
S. bovis	1	1 (100%)
Other streptococcus species	9	9 (100%)
Group D streptococcus (enterococcus)	7	4 (57%)
Branhamella catarrhalis	2	2 (100%)
N. meningitidis	1	1 (100%)
H. influenzae	52	45 (87%)
H. parainfluenzae	5	5 (100%)
E. coli	18	16 (89%)
P. mirabilis	17	5 (29%)
P. vulgaris	1	0
K. pneumoniae	23	19 (83%)
K. oxytoca	1	1 (100%)
K. ozaenae	1	1 (100%)
Klebsiella spp.	1	1 (100%)
E. aerogenes	3	2 (67%)
E. cloacae	10	9 (90%)
E. agglomerans	1	1 (100%)
Hafnia alvei	1	0
Providencia stuartii	1	1 (100%)
P. multocida	2	2 (100%)
Citrobacter freundii	1	0
Citrobacter spp.	1	1 (100%)
P. aeruginosa	54	18 (33.3%)***

*S = Penicillin-sensitive   **R = Penicillin-resistant
*** = Forty of the 54 patients with lower respiratory tract infections had serious underlying lung diseases (e.g. COPD, cystic fibrosis, cancer of the lung), and 21 required some degree of respiratory assistance during study drug therapy. These patients had failed previous courses of antibiotic therapy.

All these factors contributed to the low eradication rate of P. aeruginosa (as it is usually the case). However, 67% of the patients were considered to have had a satisfactory clinical response.

| ORGANISM | | BACTERIOLOGIC RESPONSE |
LOWER RESPIRATORY	NO.	ERADICATED
Pseudomonas spp.	1	1 (100%)
A. hydrophilia	1	1 (100%)
S. marcescens	6	4 (67%)
Alcaligens spp.	1	1 (100%)

(Continued)

ORGANISM		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	NO.	ERADICATED
A. calcoaceticus	4	4 (100%)
Acinetobacter spp.	2	2 (100%)
Corynebacterium acnes	1	1 (100%)
Peptostreptococcus spp.	3	3 (100%)
Fusobacterium spp.	1	1 (100%)
Bacteroides spp.	3	3 (100%)
Eikenella corrodens	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
	NO.	ERADICATED
URINARY TRACT (UNCOMPLICATED)		
S. aureus^S	1	1 (100%)
Group D Streptococcus (enterococci)	1	1 (100%)
S. faecalis	1	1 (100%)
E. coli	32	29 (91%)
P. mirabilis	3	3 (100%)
P. vulgaris	2	2 (100%)
K. pneumoniae	2	2 (100%)
K. oxytoca	1	1 (100%)
E. cloacae	2	2 (100%)
Enterobacter spp.	1	1 (100%)
P. aeruginosa	1	1 (100%)
URINARY TRACT COMPLICATED)		
S. aureus^R	6	5 (83%)
S. epidermidis	4	4 (100%)
Group B Streptococcus	2	2 (100%)
Group D Streptococcus (enterococci)	10	9 (90%)
S. faecalis	2	1 (50%)
E. coli	43	26 (60%)
P. mirabilis	12	6 (50%)
P. vulgaris	1	0
P. rettgeri	3	2 (67%)
M. morganii	3	3 (100%)
K. pneumoniae	8	7 (87.5%)
K. oxytoca	1	1 (100%)
E. aerogenes	1	1 (100%)
E. cloacae	7	6 (85.7%)
Enterobacter spp.	1	1 (100%)
Providencia stuartii	4	1 (25%)

		BACTERIOLOGIC RESPONSE
ORGANISM	NO.	ERADICATED

URINARY TRACT
COMPLICATED)

Organism	No.	Eradicated
Providencia spp.	1	0
Citrobacter diversus	2	0
Citrobacter freundii	2	0
Citrobacter spp.	1	1 (100%)
P. aeruginosa	43	36 (84%)
Pseudomonas spp.	2	2 (100%)
S. marcescens	2	1 (50%)
Serratia spp.	1	1 (100%)
Bifidobacterium spp.	1	1 (100%)
Peptococcus spp.	1	1 (100%)

INTRA-ABDOMINAL

Organism	No.	Eradicated
S. aureus^S	3	3 (100%)
S. aureus^R	6	5 (83%)
S. epidermidis	6	6 (100%)
Streptococcus (Group A)	1	1 (100%)
S. viridans group	15	14 (93%)
Alpha-hemolytic streptococus	1	1 (100%)
Beta-hemolytic streptococcus	2	2 (100%)
Non-hemolytic streptococcus	2	2 (100%)
S. intermedius	4	4 (100%)
S. mitis	1	1 (100%)
S. salivarius	1	1 (100%)
S. sanguis	1	1 (100%)
S. morbillorum	2	2 (100%)
S. bovis	1	1 (100%)
S. faecium	1	1 (100%)
Other streptococus spp.	9	9 (100%)
Group D streptococcus (enterococcus)	13	11 (85%)
S. faecalis	10	7 (70%)
Haemophilus spp.	1	1 (100%)
E. coli	89	74 (83%)
P. mirabilis	9	6 (67%)
P. vulgaris	4	3 (75%)
P. rettgeri	1	1 (100%)
M. morganii	5	4 (80%)
K. pneumoniae	20	18 (90%)
K. oxytoca	3	3 (100%)
Klebsiella spp.	1	1 (100%)

| | | BACTERIOLOGIC RESPONSE |
| ORGANISM | | |
INTRA-ABDOMINAL	NO.	ERADICATED
Enterobacter a. rogenes	3	3 (100%)
E. cloacae	6	4 (67%)
Enterobacter spp.	1	1 (100%)
Enterobacter agglomerans	2	2 (100%)
Hafnia alvei	1	1 (100%)
P. multocida	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	3	2 (67%)
Citrobacter spp.	3	3 (100%)
Acinetobacter calcoaceticus	2	2 (100%)
P. aeruginosa	18	12 (67%)
P. alcaligenes	1	1 (100%)
Pseudomonas spp.	1	1 (100%
Salmon ila typhi	1	1 (100%)
Salmonella choleraesuis	1	1 (100%)
Serratia liquefaciens	1	1 (100%)
Lactobacillus	3	3 (100%)
Eubacterium lentum	1	1 (100%)
Eubacterium spp.	2	2 (100%)
Propionibacterium acnes	3	3 (100%)
Propionibacterium spp.	1	1 (100%)
C. perfringens	4	4 (100%)
Clostridium spp.	22	22 (100%)
Bifidobacterium adolescentis	1	1 (100%)
Bifidobacterium spp.	1	1 (100%)
Peptococcus spp.	6	6 (100%)
Peptostreptococcus spp.	9	8 (89%)
Bacteroides spp.	21	20 (95%)
B. fragilis	35	34 (97%)
B. melaninogenicus	1	1 (100%)
B. ruminicola	1	1 (100%)
B. bivius	1	1 (100%)
Fusobacterium spp.	9	9 (100%)
Veillonella parvula	1	1 (100%)
Veillonella spp.	1	1 (100%)

ENTERITIS

| Campylobacter spp. | 1 | 1 (100%) |
| Salmonella type B | 1 | 0 |

ORGANISM	BACTERIOLOGIC RESPONSE	
GYNECOLOGIC	NO.	ERADICATED
S. aureus^{S*}	3	3 (100%)
S. aureus^{R*}	8	7 (88%)
S. epidermidis	17	17 (100%)
Alpha-hemolytic streptococus	3	3 (100%)
S. viridans group	2	2 (100%)
Non-hemolytic streptococcus	3	3 (100%)
Group B streptococcus	20	20 (100%)
Other streptococcus spp.	7	7 (100%)
Group D streptococcus (enterococcus)	14	12 (86%)
S. faecalis	11	10 (91%)
H. influenzae	1	1 (100%)
E. coli	33	28 (85%)
Proteus mirabilis	6	5 (83%)
Proteus vulgaris	1	1 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	6	6 (100%)
Klebsiella spp.	1	1 (100%)
Enterobacter aerogenes	2	2 (100%)
Enterobacter cloacae	1	1 (100%)
Enterobacter agglomerans	1	1 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Pseudomonas aeruginosa	1	0
N. gonorrhoeae	3	3 (100%)
Propionibacterium granulosum	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Bifidobacterium spp.	3	3 (100%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	5	5 (100%)
Peptostreptococcus spp.	9	9 (100%)
Bacteroides fragilis	9	8 (89%)
Bacteroides spp.	31	29 (94%)
Veillonella parvula	2	2 (100%)
Gardnerella vaginalis	7	7 (100%)
M. hominis	1	1 (100%)
Ureaplasma urealyticum	2	2 (100%)

ORGANISM GYNECOLOGIC	NO.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus^{S*}	3	3 (100%)
S. aureus^{R*}	8	7 (88%)
S. epidermidis	17	17 (100%)
Alpha-hemolytic streptococus	3	3 (100%)
S. viridans group	2	2 (100%)
Non-hemolytic streptococcus	3	3 (100%)
Group B streptococcus	20	20 (100%)
Other streptococcus spp.	7	7 (100%)
Group D streptococcus (enterococcus)	14	12 (86%)
S. faecalis	11	10 (91%)
H. influenzae	1	1 (100%)
E. coli	33	28 (85%)
Proteus mirabilis	6	5 (83%)
Proteus vulgaris	1	1 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	6	6 (100%)
Klebsiella spp.	1	1 (100%)
Enterobacter aerogenes	2	2 (100%)
Enterobacter cloacae	1	1 (100%)
Enterobacter agglomerans	1	1 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Pseudomonas aeruginosa	1	0
N. gonorrhoeae	3	3 (100%)
Propionibacterium granulosum	1	1 (100%)
Propionibacterium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Bifidobacterium spp.	3	3 (100%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	5	5 (100%)
Peptostreptococcus spp.	9	9 (100%)
Bacteroides fragilis	9	8 (89%)
Bacteroides spp.	31	29 (94%)
Veillonella parvula	2	2 (100%)
Gardnerella vaginalis	7	7 (100%)
M. hominis	1	1 (100%)
Ureaplasma urealyticum	2	2 (100%)

| ORGANISM | | BACTERIOLOGIC RESPONSE |
BACTERIAL SEPTICEMIA	NO.	ERADICATED
S. aureus[S]	7	7 (100%)
Micrococcus	1	1 (100%)
S. aureus[R]	21	19 (90%)
S. epidermidis	6	6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic streptococcus	1	1 (100%)
Beta-hemolytic streptococcus	1	1 (100%)
Group A streptococcus	1	1 (100%)
Streptococcus sanguis	1	1 (100%)
Streptococcus bovis	1	1 (100%)
Other streptococcus spp.	10	10 (100%)
Group D streptococcus (enterococcus)	4	4 (100%)
S. faecalis	3	3 (100%)
Bacillus subtilis	1	1 (100%)
H. influenzae	2	2 (100%)
E. coli	45	44 (98%)
P. mirabilis	2	2 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	8	8 (100%)
K. oxytoca	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Enterobacter cloacae	3	3 (100%)
Providencia stuartii	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Acinetobacter spp.	2	2 (100%)
Yersinia enterocolitica	1	1 (100%)
Pseudomonas aeruginosa	3	3 (100%)
Serratia marcescens	6	5 (83%)
Serratia spp.	1	1 (100%)
N. gonorrhoeae	1	1 (100%)
Salmonella spp.	3	3 (100%)
Clostridium bifermentans	1	1 (100%)
Clostridium spp.	1	0
Corynebacterium acnes	1	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides corrodens	1	1 (100%)
Bacteroides melaninogenicus	1	1 (100%)
Bacteroides spp.	4	4 (100%)
Fusobacterium spp.	2	2 (100%)
Flavobacterium spp.	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
BACTERIAL SEPTICEMIA	NO.	ERADICATED
S. aureus^S	7	7 (100%)
Micrococcus	1	1 (100%)
S. aureus^R	21	19 (90%)
S. epidermidis	6	6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic streptococcus	1	1 (100%)
Beta-hemolytic streptococcus	1	1 (100%)
Group A streptococcus	1	1 (100%)
Streptococcus sanguis	1	1 (100%)
Streptococcus bovis	1	1 (100%)
Other streptococcus spp.	10	10 (100%)
Group D streptococcus (enterococcus)	4	4 (100%)
S. faecalis	3	3 (100%)
Bacillus subtilis	1	1 (100%)
H. influenzae	2	2 (100%)
E. coli	45	44 (98%)
P. mirabilis	2	2 (100%)
M. morganii	1	1 (100%)
K. pneumoniae	8	8 (100%)
K. oxytoca	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Enterobacter cloacae	3	3 (100%)
Providencia stuartii	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
Acinetobacter spp.	2	2 (100%)
Yersinia enterocolitica	1	1 (100%)
Pseudomonas aeruginosa	3	3 (100%)
Serratia marcescens	6	5 (83%)
Serratia spp.	1	1 (100%)
N. gonorrhoeae	1	1 (100%)
Salmonella spp.	3	3 (100%)
Clostridium bifermentans	1	1 (100%)
Clostridium spp.	1	0
Corynebacterium acnes	1	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides corrodens	1	1 (100%)
Bacteroides melaninogenicus	1	1 (100%)
Bacteroides spp.	4	4 (100%)
Fusobacterium spp.	2	2 (100%)
Flavobacterium spp.	1	1 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
BACTEREMIA	NO.	ERADICATED
S. aureus^S	1	1 (100%)
S. aureus^R	2	2 (100%)
S. epidermidis	1	1 (100%)
S. pneumoniae	1	1 (100%)
Group D streptococcus (enterococcus)	1	1 (100%)
H. influenzae	1	1 (100%)
E. coli	7	7 (100%)
E. cloacae	3	3 (100%)
Providencia stuartii	1	1 (100%)
Citrobacter diversus	1	1 (100%)
P. aeruginosa	4	4 (100%)
Bacteroides bivius	1	1 (100%)
ENDOCARDITIS		
S. aureus^S	1	1 (100%)
S. aureus^R	6	6 (100%)
S. pneumoniae	1	1 (100%)
S. sanguis	1	1 (100%)
Streptococcus spp.	1	1 (100%)
S. viridans group	1	1 (100%)
BONE/JOINT		
S. aureus^S	8	8 (100%)
S. aureus^R	23	22 (96%)
S. epidermidis	5	5 (100%)
S. pyogenes	1	1 (100%)
Beta-hemolytic streptococcus	2	2 (100%)
Streptococcus spp.	12	12 (100%)
Group D Streptococcus (enterococci)	5	5 (100%)
S. faecalis	5	5 (100%)
E. coli	5	4 (80%)
P. mirabilis	8	5 (63%)
P. vulgaris	2	1 (50%)
M. morganii	3	3 (100%)
Proteus spp.	1	0
Providencia stuartii	1	0
Enterobacter aerogenes	3	3 (100%)
Enterobacter cloacae	6	6 (100%)
Citrobacter diversus	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
P. aeruginosa	28	22 (79%)

| ORGANISM | BACTERIOLOGIC RESPONSE | |
BONE/JOINT	NO.	ERADICATED
Serratia marcescens	3	1 (33%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides spp.	3	2 (67%)
Fusobacterium spp.	1	1 (100%)

SKIN & SKIN STRUCTURE

Gemella	1	1 (100%)
S. aureus^S	25	21 (84%)
S. aureus^R	116	98 (84%)
S. epidermidis	23	18 (78%)
Alpha-hemolytic streptococcus	11	11 (100%)
S. viridans	3	3 (100%)
Beta-hemolytic streptococcus	24	22 (92%)
Group A streptococcus	28	26 (93%)
Group B streptococcus	13	11 (85%)
Group C streptococcus	1	1 (100%)
S. intermedius	1	1 (100%)
Streptococcus spp.	38	35 (92%)
Group D streptococcus	30	24 (80%)
S. faecalis	22	19 (86%)
Corynebacterium spp.	5	5 (100%)
E. coli	59	49 (83%)
P. mirabilis	37	20 (54%)
P. vulgaris	7	6 (86%)
P. rettgeri	3	3 (100%)
Proteus spp.	1	1 (100%)
M. morganii	14	12 (86%)
K. pneumoniae	11	9 (82%)
K. oxytoca	12	11 (92%)
Klebsiella spp.	2	2 (100%)
Providencia stuartii	3	3 (100%)
P. multocida	1	1 (100%)
Enterobacter aerogenes	8	7 (88%)
Enterobacter cloacae	13	13 (100%)
Enterobacter agglomerans	1	1 (100%)
Enterobacter spp.	5	4 (80%)
Citrobacter freundii	4	4 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter spp.	2	2 (100%)
Acinetobacter calcoaceticus	6	6 (100%)

ORGANISM		BACTERIOLOGIC RESPONSE
SKIN & SKIN STRUCTURE	NO.	ERADICATED
Acinetobacter spp.	2	1 (50%)
Alcaligenes odorans	1	1 (100%)
Alcaligenes spp.	1	1 (100%)
P. aeruginosa	56	37 (66%)
Pseudomonas spp.	1	1 (100%)
Aeromonas hydrophilia	4	3 (75%)
Serratia marcescens	9	8 (89%)
Serratia spp.	2	2 (100%)
Vibrio parahemolyticus	1	1 (100%)
Lactobacillus	1	1 (100%)
Gaffkia anaerobia	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Peptococcus spp.	22	22 (100%)
Peptostreptococcus spp.	13	13 (100%)
Eubacterium spp.	1	1 (100%)
A. eriksonii	1	1 (100%)
Bacteroides fragilis	27	27 (100%)
B. melaninogenicus	3	3 (100%)
B. bivius	1	1 (100%)
Bacteroides spp.	32	32 (100%)
Eikenella corrodens	1	1 (100%)
Eikenella spp.	1	1 (100%)
A. fermentans	1	1 (100%)
Fusobacterium spp.	5	5 (100%)
Fusobacterium rusii	1	1 (100%)
Veillonella parvula	2	2 (100%)
Mixed anaerobes	2	2 (100%)

OTITIS

S. pneumoniae	1	1 (100%)

UPPER RESPIRATORY

S. aureus[R]	1	1 (100%)
Streptococcus spp.	1	1 (100%)
E. aerogenes	1	1 (100%)
K. pneumoniae	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	1	1 (100%)
Fusobacterium spp.	1	1 (100%)

MEDIASTINITIS

S. aureus[R]	1	1 (100%)

BRAIN ABSCESS	NO.	ERADICATED
S. aureus^R	1	1 (100%)

SAFETY

NO. OF CASES EVALUABLE --------------------------- 1,696

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS ----------- 79 (4.7%)

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS --------- 181 (10.7%)

LOCAL SIDE
EFFECTS

	NO.	Probably Not	Possibly	Probably	Definitely
Infused vein pain	17 (1.0%)	5 (0.3%)	4 (0.2%)	5 (0.3%)	3 (0.2%)
Infused vein induration	11 (0.6%)	7 (0.4%)	4 (0.2%)		
Infused vein infection	3 (0.2%)	2 (0.1%)	1 (0.1%)		
Erythema I.V. site	13 (0.8%)	7 (0.4%)	6 (0.4%)		
Phlebitis/ thrombophlebitis	56 (3.3%)	3 (0.2%)	24 (1.4%)	22 (1.3%)	7 (0.4%)

SYSTEMIC SIDE EFFECTS

	NO.	Probably Not	Possibly	Probably	Definitely
Anxiety	1 (0.05%)	1 (0.05%)			
Confusion	4 (0.2%)	3 (0.15%)	1 (0.05%)		
Seizures	11 (0.6%)	4 (0.2%)	3 (0.15%)	4 (0.2%)	
Encephalopathy	1 (0.05%)			1 (0.05%)	
Dizziness	6 (0.3%)	1 (0.05%)	1 (0.05%)	1 (0.05%)	3 (0.15%
Vertigo	2 (0.1%)		2 (0.1%)		
Headache	5 (0.3%)	3 (0.15%)	2 (0.1%)		
Myoclonus	2 (0.1%)			2 (0.1%)	
Meningitis	1 (0.05%)		1 (0.05%)		
Intracerebral hemorrhage	1 (0.05%)	1 (0.05%)			
Paresthesia	1 (0.05%)				1 (0.05%)
Somnolence	3 (0.15%)		1 (0.05%)	2 (0.1%)	
Nystagmus	1 (0.05%)	1 (0.05%)			
Asthenia/weakness	2 (0.1%)		1 (0.05%)		1 (0.05%
Chest discomfort/pain	4 (0.2%)	3 (0.15%)	1 (0.05%)		
Syncope	1 (0.05%)	1 (0.05%)			
Hypotension	10 (0.6%)	4 (0.2%)	3 (0.15%)	3 (0.15%)	
Palpitation	2 (0.1%)		2 (0.1%)		
Tachycardia	1 (0.05%)		1 (0.05%)		
Apnea	2 (0.1%)	2 (0.1%)			
Dyspnea	2 (0.1%)	1 (0.05%)	1 (0.05%)		
Hyperventilation	1 (0.05%)				1 (0.05%
Hemoptysis	1 (0.05%)	1 (0.05%)			
Respiratory distress syndrome	1 (0.05%)	1 (0.05%)			

SYSTEMIC SIDE
EFFECTS

	NO.	Probably Not	Possibly	Probably	Definitely
Cyanosis	1 (0.05%)		1 (0.05%)		
Septic Shock	2 (0.1%)	2 (0.1%)			
Flushing	1 (0.05%)				1 (0.05%)
Fever	10 (0.6%)	2 (0.1%)	5 (0.3%)	1 (0.05%)	2 (0.1%)
Chills	2 (0.1%)	2 (0.1%)			
Hyperhydrosis	2 (0.1%)	1 (0.05%)	1 (0.05%)		
Facial edema	1 (0.05%)			1 (0.05%)	
Pruritus	6 (0.3%)	1 (0.05%)	1 (0.05%)	3 (0.15%)	1 (0.05%)
Rash	17 (1.0%)	1 (0.05%)	8 (0.5%)	5 (0.3%)	3 (0.15%)
Urticaria	3 (0.15%)			2 (0.1%)	1 (0.05%)
Erythema multiforme	1 (0.05%)				1 (0.05%)
Polyarthropathy	1 (0.05%)		1 (0.05%)		
Thoracic spine pain	1 (0.05%)				1 (0.05%)
Pharyngeal pain	1 (0.05%)			1 (0.05%)	
Increased salivation	1 (0.05%)			1 (0.05%)	
Glossitis	1 (0.05%)				1 (0.05%)
Brown tongue	3 (0.2%)			3 (0.2%)	
Heartburn	2 (0.1%)		1 (0.05%)	1 (0.05%)	
Hiccups	1 (0.05%)	1 (0.05%)			
Nausea	38 (2.2%)	3 (0.2%)	14 (0.8%)	16 (0.9%)	5 (0.3%)
Vomiting	31 (1.8%)	6 (0.4%)	11 (0.6%)	6 (0.4%)	8 (0.5%)
Diarrhea	45 (2.7%)	15 (0.9%)	14 (0.8%)	10 (0.6%)	6 (0.4%)
Abdominal pain	3 (0.15%)	1 (0.05%)	1 (0.05%)	1 (0.05%)	
Pseudomembranous colitis	3 (0.15%)			3 (0.15%)	
Hemorrhagic colitis	1 (0.05%)			1 (0.05%)	
Oral candidiasis	1 (0.05%)				1 (0.05%)
Vaginal candidiasis	1 (0.05%)		1 (0.05%)		
Pruritus vulvae	1 (0.05%)		1 (0.05%)		
Menorrhagia	1 (0.05%)	1 (0.05%)			
Dysuria	1 (0.05%)	1 (0.05%)			
Oliguria and anuria	2 (0.1%)	1 (0.05%)		1 (0.05%)	
Polyuria	1 (0.05%)			1 (0.05%)	
Fullness in ears	1 (0.05%)	1 (0.05%)			
Hearing loss	3 (0.15%)	2 (0.1%)	1 (0.05%)		
Tinnitus	1 (0.05%)		1 (0.05%)		

	NO.	Definitely Not	Probably Not	Probably
DEATHS	88 (5.3%)	83 (5.0%)	4 (0.2%)	1 (0.1%)

Abnormal Laboratory Tests

	NO ABNORMAL (%)
Decreased RBCs	1 (0.1%)
Decreased hemoglobin	17 (1.0%)
Decreased hematocrit	14 (0.8%)
Decreased WBC	22 (1.3%)
Decreased neutrophils	10 (0.6%)
Increased lymphocytes	2 (0.1%)
Increased monocytes	13 (0.8%)
Increased eosinophils	69 (4.1%)
Increased basophils	3 (0.2%)
Increased platelets	27 (1.6%)
Decreased platelets	12 (0.7%)
Prothrombin time (abnormal)	13 (0.8%)
Increased BUN	10 (0.6%)
Increased blood urea	4 (0.2%)
Increased creatinine	13 (0.8%)
Increased bilirubin	13 (0.8%)
Increased AST (SGOT)	76 (4.5%)
Increased ALT (SGPT)	83 (4.9%)
Increased alkaline phosphatase	61 (3.6%)
Increased LDH	6 (0.4%)
Increased blood glucose	2 (0.1%)
Increased potassium	1 (0.1%)
Decreased potassium	1 (0.1%)
Increased chloride	4 (0.2%)
Decreased chloride	1 (0.1%)
Positive Coombs' test	33 (1.9%)
Urine protein	7 (0.4%)
Urine RBCs	6 (0.4%)
Urine WBCs	9 (0.5%)
Urine epithelial cells	1 (0.1%)
Urine casts	5 (0.3%)
Urine bilirubin	3 (0.2%)
Urine urobilinogen	4 (0.2%)

Summary of Safety Update Report

The Safety Update Report includes information on 1502 patients in MSDRL-sponsored studies for whom information was available between the U.S. NDA cutoff (November 7, 1983) and September 30, 1984. All adverse experiences from both domestic and foreign studies are included.

The adverse experiences of 1369 patients treated with multiple doses of Primaxin are reported separately from those which occur in 133 patients who received the study drug in pharmacokinetic studies (mainly single doses).

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Decreased hemoglobin	17 (1.0%)
Decreased hematocrit	14 (0.8%)
Decreased WBC	22 (1.3%)
Decreased neutrophils	10 (0.6%)
Increased lymphocytes	2 (0.1%)
Increased monocytes	13 (0.8%)
Increased eosinophils	69 (4.1%)
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The adverse experiences of 1369 patients treated with multiple doses of
Primaxin are reported separately from those which occur in 133 patients who
received the study drug in pharmacokinetic studies (mainly single doses).

Adverse Experiences in 1369 Patients

	NO.	DRUG RELATIONSHIP Probably Not	Possibly	Probably	Definitel;
LOCAL SIDE EFFECTS					
Infusion site ulcer	).07%)			1 (0.07%)	2 (0.1%)
Infused vein induration	⌐ ((0.07%)			1 (0.07%)	
Erythema I.V. site	5 (0.4%)	3 (0.22%)	2 (0.15%)		
Phlebitis/ thrombophlebitis	53 (3.9%)	12 (0.9%)	13 (1.0%)	21 (1.5%)	7 (0.5%)
SYSTEMIC SIDE EFFECTS					
Nervousness	1 (0.07%)			1 (0.07%)	
Insomnia	1 (0.07%)			1 (0.07%)	
Disorientation	1 (0.07%)		1 (0.07%)		
Tremor	2 (0.15%)		2 (0.15%)		
Hallucinations	1 (0.07%)		1 (0.07%)		
Grand mal seizures	1 (0.07%)		1 (0.07%)		
Convulsive disorder	7 (0.5%)	3 (0.22%)	3 (0.22%)	1 (0.07%))	
Asterixis	1 (0.07%)		1 (0.07%)		
Hemiplegia	1 (0.07%)	1 (0.07%)			
Vertigo	1 (0.07%)	1 (0.07%)			
Headache	3 (0.22%)	2 (0.15%)		1 (0.07%)	
Chest discomfort	1 (0.07%)	1 (0.07%)			
Asthma	1 (0.07%)	1 (0.07%)			
Pulmonary embolism and infarction	1 (0.07%)	1 (0.07%)			
Cardiac arrest	1 (0.07%)	1 (0.07%)			
Cardiogenic shock	1 (0.07%)	1 (0.07%)			
Tachycardia	2 (0.15%)		1 (0.07%)	1 (0.07%)	
Atrial fibrillation	1 (0.07%)	1 (0.07%)			
Transient ischemic shock	1 (0.07%)	1 (0.07%)			
Myocardial infarction	1 (0.07%)	1 (0.07%)			
PVCs	1 (0.07%)	1 (0.07%)			
Fever	3 (0.22%)		1 (0.07%)	1 (0.07%)	1 (0.07%
Hyperhydrosis	2 (0.15%)		1 (0.07%)		1 (0.07%
Edema	1 (0.07%)			1 (0.07%)	
Fluid overload	1 (0.07%)		1 (0.07%)		
Peripheral edema	2 (0.15%)			2 (0.15%)	
Petechiae	1 (0.07%)	1 (0.07%)			
Pruritus	7 (0.5%)		2 (0.15%)	5 (0.4%)	
Drug eruption	1 (0.07%)			1 (0.07%)	
Rash	33 (2.4%)	4 (0.3%)	12 (0.9%)	15 (1.1%)	2 (0.15
Urticaria	5 (0.4%)	2 (0.15%)	2 (0.15%)		1 (0.07
Toxic erythema	1 (0.07%)			1 (0.07%)	
Skin inflammation	1 (0.07%)			1 (0.07%)	
Intertrigo	1 (0.07%)			1 (0.07%)	

Adverse Experiences in 1369 Patients

SYSTEMIC SIDE EFFECTS	NO.	DRUG RELATIONSHIP			
		Probably Not	Possibly	Probably	Definitely
Pharyngeal discomfort	1 (0.07%)		1 (0.07%)		
Dry mouth	2 (0.15%)		2 (0.15%)		
Glossitis	2 (0.15%)			2 (0.15%)	
Heartburn	1 (0.07%)			1 (0.07%)	
Nausea	38 (2.8%)	1 (0.07%)	13 (0.9%)	23 (1.7%)	1 (0.07%)
Vomiting	19 (1.4%)	1 (0.07%)	5 (0.4%)	12 (0.9%)	1 (0.07%)
Diarrhea	38 (2.8%)	9 (0.6%)	16 (1.2%)	11 (0.8%)	2 (0.15%)
Gastroenteritis	1 (0.07%)		1 (0.07%)		
Abdominal cramps	2 (0.15%)			1 (0.07%)	1 (0.07%)
Abdominal pain	5 (0.4%)	2 (0.15%)	1 (0.07%)	2 (0.15%)	
Pseudomembranous colitis	2 (0.15%)			1 (0.07%)	1 (0.07%)
Oral candidiasis	4 (0.3%)			4 (0.3%)	
Taste perversion	4 (0.3%)	1 (0.07%)	2 (0.15%)	1 (0.07%)	
Visual disturbance	1 (0.07%)		1 (0.07%)		
Paralytic lens	1 (0.07%)			1 (0.07%)	
Tooth discoloration	1 (0.07%)	1 (0.07%)			
Hematuria	2 (0.15%)	1 (0.07%)	1 (0.07%)		
Abnormal urine color	3 (0.22%)	1 (0.07%)	1 (0.07%)	1 (0.07%)	

Adverse Experiences in 133 Patients (usually one dose)

SYSTEMIC SIDE EFFECTS	NO.	DRUG RELATIONSHIP			
		Probably Not	Possibly	Probably	Definitely
Chills	3 (2.3%)			3 (2.3%)	
Abdominal pain	1 (0.8%)		1 (0.8%)		
Nausea	2 (1.5%)			2 (1.5%)	
Oral candidiasis	1 (0.8%)		1 (0.8%)		
Vomiting	1 (0.8%)	1 (0.8%)			
Euphoria	1 (0.8%)		1 (0.8%)		
Dizziness	1 (0.8%)			1 (0.8%)	
Hyperhydrosis	2 (1.5%)			2 (1.5%)	
Urticaria	1 (0.8%)		1 (0.8%)		
Taste perversion	1 (0.8%)		1 (0.8%)		
Headache	1 (0.8%)	1 (0.8%)			

Deaths

There were 113 deaths reported, all of which were considered not drug
related. Of these, 25% occurred in patients under compassionate protocols.

The adverse experiences reported in the post NDA patients were, in general,
similar to those reported in the NDA studies.
The predominant nervous system adverse experiences in the post NDA patients
related to seizures and occurred at about the same frequency as in the NDA
patients.
One patient with renal failure and one with marked renal insufficiency were
inadvertently given four times the recommended maximum dose of study drug and
had seizures. Both patients were treated under the compassionate protocol and
had significant background CNS disturbances. Four other patients who had
seizures had marked renal impairment and major CNS background disturbances and
were given more study drug than defined for their level of renal function.
The frequency of seizures during Primaxin therapy appears to be similar to
that for other antibiotics in general. However, as with beta-lactams in
general, the administration of Primaxin may be associated with grand mal
seizures.

In general, the majority of the patients who developed seizures had
pre-existing CNS disturbances.

Clinical Development Study Program (CDSP)

A total of 760 patients entered the CDSP in Germany as of September 30, 1984.
Eighty-six investigators participated in these studies and contributed
patients to this program. All patients enrolled were evaluated for safety.
A total of 37 deaths were reported, and according to the investigators none of
the deaths were drug related. These patients had severe infections and
serious concomitant diseases and many of them received Primaxin as a "last
resort" antibiotic with the hope that the patient would survive.

Based on the type of patients treated, the number of deaths in the program was
not considered unexpected. There were no unusual or high frequency adverse
experiences noted.

Japan Studies

As of September, 1984, Primaxin had been administered to 1,227 adult patients
in open clinical studies in Japan.
The overall incidence of adverse clinical experiences was 4.6% (56/1,227), and
the most frequent events reported were nausea 1.7%, diarrhea 0.8%, skin
eruption 0.7%, and vomiting 0.7%. None of the patients experienced a seizure.
The most frequent abnormal laboratory findings were elevation of SGOT - 6.2%,
SGPT - 6.1%, alkaline phosphatase - 2.4%, and gamma - GTP - 1.7%.
None of these patients experienced serious hepatic dysfunction. Eosinophils
were increased in 2.0% of the cases and BUN in 1.0%, but no patient had renal
function compromised by Primaxin. A total of 18 deaths were reported; none
was considered drug related.

LABORATORY VARIATIONS FROM THE NORMAL RANGE
POST NDA SAFETY UPDATE
1369 PATIENTS

	Def. Not	Prob. Not	Poss.	Prob.	Def.	Total	%
Hemoglobin decrease	2	4	1	1	0	8	.58
Hematocrit decrease	1	5	2	0	0	8	.58
WBC decrease	3	2	6	3	1	15	1.1
WBC increase	4(1)	4	1	0	0	9(1)	.66
Neutrophils decrease	0	0	1	0	0	1	.07
Seg. Neutrophils decrease	1	1	4	5	0	11	.80
Lymphocytes decrease	0	3	0	0	0	3	.22
Monocytes increase	2	1	4	1	0	8	.58
Eosinophils increase	1	4	27	13	2	47	3.4
Atypical Lyc	0	1	0	0	0	1	.07
Platelets decrease	4(1)	6(2)	6(1)	2(1)	0	18(5)	1.3
Platelets increase	2	13	21	10	0	46	3.4
SED Rate increase	0	1	3	0	0	4	0.3
Pro Time (abnormal)	2	6(1)	4	1	0	13(1)	.95
RBC Morph. Abnormal	1	1	0	0	0	2	.15
BUN increase	7(2)	8(3)	2(1)	0	0	17(6)	1.2
Creatinine increase	7(2)	12(2)	7(2)	1	0	27(6)	2.0
Bilirubin increase	4	5(1)	2	1	0	12(1)	.88
AST increase	6(1)	17	30	14	0	67(1)	4.9
ALT (abnormal)	10(1)	11	25	12	1	50(1)	3.7
Alkaline Phosphatase	7	17(1)	32	9	0	65(1)	4.7
GGT	0	0	0	1	0	1	.07
Bl. Glucose	1(1)	1	0	0	0	2(1)	.15
S. Lactate	0	1(1)	0	0	0	1(1)	.07
S. Uric Acid	1	0	0	0	0	1	.07
S. Sodium	1	0	0	0	0	1	.07
S. Potassium	2(1)	5(1)	2	0	0	9(2)	.66
S. Chloride	0	1	4	1	0	6	.44
Magnesium	1(1)	0	0	0	0	1(1)	.07
Coombs (+)	1	1	8	17	0	27	2.0
Urine Protein	1	2	4	1	0	8	.58
Urine WBCs	5	2	4	0	0	11	.80
Urine RBCs	5	4	0	0	0	9	.66
Urine Epithelial Cells	2	0	0	0	0	2	.15
Urine Casts	0	0	1	0	0	1	.07
WBC Casts	0	0	1	0	0	1	.07
Calcium Oxalate Crystals	0	1	0	0	0	1	.07
Urine Yeast	0	0	1	0	0	1	.07
C. difficile (stool)	0	0	0	2(2)	0	2(2)	.15

The counts not in parenthesis represent total counts, including serious and non-serious
laboratory results. The counts in parenthesis are serious laboratory results only.

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Other Studies

In addition to the MSDRL - Japan and the CDSP studies in Germany, local
studies to support registration are on-going in Italy, Spain, France, and the
United Kingdom.
Of the total 339 patients entered in these studies, there were four deaths
(all considered not drug related), and the only adverse experiences considered
to be probably drug related were leukopenia and hypotension. Both patients
recovered.

Marketing of Primaxin Outside the United States

On October 5, 1984, Merck notified the DAIDP that the West German Federal
Health Authority (the BGA) had suspended the registration of Primaxin. This
action was taken prior to the initial marketing of the drug by Merck. The
reason given for the suspension was that the BGA desired to have more time to
review data which Merck provided at their request.

On April 8, 1985, Merck informed the DAIDP that the BGA had completed its
review of the information provided, and that the suspension of the
registration had been removed. Therefore, Merck was to initiate marketing of
Primaxin in West Germany in April, 1985.

Conclusions
The results obtained in controlled and uncontrolled studies conducted by
well-qualified investigators demonstrate that Primaxin (imipenem/cilaslatin)
given in appropriate dosages is safe and effective in the treatment of serious
infections caused by susceptible strains of the designated microorganisms in
the conditions listed below:

1. Lower Resp'ratory Tract Infections caused by S. aureus (penicillinase
    producing strains), E. coli, Klebsiella species, Enterobacter species,
    P. aeruginosa, H. influenzae, H. parainfluenzae, Acinetobacter species,
    S. marcescens.

2. Urinary Tract Infections (complicated and uncomplicated) caused by
    S. aureus (penicillinase producing strains), Group D streptococci
    (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus
    vulgaris, Providencia rettgeri, M. morganii, P. aeruginosa.

3. Intra-Abdominal Infections caused by S. epidermidis, Group D streptococci
    (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus
    species (indole positive and indole negative), M. morganii, P. aeruginosa,
    Citrobacter species, Clostridium species, Gram-positive anaerobes,
    including Peptococcus species, Peptostreptococcus species and
    Propionibacterium species, Bacteroides species, including B. fragilis, and
    Fusobacterium species.

4. Gynecologic Infections caused by S. aureus, (penicillinase producing strains), S. epidermidis, Group B streptococci, Group D streptococci (enterococci), E. coli, Klebsiella species, Proteus species (indole positive and indole negative), Enterobacter species, Gram-positive anaerobes, including Peptococcus species, Peptostreptococcus species, Propionibacterium species and Bifidobacterium species, Bacteroides species, including B. fragilis, and Gardnerella vaginalis.

5. Bacterial Septicemia caused by S. aureus (penicillinase producing strains), Group D streptococci (enterococci), E. coli, Klebsiella species, P. aeruginosa, Serratia species, Enterobacter species, Bacteroides species, including B. fragilis.

6. Bone and Joint Infections caused by S. aureus (penicillinase producing strains), S. epidermidis, Group D streptococci (enterococcis), Enterobacter species, P. aeruginosa.

7. Skin and Skin Structure Infections caused by S. aureus (penicllinase producing strains), S. epidermidis, Group D streptococci (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus vulgaris, P. rettgeri, M. morganii, P. aeruginosa, Serratia species, Citrobacter species, Acinetobacter species, Gram-positive anaerobes, including Peptococcus species and Peptostreptococcus species, Bacteroides species, including B. fragilis, and Fusobacterium species.

8. Endocarditis due to S. aureus (penicillinase producing strains).

9. Polymicrobic Infections

Review of Package Insert
The proposed package insert for Primaxin was discussed with representatives from MSDRL during conferences held April 20, 1985 and June 5, 1985 (see memos of conferences). Subsequently, a revised copy of the insert, dated June 18, 1985, was submitted for further evaluation.

The following labeling revisions should be made:

Page 7, under Susceptibility Testing, first paragraph, imipenem spelling should be corrected.

Page 8, underline E. coli, S. aureus, S. faecalis and Ps. aeruginosa.

Page 9, under Urinary Tract Infections, page 10, under Intra-Abdominal and Gynecologic Infections, page 11, under Bacterial Septicemia and Bone and Joint Infections and page 12 under Skin and Skin Structure Infections change Group D streptococcus (enterococcus) to Group D streptococci (enterococci).
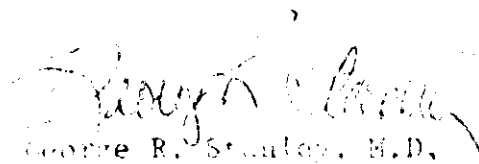
July 17, 1985

I concur with Dr. Albourne's review. As a result of our conclusions at the Medical Officer's Meeting of July 17, 1985, the final printed revised draft will include the following statement immediately following the listing of organ systems and organisms in the Indications section:

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

Dr. Albourne should specify which organisms in which organ systems require an asterisk.

George R. Stanley, M.D.

cc:
Orig NDA 50-587
HFN-036
HFN-045
HFN-815/CSO
HFN-040
Division File/Stanley 7/17/85
GD:jm

Pharm Rev

NDA Number (Original Submission):

Date Review Completed: 6/15/85

Applicant: Merck Sharp & Dohme

Drug: Primaxin® (Imipenem/Cilastatin sodium for injection)

Category: Broad spectrum beta-lactam antibiotic/renal dehydropeptidase inhibitor

Chemical names:

Imipenem: [5 R - [5 a, 6a (R)]] 6 (1-hydroxyethyl) 3 [[2-[(iminomethyl) amino] ethyl] thio] 7 oxo 1 azabicyclo [3.2.0] hept 2 ene 2 carboxylic acid monohydrate

Cilastatin: [z, 7(R)] 2(2,2-dimethylcyclopropane ... [(2 amino 2 carboxyethyl) thio] ... sodium salt

Chemical structures:

Imipenem:

Cilastatin:

Composition of Sterile Vials to be Marketed: the drug (Primaxin)

Proposed Clinical Use: Treatment of infection due to sensitive organisms

Related Submission: IND 18,638 (Primaxin)

Preclinical Studies: [The order of this review will follow the order in which the pharm/tox data is contained in the "Antibiotic Certification Request" (Form 5).]

I. MICROBIOLOGY

II. BIOCHEMICAL, METABOLIC & PHARMACOLOGIC STUDIES

Animals: rabbit, rhesus monkey, rat

Reason for Creating Imipenem from Thienamycin: The NH_2^+ group of thienamycin is highly ionizable in aqueous sol'n; therefore, its relatively high alkaline pH is high enough to induce the hydrolysis of the beta-lactam ring leading to the inactivation of the antibiotic.

Solution: By creating a formamidine derivative of thienamycin at the NH_2^+ group, the ionization of the alkaline moiety of thienamycin is wiped out. Note that this alkyl end of the drug shows a new pharmacologically active moiety, an amidine; however, since this amidine is attached at its nitrogen atom to the alkyl chain of the very right ring, we should call it a derivative of alkylated amidine. The well known effects of the amidino-guanidino groups of drugs (particularly di-) is not evident, and the results of pharmacological studies. There is no reason to be concerned.

The Mechanism of Toxic Action of Both Antibiotics

renal pathology. The coadministration of cilastatin had no effect on the excretion pattern of RA.

Radioactivity in the Feces: Negligible

Man: Urinary recovery of intact imipenem was 20%. The coadministration of cilastatin raised the amount of intact imipenem to 70%. The corresponding renal clearance estimates of imipenem were 74 & 162 ml/min. 95% of the RA in human urine was associated with intact imipenem & metabolite I.

The ratio of intact imipenem to metabolite I in human urine with or without coadministered cilastatin was determined by using combined radiometric & chromatographic analysis. With imipenem alone, greater than 80% of the RA derived from metabolite I. After coadministering cilastatin, 70% of the dose was identified as intact imipenem.

Rat, Rabbit & Monkey: The chromatogram exhibited 2 peaks. One (major) corresponded to the imipenem & metabolite I peak; the other (minor) to the cysteine adduct (III) peak.

Plasma Levels in Animals & Man: Plasma levels of RA disappeared rapidly. AUCs of plasma RA were similar for a given species (except man) when imipenem was given alone or in combination with cilastatin Na. In man, cilastatin coadministration decreased the plasma clearance of intact imipenem by 20%.

Tissue Distribution Studies in Rats: The RA of imipenem (^{14}C & ^{35}S) alone was distributed primarily in the kidneys & liver. The disappearance of RA from these tissues paralleled that from plasma. Analysis of selected tissues for the intact imipenem and metabolite indicated that cilastatin drastically increased the level of intact imipenem, and decreased the level of metabolite I in these tissues. The disappearance pattern of imipenem & metabolite I from the tissues was similar to that from plasma.

Physiological Disposition of Radiolabeled Cilastatin Sodium

Species Used: rhesus monkey, rat, rabbit, dog & man

Administration: Radiolabeled cilastatin Na alone or in combination with an equal dose of nonradioactive imipenem was administered IV at doses of 5, 10 or 20 mpk of either drug in animals. Humans were given 250 mg of ^{14}C-cilastatin Na alone or in combination with 250 or 1000 mg of imipenem.

Renal Excretion: In monkey, rabbit & man, this was the sole route of elimination of cilastatin Na drug-related materials. (The RA found in the feces was negligible.) In the rat & dog, though renal excretion was over 50%, fecal excretion was also substantial (approx. 40%). In the rat, biliary excretion was significant, and enterohepatic circulation was evident.

Imipenem does not alter the excretion of intact cilastatin Na. Approx. amounts of intact cilastatin Na excreted in the urine were 15% for the rabbit, 45% for the monkey & 77% for man, whether or not imipenem was coadministered. For a given species, renal clearance of intact cilastatin Na are similar

between treatments; the values for the rabbit, monkey & man are estimated to be 10, 30 & 180 ml/min., respectively. In man, N-acetyl cilastatin Na accounted for 10% of the dose in the presence or absence of imipenem. Plasma RA levels decreased rapidly in all species; greater than a 100-fold reduction occurred within 6 hrs. with or without the coadministration of imipenem. The metabolism of cilastatin Na in primates appears to be mainly acetylation to the N-acetyl conjugate. In the rat, lower urinary recoveries of ^{35}S-RA vs. ^{14}C-RA suggest cleavage of the cysteinyl moiety of cilastatin Na

There was no accumulation of radiolabeled material by rat tissues. Liver, kidney & small intestine gave the highest tissue-plasma ratios. Although the levels were high in the early time periods, the tissue conc'ns of RA decreased rapidly, concomitantly with the decrease in plasma RA. Parallel studies conducted following coadministration of unlabeled imipenem resulted in no significant change in the disposition profiles of RA.

Imipenem did not alter the renal excretion or plasma clearance of intact cilastatin Na in any of the species studied. In man, no change was noted in the extent of the N-acetyl conjugate formed.

III. SECONDARY PHARMACOLOGY

IMIPENEM

G.I. System

Imipenem, at an oral dose of 20 mpk in fistula dogs, significantly reduced gastric volume evoked by gastrin tetrapeptide in the period of 0-30 min. after stimulation. However, the integrated secretion over 0-90 min. did not differ from the placebo trial. In a second trial at 10 mpk, output volume response was increased during the first collection period. Imipenem at either dose level did not affect basal gastric secretion.

At IV doses up to 100 mpk, it did not affect basal gastric secretion in pylorus-ligated rats as measured by pH, acidity, volume or acid pepsin output.

Imipenem did not alter the transit time of charcoal test meal in mice at doses up to 20 mpk SC & 100 mpk IV.

Cardiovascular System

Blood pressure, heart rate & autonomic activity in anesthetized dogs were not altered by imipenem at 4 mpk IV. The autonomic response of BP to high IV doses of imipenem were measured in the anesthetized dog. At doses up to 100 mpk, it did not affect autonomic activity.

Tested at 20 mpk IV in 5 spontaneously hypertensive rats, it did not significantly lower BP. It did, however, cause a slight, transient pressor response.

The effects of high doses of imipenem (20 & 100 mpk IV) on BP, resp. rate & lead II of ECG were studied in anesthetized dogs. No effects were observed at

25 mpk or in 2/3 dogs at 100 mpk; the third dog at 100 mpk had a transient increase in resp. rate, systolic BP & HP.

Central Nervous System

In a standard pharmacometric screen for CNS effects in the mouse, imipenem gave no significant effects at doses of 6, 30 & 150 mpk IP.

Imipenem had no behavioral or overt effects in squirrel monkeys trained in the Sidman avoidance procedure.

The effects of high doses (50 & 200 mpk IV) on the spontaneous EEG or EEG arousal were observed at 50 mpk. Seizure discharge in the hippocampus occurred in 1/5 rabbits given 200 mpk. EEG arousal was increased 45 min. after admin. of 200 mpk.

The effects of high doses of imipenem on locomotor activity and normal body temp. in rats at doses up to 100 mpk were little or none. Doses of 100 mpk had no effect on the neuromuscular junction of rats.

Respiratory System

In the anesthetized dog, imipenem had no effect on respiratory parameters observed (tidal vol., resp. rate, total lung resistance or dynamic compliance) at IV doses of 2.5 or 10 mpk.

Renal System

No diuretic activity was observed in conscious rats at doses of 1.25-10 mpk IP, or in conscious dogs at 5 mpk IV.

CILASTATIN

G.I. System

Basal & gastrin-stimulated gastric secretion in dogs was not significantly changed by 1 mpk of cilastatin Na given IV.

IV doses up to 100 mpk did not affect basal gastric secretion in pylorus-ligated rats as measured by pH, acidity vol. or acid pepsin output.

Intestinal propulsion of charcoal test meal in mice was not affected at doses up to 100 mpk IV.

Cardiovascular System

Arterial BP in spontaneously hypertensive rats was not affected by cilastatin at doses up to 10 mpk IP. In 3 dogs treated at 10 mpk IV, the compound did not alter BP or HP and it neither blocked nor enhanced any of a variety of autonomic stimuli.

The autonomic responses of BP to high IV doses were measured in the anesthetized dog. Cilastatin did not affect BP, HR, resp. rate or ECG.

25 mpk or in 2/3 dogs at 100 mpk; the third dog at 100 mpk had a transient increase in resp. rate, systolic BP & HR.

Central Nervous System

In a standard pharmacometric screen for CNS effects in the mouse, imipenem gave no significant effects at doses of 6, 30 & 150 mpk IP.

Imipenem had no behavioral or overt effects in squirrel monkeys trained in the Sidman avoidance procedure.

The effects of high doses (50 & 200 mpk IV) on the spontaneous EEG or EEG arousal were observed at 50 mpk. Seizure discharge in the hippocampus occurred in 1/5 rabbits given 200 mpk. EEG arousal was increased 45 min. after admin. of 200 mpk.

The effects of high doses of imipenem on locomotor activity and normal body temp. in rats at doses up to 100 mpk were little or none. Doses of 100 mpk had no effect on the neuromuscular junction of rats.

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IV doses up to 100 mpk did not affect basal gastric secretion in pylorus-ligated rats as measured by pH, acidity vol. or acid pepsin output.

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Cardiovascular System

Arterial BP in spontaneously hypertensive rats was not affected by cilastatin at doses up to 10 mpk IP. In 3 dogs treated at 10 mpk IV, the compound did not alter BP or HR and it neither blocked nor enhanced any of a variety of autonomic stimuli.

The autonomic responses of BP to high IV doses were measured in the anesthetized dog. Cilastatin did not affect BP, HR, resp. rate or ECG.

Central Nervous System

Cilastatin Na was tested at doses of 6, 30 & 150 mpk IP in the pharmacometrics procedure, a battery of tests useful for detecting various types of actions in the CNS in mice. The compound was essentially inactive.

At cumulative oral doses of 5, 10 & 20 mpk in squirrel monkeys, it did not cause any alteration in continuous avoidance responding or any overt signs of CNS activity.

The effect of high doses were studied on locomotor activity & normal body temp. in rats. Doses up to 100 mpk had little or no effect.

A dose of 100 mpk had no effect on the neuromuscular junction of rats.

Respiratory System

Cilastatin Na at 10 & 40 mpk IV was tested in anesthetized dogs for possible effects on various respiratory system parameters. Changes, if any, were minimal and generally no different from those occurring in dogs receiving the drug solvent (water injected IV).

Renal System

Urinary electrolyte excretion in 6 conscious dogs was unaffected by cilastatin Na at 10 mpk IV.

IMIPENEM/CILASTATIN

G.I. System

IV doses up to 100 mpk each of imipenem & cilastatin Na in combination did not affect basal gastric secretion in pylorus-ligated rats, as measured by pH, acidity, volume or acid pepsin output.

Intestinal propulsion of a charcoal test meal in mice was not affected by cilastatin combined with imipenem at doses up to 100 mpk.

Cardiovascular System

The autonomic responses of BP to high doses of the combination were measured in the anesthetized dog. At doses of 25:25 or 100:100 mpk, there was no sig. inhibition of the carotid sinus reflex which may be related to a decrease in mean BP.

When studied for effect on BP, HR, resp. rate & ECG in anesthetized dogs, the combination at 100:100 mpk IV slightly decreased mean BP; lower doses (25:25 mpk) had no effect on BP or other parameters.

Central Nervous System

In mice, the combination in doses up to 100:100 had no effect on gross behavior or pupil size and possessed no anticonvulsant activity.

The effect of the combination was studied in rats in locomotor activity and normal body temp. Doses of 10, 100 mpk had no effect on the neuromuscular junction of rats.

CONCLUSIONS

Imipenem

- Devoid of any pronounced actions on the G.I. tract.
- Lacked important actions on the CVS.
- Produced no noteworthy actions in the CNS.
- Produced no major effects on the respiratory system.
- Devoid of sig. actions in the renal system.

Cilastatin Sodium

- Devoid of sig. effects on G.I. acid secretion.
- Produced no sig. action on the CVS.
- Possessed no marked or pronounced actions on the CNS.
- Did not affect renal function.
- Produced no sig. change on respiratory parameters.

Imipenem/Cilastatin Sodium

- Inhibited the carotid sinus reflexes and slightly decreased mean BP.
- Showed no sig. effect on the CNS.
- Produced no appreciable change in BP, resp. rate or ECG.

IV. GENERAL TOXICITY

Introduction: The bulk of the studies were reviewed in my pharm. rev. of IND 18,538. The applicant submitted the results of newer studies in this NDA. For a better overview of the toxicity, the results of all toxicity studies will be summarized here, following that of the applicant.

A. Studies with Imipenem

The acute parenteral toxicity of imipenem was evaluated in rats & mice. No oral toxicity studies were performed, as the drug degrades extensively in the acid environment of the stomach. The IV LD_{50} values for imipenem in both species ranges approx. 1500 to greater than 2000 mpk with no sex- or species-related differences apparent.

Rats administered imipenem alone at dosage levels up to 180 mpk/day for 6 mos. showed no evidence of adverse effects. Renal tubular necrosis was observed in monkeys after single or multiple doses of imipenem of 180 mpk/day. Some variability & sensitivity to this renal effect is seen in this species, as some animals receiving this dose level survived for 5 wks of continuous daily admin. with no histomorphologic evidence of renal damage. It is noteworthy that admin. of imipenem to this same species at a level of 120 mpk/day for 6 mos. produced no evidence of renal damage. Thus, a rather high threshold exists for induction of nephrotoxicity by this antibiotic in this species.

B. Studies with Cilastatin

The low order of toxicity of cilastatin Na was demonstrated initially in acute toxicity tests. Oral LD_{50} values in mice & rats are greater than 10 gm/kg. IV LD_{50} values for both species are greater than 5 gm/kg.

Cilastatin Na has been administered to rats & rhesus monkeys IV at doses up to 500 mpk/day; rats received daily admin. for up to 3 mos. and monkeys received daily admin. for up to 5 wks. No evidence of treatment-related adverse effects was observed in either species. Admin. of cilastatin Na SC to rats for 5 wks at doses up to 3125 mpk/day produced renal changes characterized by very slight vacuolar degeneration in the proximal tubular epithelial cells at 1250 mpk & higher. In addition to those changes, slight-moderate tissue damage was observed at the site of SC injection, indicating slight local irritation produced by this route of admin. This route was necessitated by the high viscosity of the dosing sol'ns required to achieve these conc'ns. In addition, slight decreases in serum protein & albumin conc'ns were observed at the highest dose level. No other evidence of adverse effects was seen in this study.

C. Studies with Imipenem/Cilastatin Combination

The acute toxicity of imipenem/cilastatin was evaluated in rats & mice. In contrast to the protective effects observed with coadministration of these 2 agents to rabbits or monkeys, the acute toxicity of the combination was slightly greater than that observed with imipenem alone and significantly greater than with cilastatin alone. The IV LD_{50} values ranged from approx. 900-1200 mpk/day in mice & rats.

SC studies in rhesus monkeys with imipenem/cilastatin revealed a protective effect of coadministration of the DHP inhibitor similar to that observed in rabbits. Admin. of a nephrotoxic dose (180 mpk/day) or imipenem with an identical dose level of cilastatin produced no evidence of renal damage after daily admin. for up to 6 mos. [The reader should keep this in mind; in my "Comments & Recommendations", I will discuss the increased sensitivity (at least 4-5 fold) of pregnant rabbits to the drug combination.]

Imipenem/cilastatin has been administered to rats at doses up to 320 mpk/day of each drug for up to 6 mos. without evidence of sig. toxicity. Although slight elevation of kidney weights was observed in animals given this high dose level of each drug for 3 mos., no similar changes were observed at lower dose levels. No other evidence of adverse effect was observed with this combination of drugs in this species.

D. Studies in Infant Monkeys

The toxicity of imipenem/cilastatin Na was evaluated in neonatal & infant rhesus monkeys at dosage levels up to 180:180 mpk/day. In the former study, drug admin. was begun within 3 days of birth and continued for 10-12 wks. The latter study began within 5-8 wks of age and continued for 14 wks. No evidence of induced toxicity was observed in either study.

V.   REPRODUCTION STUDIES

IMIPENEM - IV Teratology in the Rat & Rabbit

A. Rats: No evidence of adverse effects on the embryo were observed and no evidence of teratogenicity was seen. The rats received up to 900 mpk/day during the period of organogenesis. The rat, being the least sensitive animal to the toxicity of the drug, showed an unusually high level of tolerance, even in these studies.

B. Rabbits: Dosage levels up to 60 mpk/day during organogenesis did cause embryo- & fetotoxicity at maternotoxic dose levels, but no evidence of fetal malformation. The level tolerated by the dams & embryos/feti was 30 mpk/day.

CILASTATIN SODIUM

A. SC Teratology in the Rat: Doses of 40, 200 & 1000 mpk administered during the period of major organogenesis.

B. IV Teratology in Rabbits: Doses of 30, 100 & 300 mpk/day during organogenesis.

Results: No evidence of embryo- or fetotoxicity was observed in either species, and no drug-induced fetal malformations were seen.

IMIPENEM/CILASTATIN COMBINATION

A. Male & Female Fertility in Rats (IV; SC)

Dosage & Admin.: Doses up to 320:320 mpk/day, IV/SC to M for 12 wks prior to mating & throughout mating; to F, the same doses IV/SC for 15 days prior to mating through Day 19 of gestation.

Results: No evidence of drug-induced adverse effects was observed on fertility or fetal viability.

B. Effect on Fetal Development in Rats & Mice

N.B.: The applicant's remarks: "Excessive toxicity observed in rabbits at low dosage levels in range finding studies precluded the use of this species for evaluation." (Though the details of the range-finding study are submitted, the study will not be reviewed until the problem is resolved.)

Reviewer's Comments: This unusual change of toxicity in the same species (180:90 mpk/day = nephrotoxicity) vs other rabbit studies where the "no nephrotoxicity dose effect level" was 320:320 mpk/day (single dose, 180:180 mpk/day for b nos.) is presently discussed with the reviewing group and Dr. Blois of MSD. Though this appears to be a cosmetic problem, it is not. If there is so much difference in nephrotoxicity among rabbits, the same thing might happen in humans. Dr. Blois called me

recently. I explained the problem and asked him to give me an acceptable argument for the increased sensitivity of the pregnant rabbit to the drug combination. He promised to call again the next day.

Three studies will be reviewed below in one paragraph.

1. IV Teratology Study in the Mouse
2. IV/SC Teratology Study in the Rat
3. IV/SC Range-finding Study in Pregnant Rabbits

"Dosage levels employed for both mice & rats ranged up to 320:320 mpk/day. Slight decreases in fetal wt were observed for rats at this high dose level; no similar change was seen in mice. No evidence of embryo- or fetotoxicity was observed at lower dose levels and no treatment-related fetal malformations were observed. A slight increase in age of testes descent was seen in F_1 pups at 80:80 mpk/day. Although no consistent similar response was observed at higher dose levels, it is not possible to exclude this slight effect as a possible treatment-related change. No other evidence of adverse effect on postnatal growth or behavior was observed in rats. The effect of imipenem/cilastatin Na on the fetus/neonate when administered late in gestation and during lactation was evaluated in rats at dose levels up to 320:320 mpk/day. No evidence of adverse effects was observed."

VI.   GENETIC TOXICITY

A. Studies with Imipenem: V-79 mammalian cell; forward mutation; with & without metabolic activation.

   Results: No evidence of mutagenesis.

B. Studies with Cilastatin Na: Bacterial cell (Ames); reverse mutation; with & without metabolic activation.

   Results: No evidence of mutation.

C. Studies with Imipenem/Cilastatin Na

   1. V-79 mammalian cell; forward mutation; without metabolic activation.

      Results: No evidence of mutation.

   2. Hepatocyte unscheduled DNA synthesis; without metabolic activation.

      Results: No evidence of mutagenesis; no clastogenic potential.

Conclusions: "The results of in vitro & in vivo assays with imipenem and cilastatin Na alone and in combination have revealed no potential for interaction with genetic material."

VII.   SPECIAL TOXICITY STUDIES

In the write-up of these studies, the appl cant repeats certain data which are evident from the "Biochemical, Metabolic & Pharmacologic Studies", reviewed above. For "Introduction", please refer to that section of the review.

A.   Nephrotoxic Potential of Imipenem

The Study Proper: Renal damage after high dose levels of imipenem alone has been demonstrated in rabbits & rhesus monkeys. This effect is seen after single or multiple doses and with IV or SC admin. The renal toxicity seen is quantitatively & qualitatively identical in both species after SC or IV admin of the same dose level.

Exploration of the time course of renal tubular change produced by a nephrotoxic dose at the light & electron microscopic level revealed that the earliest change was visible as early as 0.5 hrs after treatment. This change was characterized by swelling & loss of the parallel configuration of the basilar cytoplasmic compartments, as well as increased electron density of cytoplasm. These changes progressed through vacuolation of the apical portion of the cell accompanied by loss of microvilli, distention of the citernae of the rough endoplasmic reticulum, and loss of ribosomes; mitochondrial injury was not apparent unti, 8 hrs after treatment.

To more closely approximate the clinical dosage regimen, the nephrotoxic potential of imipenem in a split dose regimen was evaluated in rabbits. A series of studies explored the effects of a nephrotoxic dose split into 2 or 3 equal doses spaced 2 or 6 hrs apart. Although this split dose regimen clearly reduced the severity of renal damage, tubular necrosis was still evident.

B.   Effect of Cilastatin Na on Imipenem-induced Nephrotoxicity

A series of studies was performed to evaluate the effect of cilastatin on the nephrotoxic potential of imipenem. Coadministration of a frankly nephrotoxic dose of imipenem to rabbits with increasing dose level of cilastatin produced decreasing degrees of renal damage; at a ratio of 1:1, no evidence of renal damage was seen. Protection was apparent at this ratio, regardless of the total dose of antibiotic given. In addition, complete protection was also observed in the split-dosage regimen referred to above with both agents coadministered in a 1:1 ratio

Multiple dose nephrotoxicity studies in rabbits evaluated nephrotoxicity potential of repeated admin of imipenem/cilastatin Na.

In a range-finding study in rabbits prior to a proposed teratology study, mortality & renal tubular degeneration were observed at relatively low dose levels (4 40, mg/day). The morphologic appearance of these changes was different from that observed in rabbits receiving imipenem alone. In addition, no evidence of renal damage was observed in rabbits given the combination at much higher dose levels (up to 360:360 mpk). The additional multiple dose nephrotoxicity studies described in this volume

reproduced the mortality & renal functional changes, but renal tubular degeneration was not observed. Rabbits in both of these studies had diarrhea. The renal changes observed in the range-finding study were thus considered secondary to excessive toxicity produced in this species as a result of alteration of gut flora. These studies further support the statement that the rabbit is an inappropriate species for multiple-dose teratology studies of antibiotics.

The inhibitory effect of cilastatin Na on renal DHP, and thus the inhibition of imipenem metabolism by this enzyme, is documented in the "Biochemical, Metabolic & Pharmacologic Studies" section of this review.

The protective effect of cilastatin on imipenem-induced nephrotoxicity led to a suggestion that inhibition of nephrotoxicity was a result of inhibition of metabolism. This protective effect appears to be a function of exclusion of the antibiotic from the renal tubule in a manner analogous to that proposed for probenicid & cephaloridine.

Studies were performed in rabbits to evaluate the nephrotoxic potential of the principal metabolites of imipenem. Metabolites were administered IV at doses shown to achieve sig. intracellular conc'ns in the kidney cortex. No evidence of renal damage was observed.

Further studies were performed to explore the relationship between nephrotoxicity & alterations in tissue glutathione levels. Treatments designed to alter the intracellular content of glutathione had no effect on degree of renal damage.

In vitro studies performed to explore the mechanism of imipenem induced nephrotoxicity were conducted in rabbit kidney cortex slices & cortical mitochondria. Studies with both preparations indicated that sig. changes in PAH accumulation & mitochondrial respiration were not observed until relatively high conc'ns of drug were used in incubation media. Although these studies are clearly not definitive, they suggest that alteration of mitochondrial respiration does not play a sig. role in initiating the nephrotoxic response to high dose levels of imipenem.

The hemolytic activity of imipenem & cilastatin alone and in combination was evaluated in vitro. No evidence of hemolytic activity was observed. Conc'ns of imipenem alone at 10 mg/ml & higher produced a positive direct Coomb's test; no similar results was observed at lower conc'ns.

Ocular & dermal irritation studies were done in rabbits with imipenem or cilastatin Na. Very slight dermal irritation was observed with either agent after placing 500 mg of the test agent in direct contact with abraded skin for 24 hrs; no irritation was observed in intact skin.

Ocular irritancy of the bulk compound was evaluated by placing 100 mg of the dry powder into the conjunctival sacs of rabbits. The eye was closed for 30 secs, then degree of irritancy assessed. Moderate irritation with cilastatin & slight irritation with imipenem were observed.

COMMENTS & RECOMMENDATIONS

Introduction: After reviewing all the preclinical studies pertaining to
pharmacology/toxicology, I found the drug relatively safe for human use. This
is based on (in the applicant's order of presentation) Biochemical, Metabolic
& Pharmacologic Studies, Primary & Secondary Pharmacologic Studies, Genetic
Toxicity Studies & Special Toxicity Studies. However, there are some
discrepancies in the submission with respect to the General Toxicity &
Reproduction Studies, i.e., the data are acceptable as such, but not so after
comparing certain data with those derived from similar studies in pregnant
rabbit studies. (The results of the 2 studies are contradictory, and this
needs clarification.) In the following paragraphs, I will not only discuss
these discrepancies, but will summarize the results and my request for
repetition of toxicity studies in pregnant rabbits. (This is in the framework
of the teratogenicity studies which will include an extra group of nonpregnant
f rabbits otherwise receiving the same treatment as the pregnant rabbits.)

Reason for the Study: In the above pregnancy range-finding study, the
applicant found & reported moderate-severe nephropathology in the rabbits
treated at 40:40 mpk/day parenterally. The elaboration of the applicant on
the etiology of the lesions is quite tranquilizing, but unacceptable. This
elaboration indicates that the nephropathology of the treated pregnant rabbits
is the result of drug-induced dehydration & diarrhea commonly associated with
antibiotic testing, and the pregnancy played no role in this seemingly
pregnancy-related increased sensitivity.

I called an emergency meeting on 6/28/85 with Drs. Blois & Bokelman and the
Chief Toxicologist at MSD (see my review of Reproduction Studies) to discuss
this phenomenon, which in my view, cannot be neglected. At this meeting, I
said that the neither study (single-dose 360:350 mpk/day or 6-mo. 180:180
mpk/day multiple-dose) showed any nephrotoxicity; therefore I feel that the
40:40 mpk/day multiple-dose pregnant rabbit study indicates pregnancy-related
increased sensitivity to the drug. The toxicologist tried to white-wash this
phenomenon, but when Dr. Bokelman saw my insistence on the repetition of this
study, and since I stated that the drug could be approved while the study is
under preparation or in progress, they suddenly changed their attitude and
shared my view on the potential hazard of the drug in pregnant women. They
also agreed that this is most likely the result of an endotoxic shock due to
the sudden death of endotoxin-producing gram-negative bacteria in the
intestine, caused by the antibiotic. N.B.: A simple and reliable test is
used in human medicine for the indication of nonspecific endotoxemia. If the
shock is already manifested, a simple drug treatment might be life-saving.

The gravity of potential endotoxic shock in humans, and in particular pregnant
women, needs no explanation. However, the point I would like to make here is
that endotoxic shock treated properly and on time is not always fatal. In
spite of this, endotoxic shock resulting from an intrauterine accident in
pregnant women is almost always fatal. If the patient recovers from the acute
episode, the extent of the adrenocortical necrosis might be very great, i.e.,
the 2 outer thirds or the center of the adrenal(s) might undergo irreversible
necrosis. This might also be superimposed with a very well known complication
syndrome leading to a severe endocrinopathy, consequently making the fatal
outcome more certain.

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The investigation of the above phenomenon in rabbits is probably the most suitable for elucidation of the problem. The conduction of the recommended study is a medical/ethical must. The species indicating the above hazards being the rabbit is fortunate, since for both phenomena discussed above, the rabbit is the animal model accepted by world authorities.

The applicant promised to submit a written commitment to undertake the rabbit study during the first week of July, 1985. Since the results will not be available at the time of approval of the drug, the package insert should be slightly changed, allowing leeway for the implicit expression of this potential hazard(s).

The following are my recommendation for changes in the labeling:

A. Pregnancy

    1. Until the results of adequate, well-controlled studies are available, I recommend this drug be categorized in Pregnancy Category "C". The reason for this is that in the IV/SC teratology Study in the Rat, "Slight decreases in fetal weight were observed for rats at 320:320 mpk/day. No evidence of embryotoxicity was observed at lower dosage levels, and no treatment-related fetal malformations were observed. A slight increase in the age of testes descent was seen in rj male pups at 80:80 mpk/day. Although no consistent similar response was observed at higher dosage levels, it is not possible to exclude this slight effect as a possible treatment-related change."

    2. Additionally, "Excessive nephrotoxicity in rabbits at low dosage levels (40:40 mpk/day)* in range-finding studies for teratogenicity studies precluded the use of this species for evaluation." As I explained at our meeting the the applicant (6/28/85), the nephrotoxicity of the drug might be very well due to endotoxic shock induced by the antimicrobial effects of the drug on gram-negative bacteria living in any healthy mammalian intestine, leading to endotoxin liberation. The applicant agreed with this potential mechanism of this indirect nephrotoxicity, and promised to elucidate the problem. For more information, the reader is referred to my comments on this problem in an earlier chapter of this review.

    *Note that the rabbit dose is very close to the actual human dose.

B. Warnings: Whether or not a warning is justified, in my view, is up to the judgment of the reviewing Medical Officer.

C. Drug Interaction: My concern is the potential interaction of theophylline with primaxin, with particular attention to the convulsigenic effects of primaxin itself. As I understand it, the applicant is planning special human studies for this. I leave the inclusion of this potential interaction also to the MO.

    . The use of the Term "poly- theopathy": this term is interpreted in animal pathology at the scientific level for disease associated with urinary

quinolone-azaquinolone antibacterials, there is no other drug-induced
"honest-to-goodness" arthropathy known in animals. I know of no
drug-induced human arthropathy. For the purpose of academic precision,
the above term is justified if the gross and/or micropathology confirms
the existence of the entity   Since animal arthropathy is a synonymous
term with the human osteoarthritis, the indiscriminate use of the two
terms might confuse the attending physician. Without knowing the
histopathology of the above "polyarthropathy", I would go no further with
my clinical terminology than "polyarthralgia". Dr. Albrecht should be
consulted about this.

Lorant Buko, D.V.M., M.Sc.

cc: Orig. NDA
HFN-815
HFN-815/MO
        CSO
HFN-340
HFN-815/L.Buko/smc/8/27/85
R/d init.by:JMDavitt
0045p