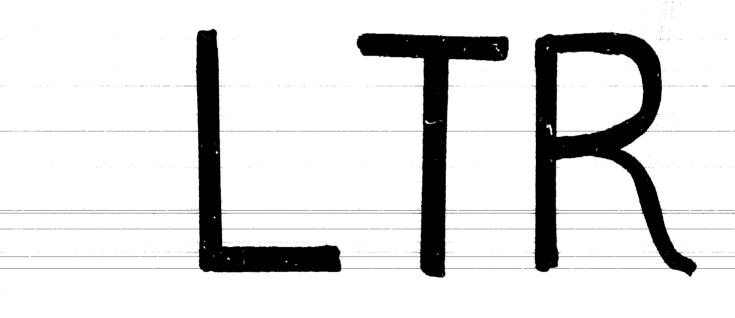
These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA: 50-587 SPONSOR: MERCK SHARP & DOHME 1 OF 3 TRADE: PRIMAXIN GENERIC: IMIPENEM

NDA: 50-507 TRADE: PRIMAXIN SPONGOK: MERCK SHARP & DOHME GENERIC: IMIFENEM STATISTICIAN'S REVIEW: Y APPROVAL LETTER: Y BIO/DISSOLUTION REVIEW: Y Highway 14 FIRM CONTROL LABEL: Y MICROBICLOUIST'S REVIEW: N Madecal OFFICER'S REVIEW: Y NAS/BRC REVIEW: N FEDERAL REGISTED MOTICE: N CHEMIST S REVILWE V TO A CONTRACTOR OF STREET TO THE STREET OF STREET S





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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."
- 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 imprenem and theophylline, with specific attention to CNS adverse events. The results are to be reported by October 1986.
- 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 cony 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

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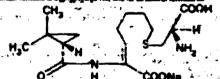
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James R. Kung 12/9/25 NUMECTION JAK.

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PRIMAXINE (IMIPENEM-CILASTATIN SODIUM, MSD)



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#### Medical Officer's Review of NDA 50-587

M.O. Review #1

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: Imipenen and Cilastatin Sodium
- (2) Trade: PRIMAXIN
- (3) Chemical:

Imipenem  $[5R-15 \, \alpha, 6 \, \alpha, (R)]$  -6-(1-hydroxyethy1)-3-[[2-[(iminomethy1) 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 MKO787, 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 MKO787/MKO791, is a broad spectrum, antibiotic consisting of equal parts of imipenem and cilastatin.

## (4) Chemical Structure

#### ïmi penem

#### Cilastatin Sodium

## B) Pharmacologic Category

Imipenes is a new broad spectrum beta-lactem 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 serobic 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
- 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
- Related Drugs: There are no pharmacologically or chemically analogous substances to imipenem or cilaritatin 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 C3 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 vide 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
C	2005	2 23	3.06				
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
5. aureus	2867	0.02	0.04	6.3	3.8	20.0	0.63
S. aureus	4428 <sup>D</sup>	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 <b>.3</b> 2	6.3	1.00	> 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°	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	<b>≻</b> 100	>100	5.0	1.3
Enterobacter spp.	<del>29</del> 02	1.3	2.5	<b>≯1</b> 00	>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	2 <del>9</del> 22	0.63	0.63	6.3	100	> 80	> 20
Klebsiella spp.	2888	0.63	1.3	>100	>100	10.0	1.3
Klehsiella 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

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

b) Methicillin resistant

TABLE 2

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

STRAIN	(105CFI)	IMIPENEM	THM	CAB	GEN	AMK	PIP
							1
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	<b>→</b> 20		
<b>3286</b>		2.5	10	80	5.0	6.3	6.3
3287°		2.5	10	>80	5.0		
3288 <sup>d</sup>		20.0	40	80	5.0		
4293		6.3	25	100	12.5	25	6.3
0294		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 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 thienanycin-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<sup>5</sup> and 10<sup>7</sup>CFU, were employed. Comparisons were made with two anti-pseudomonal cephalosporins, moxalactem 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)

	10 <sup>5</sup> CFU Inoc			107CFU Inoculu	.m		
	For % Str	rains		For % Stra	ains		
Compound	Range	50	90	Range	50	90	_
Imipenem	0.8 - 12.5	3.1	6.3	3.1 - 25	6.3	12,5	
Thinamycin	1.6 - 50	6.3	25	3.1 - 50	12.5	25	
Moxalactam	12.5 -> 50	25	50	50 ->50	<i>&gt;</i> 50	<i>&gt;</i> 50	
Cefotaxime	12.5 -7 100	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	<del>&gt;</del> 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 (103 and 105 CFU per microtiter well), imipenem is bactericidal at its MIC. At the high inoculum level(107 CFU), 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 MKO787 WITH BETA-LACTAM AND AMINOGLYCOSIDE ANTIBIOTICS

TABLE 5	GRAM POSITIVE O	RGANISMS			
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000 NUTSU				MI	- J
ORGANISM	ANTIBIOTIC	Ī	N	50%	90%
STAPH. AUREUS	MK0787	14	379	≤0.04	<b>≤</b> 0.06
	CEFCTAXIME	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	MK0787	8	163	<b>£0.06</b>	0.44
EPIDERMIDIS	CEPHALOTHIN	5	105	≤0.16	1.2
	CEFTAZIDTME	1	12	8.0	32.0
	MOXALACTAM	3	40	16.6	≥ 45.0
	PENICILLIN G	6	117	0.69	5.8
	TOBRAMYCIN	· · · · · · • • • · · ·	18	0.25	> 32.0
STREPTOCOCCUS	MK0787	11	265	≤ 0.02	≤ 0.04
SPP.	CEPHALOTHIN	6	136	≤ 0.02 ≤ 0.16	
Si 1 1	MOXALACTAM				≤ 0.03
	OXACILLIN	6 3	215	2.6	4.9
	PENICILLIN G		32	0.13	0.21
		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.ü
	PIPERACILL.IN			5,4	20.5
	TICARCILLIN	<u>1</u>		100.0	200.00
	TOBRAMYCIN	ī		<b>&gt;32.0</b>	>32.0
<u></u>	VANCOMYCIN	ī	29	1.0	2.0
		<del>-</del>			

1 = # OF INVESTIGATORS
N = # OF STRAINS EXAMINED

TABLE 5 (cont'd)	GRAM NEGATIVE ORGAN	ISMS			
		<del></del>			TRIC MEAN
				MI	C mg/wl
ORGANISM	ANTIBIOTIC	Ī	N	50%	90%
ESCHERICHIA COLI	MIK0787	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
	<b>CEFTAZIDIME</b>	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
	CEFO TAX IME	7	371	0.09	0.61
	CEFOXITIN	7	281	12.0	124.0
	CEFTAZ ID IME	1	34	0.5	16.0
	MOXALACTAM	7	313	0.13	0.76
	CARBENICILLIN	4	106	5.7	47.0
	PIPERACILLIN	6	171		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
	CEFO TAX IME	4	139	0.02	0.09
	CEFOXITIN	4	48	2.7	4.8
	CEFTAZ ID IME	1	57	0,25	1.0
	MOXALACTAM	5	141		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.	MKO787	11	214	0.68	1.3
	CEFOTAXIME	4	102	0.26	2.0
	CEFOXITIN	4	47	20.0	55.0
	CEFTAZIDINE	1	30	0.25	0.25
	MOXALACTAM	6	77	0.76	2.1
	<b>CARBENICILLIN</b>	2	70	22.0	578.0
	GENTAMICIN	3	47	4.2	51.0

TABLE 5 (CONT'D)				GEOMET MIC	RIC MEAN
ORGANISM	ANTIBIOTIC	Ī	N	50%	90%
PROTEUS MIRABILIS	MK0787 CEFOPERAZONE CEFOTAXIME CEFOXITIN CEFTAZIDIME MOXALACTAM CARBENICILLIN PIPERACILLIN TICARCILLIN TOBRAMYCIN	7 2 3 2 1 4 1 3 4 2	210 74 146 26 60 101 33 101 121 38	1.4 0.61 0.02 4.6 0.06 \$0.12 0.78 \$\leq\$ 0.41 0.68 0.86	3.0 2.0 0.03 3.0 0.06 0.16 0.78 ≤1.33 ≥14.0 3.0
PROTEUS SPP. INDOLE (+)	MKO787 CEFOPERAZONE CEFOTAXIME CEFOXITIN CEFTAZIDIME MOXALACTAM PIPERACILLIN TICARCILLIN AMIKACIN	17 5 11 6 4 10 5 8	386 82 318 215 60 265 95 110 38	1.8 1.5 ≤ 0.04 4.3 0.12 0.11 0.77 ≥ 4.5 2.3	3.3 6.5 0.4 > 15.0 0.21 0.20 6.0 ≥ 48.0 5.8
PSEUDOMONAS AERUGINOSA	MK0787 CEFOPERAZONE CEFOTAXIME CEFTAZIDIME CEFTIZOXIME MOXALACTAM CARBENICILLIN PIPERACILLIN GENTAMICIN TOBRAMYCIN	12 5 7 1 1 8 4 4 5	590 254 372 59 100 389 198 230 237 138	1.5 3.9 12.2 2.0 64.0 13.0 75.0 5.2 2.3 1.4	4.9 22.4 ≥ 43.4 4.0 > 64.0 ≥ 42.4 563.0 19.6 ≥ 11.0 10.2
BACTEROIDES FRAGILIS	MKO787 CEFOTAXIME CEFOXITIN MOXALACTAM CHLORAMPHENICOL CLINDAYYCIN METRONIDAZOLE	5 2 4 4 1 2	345 47 203 180 100 156 56	0.15 4.81 9.3 0.6 4.0 ≤ 0.47 0.5	0.4 ≥25.0 20.2 4.8 8.0 1.6 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 MELITENS IS	98	2.0
HAEMOPHILUS INFLUENZAE	173	1.9
MORAXELLA SPP	28	0.125
NEISSERIA GONORRHOEAE	111	0.13
NEISSERIA MENINGITIDIS	<b>9</b> 3	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
EUBACTER IUM SPP	6	2.0
PEPTOCOCCUS SPP	49	0.07
PETOSTREPTOCCCUS SPP	32	0.14
ANAEROBES - GRAM-NEGATIVE		
CAMPYLOBACTER FETUS SS. JEJUNI	36	0.03
CAMPYLOBACTER PETUS SS. INTESTINALIS	4	0.19
EIKENELLA CORRODENS	28	0.25
FUSOBACTER IUM SPP	57	0.5
VEILLONELLA SPP	23	0.25

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

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

Gram-Fositive		<u> </u>	GEOMETRIC MEAN MIC90 mg/ml
Staphyloccus aureus (W.T.)	22	1063	<b>≤</b> 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	• =
Mycobacterium fortuitum	ī	12	0.48 (MIC <sub>70</sub> ) 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	≤ 0.26
Escherichia coli (Gen-R)	4	41	€ 0.70
Acinetobacter spp.	14	436	0.47
Campylobacter fetus	Ĩ3	92	≤ 0.07
Bacteroides fragilis	.4	906	= 0.07 ≤ 0.33

I = Number of independent investigators

N = Number of clinical isolates tested

<sup>\*</sup>A = Aminoglycosides, eg. Gentamicin, Amikacin, Tobramycin

TABLE 8

Comparative Activities Against Streptococcus faecalis Isolates

(n = 89)

<u>Antibi</u> otic	<u> </u>	Geometric Mean
A (CIDIOCIC		MIC90, mg/ml
MK0787	89	0.9
Piperacillin	35	4.0
Cephalothin	54	32.0
Cefotaxime	89	<b>&gt;</b> 128.0
Cefoperazone	89	34.3
Ceftazidime	54	> 128.0
Moxalactam	8 <del>9</del>	<b>&gt;</b> 128.0
Cefsulodin	54	128.0 ح
Ceftriaxone	54	> 128.0
Ceftizoxime	54	> 128.0
Cefuroxime	54	> 128.0
Gentamicin	35	15.0

TABLE 9

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

Antibiotic	No. of <u>Isolates</u>	MK0787 MIC <sub>90, mg/ml</sub>
Tobramycin (MIC ≥ 8)	15	8
Gentamicin (MIC ≥ 8)	65	4
Amikacin (MIC≥32)	<b>2</b> 6	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 <sub>90</sub> , mg/ml
MK0787 Gentamicin Amikacin Tobramycin Moxalactam Cefoperazone Cefotaxime Piperacillin	2 4 8 2 32 32 64 16	8 32 64 8 64 32 128 32

TABLE 11

## Carbenicillin-R. <u>Pseudomonas aeruginosa</u> Isolates

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

Antibiotic	3.13	6.25	12.5	25	50	100
MK0787 Piperacillin Cefotaxime Moxalactam	90	<b>9</b> 5	100 20	60	80 20	85 75 5

TABLE 12

Comparative Activity Against <u>Campylobacter</u> fetus, supp. jejuni n = 36

Antibiotic	MIC90, mg/ml
MK0787	0.03
Ampicillin	4.0
Moxalactam	16.0
Cefotaxime	4.0
Erythromycin	0.5
Chloramphenicol	4.0
Rifampin	> 128.0
Cefoperazone	<b>≥</b> 128.0
Vancomycin	≥ 128.0

TABLE 14

Comparative Activity Against Acinetobacter spp. n = 14

Antibio	tic	MIC90,mg/ml	
MK0787		0.25	
Amoxici.	llin	32.0	
Cefotax:	ime	16.0	
Moxalact		64.0	
Ceftazio	dime	8.0	
Ticarci.	llin	32.0	

Antibiotic	MIC <sub>90,</sub> mg/ml
MKC787 Mcxalactam Piperacillin Mezlocillin Carbenicillin Ticarcillin Azlocillin Cefoxitin Cefotaxime Cefoperazone Cefamandole Clindamycin	MIC90,mg/m1  0.25  4.0 64.0 128.0 > 256.0 > 256.0 > 256.0 16.0 256.0 256.0 256.0
Metronidazole Chloramphenicol	1.0 4.0

Susceptibility Reference List of MK0787 (N-Forminidoyl Thienamycin)

Bacterial Strain	Gram (+/-)	N,	Geom. Mean	
Bacterier Strain	( 7/ - )	<u>N</u>	MIC <sub>50</sub>	MIC90
Achromobacter Vd:				
Achromobacter Vd-1, Vd-2		10	2,0	2.0
Achromobacter xvlosoxidans		7	2.0	4.0
Actinomyces spp.		•	2,0	4,0
Actinomyces odontolyticus		5	0.06	0.13
Acinetobacter spp.	-	436	- 0.22	0.47
Acinetobacter calcoaceticus		. 2. 2		5.47
Acinetobacter calcoaceticus				
Aeromonas hydrophilia	-	5	0,05	0.10
Alcaligenes spp.	<del></del>	86	≤ 0.97	2,04
Alcaligenes faecalis		00	_ 0,37	2,04
Bacteroides app.		997	≥ 0.08	≤ 0.33
Bacteroides fragilis		2,7,	= 0.00	_ 0.33
Bacteroides disiens				
Bacteroides distasonis				
Bacteroides melanin. melani	nocenious			
Bacteroides oralis	noReurens			
Bacteroides ruminocola brev	ri e			
Bacteroides thetaiotaomicro				
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		74	= 0.07	_ 0.07
Campylobacter fetus intesti	nalia			
Citrobacter/Salmonella	nams	370	€ 0.30	0.62
Citrobacter fraundii		370	0.30	0.62
Citrobacter diversus				
(Arizona hinshawii include	4)			
Clostridia spp.	4	292	≤ 0.31	± 1.14
Clostridium septicum	<b>T</b>	© - 2 da	0.51	- 1.14
Clostridium difficile				
Clostridium perfringens				
Clostridium bifermentans				
Clostridium botulinum				
ATABLITATION PARATITUM				

## TABLE 15 (CONT'D)

Bacterial Strain	Gram	.,	Geom. Mean (mg/ml)		
Bacterial Strain	(+/-)	N N	MIC <sub>50</sub>	MIC90	
Chlamidia trachomatis		7	Geom, Mean cidal level =	27.8	
Corynebacterium sp.	+	4	> 32.0		
E. coli	<u>.</u>	1122	< 0.14	> 32.0	
Eikenella corrodens	_	56	0.15	≤ 0.26 0.22	
Enterobacter app.	-	1276	0.34	1.30	
Enterobacter cloacae		12,0	0.34	1.50	
Enterobacter aerogenes					
Enterobacter agglomerans					
55					
Erysipelothrix rhusiopathiae	+	2	€ 0.02	< 0.02	
Eubacterium sp.	+	6	≤ 0.06	2.0	
Flavebacterium spp.	-	23	≤ 2.17	20.0	
Flavobacterium IIb					
Fusobacterium sp.	-	57	0.93	0,50	
Gardnerella vaginalis	-	25	-	0.50	
Haemophilus influenzae		302	0.95	1.82	
Hafnia spp.	-	14	≤ 0.28	$\leq 0.46$	
Hafnia alvei					
Klebsiella spp.	-	952	0.18	0.41	
Klebsiella pneumoniae					
Klebsiella oxytoca					
Listeria monocytogenes	+	36	€ 0.08	بت.0	
Moraxella spp. Moraxella saloensis	-	37	≤0.08	0.37	
	_	••			
Mycobacterium avium intracellula	ite -	22		0.48	
Mycobacterium fortuitum	_	12	2 10	(MIC <sub>70</sub> )	
Neisseria gonorrhoeae	+	387	3.12	12.50	
Neisseria meningitidis	_	266	≤ 0.10	0.30	
Nocardia spp.	+	45	0.05	0.11	
Nocardia asteroides	7	7.7	≥1.15	2, 66	
Pasteurella multocida	_	10	0.50	1.00	
Peptococcus/Petostreptococcus	+	87	≤ 0.02	≤ 0.06	
Peptococcus asaccharolymicus	· ·				
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	$\leq 0.09$	$\leq 1.33$	

	Gran		Geom: Mean (mg/ml)	
Bacterial Strain (+	<del>/-)</del>	N		MIC90
Pseudomonas app. Pseudomonas aeruginosa		2278	1.57	3.54
Pseudomonas acidovorans Pseudomonas putrefaciens Pseudomonas stutzeri Pseudomonas fluorescens				
Pseudomonas cepacia		40	4.5	> 50.0
Pseudomonas maltophilia		118	> 64.0	>128.0
Rhodococcus spp.	. <del>-</del>	11	<b>≤</b> 0.39	0.39
Serratia spp. Serratia marcescens		806	<b>≤</b> 0.76	1.93
Shigella sp.	-	<b>3</b> 3	0.17	0.27
Streptococcus spp. (Grps. A,B,C,G) Streptococcus agalactiae Streptococcus pneumoniae Streptococcus durans Streptococcus pyogenes	+	1293	≤ 0.03	≤ 0.05
Streptococcus bovis				
Viridans streptoccoci	+	51	≤ 0.06	≤ 0.11
Streptococcus faecalis (Grp. D)	+	795	0.93	1.58
Streptococcus faecium	+	30	20.0	78.0
Veillonella spp. Veillonella parvula	-	23	0.05	0.25
Yersinia spp. Yersinia enterocolitica Yersinia pseudotuberculosis	-	234	₹ 0.23	0.44

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. auxeus 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. auxeus 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 synargistic against several bacterial species, such as multiply-resistant P. acruginosa, 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 tarbenicillin 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 Medicine found that imipenem provided effective therapy of lethal Pseudomas 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. 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. seruginosa).

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 antibacteria? 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 impenem 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 impenem 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 (KI) < 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 metalluenzyme 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 C3 substituent, good activity being found with the n-pentyl analog.

This inhibitor, MK-D789, was the predecessor to MK-D791 (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 critation 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. 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 ty 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 <u>per se</u> 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 radicactivity. Negligible quantities of radioactivity were recovered in the feces.

In man, the urinary recovery of intact imipenem was 20% of the cose 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 after 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,  $^{14}\text{C-imipenem}$ , 500 mg, was administered alone and with an equal dose of cilastatin sodium. In another,  $^{14}\text{C-cilastatin}$  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 clearame 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 mi/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 270-240 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 chaffected by coadministration of varying doses of imipenem. Total AUC increased in preportion 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 learance 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 I 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 socium 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. Remai 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 7D 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 citastatin 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 Reral 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 $^2 < GFR \le 99$  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 $^2 \le \text{GFR} \le 30 \text{ ml/min/1.73 m}^2$ ). 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 uninary 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, imipeness 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 \$\leftarrow\$ 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
		l g	20 minutes	< 0.3*
Sputum	5	1 g	30 minutes	2.5
	(10 samples)		60 minutes	2.1
	·		2 hours	0.88
			4 hours	0.96
			<del>-</del>	4.3
			_	2.6
			-	6.0
			_	3.4
			_	4.2
			<del>-</del>	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 Aspir	ate 3	1 g	30 minutes	< 0.3*
mount on other respect		- 6	15 minutes	< 0.3
			30 minutes	< 0.3
			30 minutes	₹ 0.3
Gastric Aspirate	1	500 mg	15 minutes	0.6
oustric hopitate	(2 samples)	Joo mg	1.5 hours	1.7
	(2 SAMPIES)		1,5 110018	1.7
Abdominal Drain	1	500 mg	2 hours	9.8
Peritoneal Fluid	1	1 g	30 minutes	3.9
				(mcg/g)
Bone	6	1 g 6 h	<b>-</b>	0.52
	(9 samples)	1 g 6 h	-	4.05
		1 g 6 h	-	1.5
		l g	10 minutes	0.42
		1 g	1.5 hours	2.5
		1 g	25 minures	5.4
		1 g	20 minutes	3.9
		1 g	~	1.6
		1 g	-	1.3

<sup>\*</sup>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: Uninflamed meninges (22 patients)

Mean Time	Mean Serum Con	centration (mcg/ml)	Mean CSF Concentration (mcg/m				
After Dose	Imipinem	Cilastatin	Imipinem	Cilastatin			
(Hours)			<del></del>				
1.2	28.7	28,2	9.62	< 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: Infla	med 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	Skin Window Fluid
	<del></del>	(intermittent)	(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

<sup>\*</sup>Dr. Tan could not explain the discrepancy between continuous and intermittent during the 0.5 and 1 hour samples.

	Treatment	f in Compassionate Time of Dose	Sample	Imipenem	(mcg/ml)	Cilastin	(mce/=1
Patient	Day	Dose	Time	CSF	Serum	CSF	Serum.
		<b>3</b> / C				<del></del>	
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 р.ж.	0.6	7.5	0.53	7.43
			1.15 p.m.	0.6	3.4	-	2.54
	8	1 g q 8 h	trough	-	0.3	_	0,43
(	iay 1 of	<b>5</b> .	1 hr post dose	2.6	21.7	0.22	32.31
-	lgher dose)		2 hr post dose	4.1	7.0	0.45	
	J		3 hr post dose	-			8.16
			o mr 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	lgq8h	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	
			2 hr post dose	-	-		35.54
			3 hr post dose	1.8	1.9	1.12	0.91
2	7	<b>-</b> ,	trough	_	0.8	_	0.93
		lgq6h	15 min p-dose	_	33,2	_	69.91
			5 h p-dose	3.7	16.9	3.57	21,53
	14	l g q 8 h	trough	_	0,3		0.33
		- 9 3	15 min p-dose	<del>-</del>	31.8	<del>-</del>	0.22
			2 h p-dose	2.6	.5.5	2.26	47.08 25.41
3		lgq6h	trough	_	0,9		
		·	peak	-		-	0.51
			5 hip-dose	3.7	27.8		29.11
			່າ ທ <sub>ູ່ໃ</sub> ນ∹ແບລະ	J. 1	-	4.02	-

#### Clinical Studies (Domestic)

#### Controlled (3 studies)

#### 1. Protocol No. 001

Title: "A Multicenter Study of the Comparative Efficacy, 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 any

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 Richard E. Bryant, M.D. University of Oregon Health Science Center	Number Primaxin 3	of Patients Cefazolin 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		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

	Number of Patients			
Investigators John Mills, M.D. San Francisco General Hospital	Primaxin 7	Cefazolin 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

Total No. of Patients	Primaxin 161	Cefazolin 158
Age Range (yrs)	17 - 83	16 - 84
Sex Male Female	99 62	90 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	<b>3</b> 0	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	Ω	3

	Primaxin	Cefazolin
DOSE (Evaluable Cases)	250 mg q 6 h	lgq6h
	(1 pt. received	2g/day)

# DURATION OF TREATMENT (days) (Evaluable Cases)

5 - 14 93 patients 94 patients 7 14 ll patients 4 patients

## RESULTS

		W-100	MAXIN L RESPONSE				AZOLIN RESPONSE	
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, cell ulitis, carbuncle/furu pyoderma, infected ulc	ncle	CURE 48(71%)	IMP 17(25%)	FAIL 3(4%)	NO. 70	CURE 48(68%)	MP. 20(28%)	FAI 2(3%
EONE/JOINT (Pyogenic arthritis, osteomyelitis)	5	2(40%)	3(60%)		4	2(50%)	2(50%)	
Cheumonia, 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%)		

		PRIMAXIN BACTERIOLOGICAL RESPONSE				BACTERIO	EFAZULIN LOGIAL RESI	PONSE	
INFECTION	NO.	ERAD!	SUPP2	NOT ERAD3	NO.		ERAC <sup>1</sup>	SUPP2	NOT ERA
SKIN AND SKIN		-							
STRUCTURE									
S. aureus (5)*	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%)
<ol><li>epidermiais</li></ol>	7	6(86%)	1(14%)			2	2(100%)		
Bet a-hem-Strep									
(6- <u>o</u> u <u>o</u> A)	20	18(90%)	2(8%)			29	29(100%)		
Alpha—hem—Strep	3	3(100%)				1	1(100%)		
Cher strepto-	10	8 (80%)		2 (20%)		11	11 (100%)		
coccus species									
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%)		
Eik <b>e</b> nella									
corroders	1	1(100%)				1	1(100%)		
E. aerogenes	1	1(100%)				-			
E. cloacae	2	2(100%)				1	1(100%)		
E. coli	6	5(8 <b>3%</b> )		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%)	i (50%)	
P. rettgeri	2	2(100%)				_			•
Providencia									
stuartii	1	1(100%)				-			
P. aeruginosa	2	2(100%)				•			•
S. marcescens	, 1	1(100%)				-			
Vibrio 🔻 🛫 🔏									
parahemolyticum	1	1(100%)				1	1(100%)		
Lactobacillus spp	1	1(100%)				-			
B. fragilis	5	5(100%)				1	1(100%)		
B. melaninogenicus		3(100%)				3	3(100%)		
B. bivius	1	1(100%)				-			
Peptococcus spp	1.	1(100%)				5	5(100%)		
Peptostreptococcus		1 / 2 = 22:							
spp	1	1(100%)				~			
Fusobacterium spp		1(100%)				2	2(100%)		
A. eriksonii	1	1(100%)				-			
Clostridium spo	-					3	3(100%)		
Bacteroides spp						6	6(100%)		

	(continued)		BACTE	PR RIOLOGI	IMAXIN CAL RESPONSE			BACTERIO	EFAZOLIN LOGIAL RESI	PONSE
	INFECTION BONE/JOINT	NO.	ERADI	SUPP2	NOT ERAD3	NO.		ERAD1	SUPP <sup>2</sup>	NCT ER
	S. aureus(R)	2	2(100%)				2	2(1 <b>00%)</b>		
	Beta-hem-Strep	~	2(200.1)				_	£ (100%)		
	(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. aurues (5)	1	1(100%)				-			
	<ol><li>pneumoniae</li></ol>	8	8(100%)				11	11(100%)		
	H. influenzae	4	3(75%)		1(25%)		6	5(83%)		1(179
	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)	í	1(100%)				_			
	Streptococcus spp	ī	1(100%)				-			
	S. epidermidis	3	3(100%)				1	1(100%)		
	S. pneumoniae	4	4(100%)				3	3(100%)		
	Beta-hem-Strep							3 ( <b>10</b> 0)		
	(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	<del>-</del>					1	1(100%)		
	ENDOCARDITIS									
	S. aureus (R)	,	1 (1000)	* * * * * * * * * * * * * * * * * * *						
	o: derena (u'	1	1(100%)				-			

(Continued)		PRIMAXIN BACTERIOLOGICAL RESPONSE			CEFAZOLI BACTERIOLOGIAL	N RESPONSE
INFECTION	NO.	ERAD <sup>1</sup> S	SUPP NOT ERAD3 NO.		ERAD <sup>1</sup> SUPP <sup>2</sup>	NOT ERAD3
UTI (Uncomplicated) E. coli	7	6(86%)	1(14%)	5	5(100%)	
UTI (Complicat∈d) E. coli C. diversus	2	2(100%)	1(100%)	2	2(100%)	

<sup>\*(</sup>S) = Sensitive to renicillin \*\*(R) = Resistant to penicillin

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

Pain at I.V.site	NO. 1(0.6%)	PROBABLY NOT RELATED	PRIMAX: POSSIBLY RELATED 1(0.5%)	PROBABLY RELATED	DEFINITELY RELATED
Vein infection	1(0.6%)	1(0.6%)			· ! !
Phlebitis/thrembo- phlebitis	8(5.0%)	2(1.2%)	5(3.1%)	3 (	
			ŒFAZO	LIN	: :
Pain at I.V. site Vein infection	1(0.6%) 1(0.6%)	1(0.6%)	1(0.6%)		
Phlebitis/thrombo- phlebitis	3(1.9%)	1(0.6%)	2(1.3%)		

<sup>1 =</sup> Eradicated

<sup>2 =</sup> Suppressed

<sup>3 =</sup> Not eradicated

PROBABLY POSSIBLY PROBABLY RELATED PROBABLY RELATED  SYSTEMIC SIDE EFFECTS  PRIMAXIN  Vomiting 2(1.2%) 1(0.6%)  Diarrhea 1(0.6%) 1(0.6%)  Pruritus 1(0.6%) 1(0.6%)	(Continued)					
SYSTEMIC SIDE EFFECTS         PRIMAXIN           Vomiting         2(1.2%)         1(0.6%)           Diarrhea         1(0.6%)         1(0.6%)           Pruritus         1(0.6%)         1(0.6%)		410				
Vomiting 2(1.2%) 1(0.6%) 1(0.6%) Diarrhea 1(0.6%) 1(0.6%) Pruritus 1(0.6%) 1(0.6%)	and the second s	NU.	NUI RELATED	RELATED	RELATED	RELATED
Diarrhea 1(0.6%) 1(0.6%) Pruritus 1(0.6%) 1(0.6%)	SYSTEMIC SIDE EFFECTS			PRIMAX	IN	
Diarrhea $1(0.6\%)$ $1(0.6\%)$ $1(0.6\%)$ $1(0.6\%)$	Vomiting	2(1.2%)		1(0.6%)		1(0.6%)
* ( T C C C C C C C C C C C C C C C C C C	Diarrhea	1(0.6%)	1(0.6%)	•		- (0.0.0)
					1(0.6%)	
	Rash	1(0.6%)	1(0.6%)			
Dizziness $1(0.6\%)$ $1(0.6\%)$						1(0.6%)
Apnea 1(0.6%) 1(0.6%)						
Chest pain/cough $1(0.6\%)$ $1(0.6\%)$			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 $1(0.6\%)$ $1(0.6\%)$	inoracic spine pain	1(0.6%)				1(0.6%)
CEFAZOLIN				CEIFAZO	LIN	
Diarrhea 1(0.6%) 1(0.6%)	Diarrhea	1(0.6%)	1(0.6%)			
Pruritus 1(0.6%)	_ :		1(0.00)			1(0 (%)
Rash $1(0.6\%)$ $1(0.6\%)$				1(0.6%)		1(0.0%)
Fever $1(0.6\%)$ $1(0.6\%)$	Fever					
Asthenia 1(0.6%) 1(0.6%)	Asthenia					
Megacolon 1(0.6%) 1(0.6%)	Megacolon					
Vaginal candidiasis 2(1.3%) 2(1.3%)	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	CIFAZOLIN
Pamoglobin	(D) 7	707
Hematocrit	(D) 5	(p) 7
WBC	(D) 3	(D) 2
Neutrophils	(D) 4	(D) 2
Eosinophils	(I) 2	(1) 4
Monocytes	(I) <b>3</b>	o o
Lymphocytes	(I) Z	
Platelets	(1) 2	(D) 1 (I) 3
Positive Coambs' Test	1	
Giucose	(I) 2	(1) 1
BUN	(I) <b>3</b>	(I) 1
Creatinine	(1) 3	(I) I
Uric acid	Š	(T) 1
SGOT (AST)	(1) 13	$(\bar{1})$ $\bar{\lambda}$
SGPT (ALT)	(1) 14	(1) 3

#### Abnormal Laboratory Tests

TEST	PRIMAXIN	CEFAZOLIN
Billrubin	(I) 3	(I) 2
Alk. phosphatase	(I) 9	(I) 1
LDH	(I) 5	(I) I
Sérum 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) l	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 Frimaxin 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 socium) 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 Alan S. Berkeley, M.D. Cornell Medical Center	Primaxin 18	Moxalactam 16
Steven Berman, M.D. Internal Medicine & Infectious Diseases Honolulu, KI	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

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	Numbe	r of Patients
Investigators Charles A. Kallick, M.D. Cook County Hospital	Primaxin 4	Moxalactam 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 patients and will be evaluated separately.

#### OVERALL SUMMARY OF STUDIES CONDUCTED UNDER PROTOCOL NO. 003

		AND ENTITION OF THE PARTY OF TH	110. 002
Total No. of Patients	Primaxin 218	Moxalact 223	tam
Age Range (yrs)	14 - 91	14 - 96	
Mean Age	43 <b>.</b> 9	48.4	
Sex Male Female	109 109	99 124	
EVALUATION			
EFFICACY			
No. of Cases Evaluable No. of Sites of Infection No. of Cases Unevaluable	Evaluable	Primaxin 145 161 73	Moxalact 148 156 75
REASONS CASES UNEVALUABLE No pre-treatment pathogen Organism resistant to stud Clinical d.agnosis not cle Inadequate bacteriological Treatment course too short Effective concomitant trea	ar cultures	45 1 2 11 11 3	42 4 1 10 11
Treative concomitant trea	-1-/	2	4

2005 (5 )	Primaxin	Moxalactam
DOSE (Evaluable Cases)	500 mg q 6 h	1-2 g q 8 h
	(2 g/day)	(3-6 g/day)

#### DURATION OF TREATMENT (days)

Infection not included in claims

Evaluable Cases)		
4 - 14	117 patients	138 patients
15 - 21	18 patients	7 patients
>21*	10 patients	3 patients

<sup>\*</sup>Four patients were treated for 41 days.

### RESULTS

			IMAXIN L RESPONSE			MOXALA		
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, absceedlulitis, carbuncle/ furuncle, ulcers)	<u>NO.</u> 44 ≥ss	CURE 27(61%)	IMP. 16(36%)	FAIL 1(2%)	NO. 48	CURE 23(48%)	RESPONSE <u>IMP.</u> 17(35%)	<u>FAIL</u> 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, tuboov abscess)	27 warian	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%)						
ENDOCARD I'TIS	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	. <u> </u>				1		1(100%)	

		BACTE	PRIMA) RIOLOGICAL	RESPONSE		MC BACTERIOL	XALACTAM OGIAL RESP	ionse
INFECTION	NO.	ERAD	SUPP	NOT ERAD	NO.	EFAD	SUPP	NOT ERAD
SKIN AND SKIN				<del></del> _			<del></del>	
STRUCTURE								
Bacillus 3pp.	-	1 ( = 584)		. /	1_	1(100%)		
S. aureus(S)	2	1(50%)	1.7.594	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 2	5(100 <b>%</b> )	1/E09/		4	4(100%)		
<pre>Strep. (Group B) Streptocuccus spp.</pre>		1 (50%) 7 ( <b>88%</b> )	1(50%) 1(12%)		2 4	2(100%)		
S. faecalis	7	7 (100%)	1(12%)		2	4(100%)		. Ener's
Acinetobacter spp.	•	/ (IOOA)			2	1(50%)		1,50%)
Citrobacter spp.	2	2(100%)			1	2(100%) I(100%)		
C. freundii	_	2(1000)			1	1(100%)		
E. aerogenes	2	2(100%)			_	1(100%)		
E. cloacae	2	2(100%)			3	3(100%)		
E. coli	5	4(80%)		1(20%)	ล์	6(75%)	1(12.5%)	1(12.59
Klebsiella spp	ĺ	1(100%)		2 ( 20/2)	ì	1(100%)	1(12.5%)	*(12.55
K. oxytoca	ī	1(100%)			5	5(100%)		
K. préumoniae	3	3(100%)			2	2(100%)		
M. morganii	2	2(100%)			ī	1(100%)		
F. mirabilis	5	1 (20%)	1 (20%)	3(60%)	12	11 (92%)		1(8%)
P. vulgaris	2	2(10CX)	,	, , , , , , ,	2	1 (50%)		1(50%)
P. stuartii	2	2(100%)			-			
Pseudomonas spp	•				1	1(100%)		
P. aeruginosa	11	6(25%)	1(%)	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%)	
Zubacterium spp.	-				1	1(100%)		
Gaffkya anaerobia	-				1	1(100%)		
Peptococcus spp.	2	2(100°)			4	4(100%)		
Bacteroides spp.	7	7(10( )			4	4(100%)		
B. fragilis	1	1(100%)			1	1(100%)		
F. russii	1	1(1.0%)			Ţ	1(100%)		
V. parvula	1	1(100%)			1	1(100%)		
BONE/JOINT								
S. aureus(R)	2	(1(A)X)			1	1(100%)		
S. faecalis	2	2 009			•	= .= ,		
E. coli	-				1	1(100%)		
P. mirabilis	2	2(:3%)			1	(100%)		
P. aeruginosa	1		1(100%)		-			
S. marcescens	1			1(160%)	-			
Bacteroides spp.	1	1(1(0%)			_			
B. fragilis	1	1(700%)			-			

(Continued)								
			PRIMAX			MC	XALACTAM	
			RIOLOGICAL			BACTERIOL	OGIAL RES	PONSE
INFECTION	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NCT ERAD
LOWER RESPIRATORY								
S. aureus (5)	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 8)	_				1	1(160%)		
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	ĩ	1(100%)						
Citrotacter spp	1	1(100%)			-			
E. aerogenes	ī			1(100%)				
E. cloacae	1	1(100%)		-(-0/	2	2(100%)		
E. coli	1	1(100%)			ï	1(100%)		
H. influenzae	6	5(83%)	1(17%)		2	2(100%)		
H. parainfluenzae	ī	1(100%)	4(4)4)		ī	1(100%)		
K. oxytoca	ī	1(100%)			2	2(100%)		
K. pneumoniae	2	2(100%)			4	3(75%)		1(25%)
M. morganii	_	11,400,47			2	2(100%)		1/2/8/
P. mirabilis	1			1(100%)	4	2(50%)	1(25%)	1(25%)
Pseudomonas spp	ī	1(100%)		I ( AUGA,	7	2(30%)	1(2)4)	1 (42/6)
P. aeruginosa	3	3(100%)			5	1(20%)	2(40%)	2(40%)
S. marcescens	_	3(1004)			2	2(100%)	2.(40%)	2(40%)
B. catarrhalis	_				1	1(100%)		
Pentostreptococcus					1	1(100%)		
spo.	1	1(100%)						
Bacteroides spp.	3	3(100%)						
packerorues app.	_	2(100%)						
GYNECOLOGIC								
Corynebacterium spp						1710063		
S. aureus (R)		7/756\	1 ( 05%)		1	1(100%)		
S. intermedius	4	3(75%)	1(25%)		4	3(75%)		1(25%)
Strep. (Group A)	-				1	1(100%)		
	- 7	7(100*)			1	1(100%)		•
Strep. (Group B)	2	7(100%)			7	7(100%)		
S. viridans	2	2(100%)			2	2(100%)		
Strep	^	0/100*\						
(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.	-	1/1000			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%)		

•								
GYNEODLOGIC	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Bifidobacterium sp	p 1	1(100%)			-			
Propionibacterium								
spp	1	1(100%)			~			
Peptococcus app	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 parvul	e 1	1(100%)			6	6(100%)		
		• ,				•		
(-)* = penicil;	linası	e negative						
(+)** = penici:		-						
( )								
5 EPTICEMIA								
S. aureus (S)	~				1	1(100%)		
S. aureus (R)					ī	1(100%)		
5. pneumonise	1	1(100%)			ī	1(100%)		
Strep. (Group A)	ī	1(100%)			ī	1(100%)		
S. viridar	-	2(2000)			1	1(100%)		
e. sanguis	1	1(100)			-	2(200%)		
S. faccalis	î	1(100%)			_			
Acinetobacter spp	î	1(100%)			_			
I. cloacae	i	1(100%)			_			
E. coli	6	6(100%)			2	2(100%)		
	1	•			3	•		
K. pneumoniae	1	1(100%)				3(100%)		
P. mirabilia		1(100%)			1	1(100%)		
P. stuartii	1	1(100%)						
P. aeruginosa	1	1(100%)		1/504)	_			
S. marcescens	2	1(50%)		1(50%)	-			
Y. enterocolitica	1	1(100%)		144000	-			
Clostridium spp.	1			1(100%)				
Peptostreptococcus		24400						
app	2	2(100%)			~			
Bacteroides app	2	2(100%)			~			
Fusobacterium app	2	2(100%)			-			
B. fragilis	-				1			1(1007
OTITIS MEDIA								
S. pasumoniae	1	1(100%)			-			

INFECTION	NO.	BACTE ERAD	PRIMAX RIOLOGICAL SUPP		NO.	BACTERIOLO	ALACTAM IGIAL RESPONSE SUPP NO
OTITIS MEDIA	110.	LIND	301	HUI EFAD	NU.	LIVAL	SUPP NC
S. pneumoniae	1	1(100%)			-		
ENDOCARDITIS							
S. sanguis	1	1(100%)			-		
INFECTED VASCULAR							
S. aureus (R)	-				1	1(100%)	
UNCOMPLICATED UTI							
E. coli	3	3(100%)			8	7(67.5%)	1 ( 4 ()
E, cloacae	-				$\bar{1}$	1(100%)	
P. mirabilis	1	1(100%)			2	2(100%)	
S. marcescens	~				ī	1(100%)	
P. aeruginosa	-				ī	1(100%)	
Klebsiella spp.	_				ī	1(100%)	
K. pneumoniae	2	2(100%)			1	1(100%)	
COMPLICATED UTI							
E. coli	2	1(50%)		1(50%)	3	3(100%)	
P. mirabilis	_	2(504)		1(204)	í	1(100%)	
E. aerogenes	1	1(100%)			-	1(1004)	
K. pneumoniae	_	2(200,0)			1	1(100%)	
P. aeruginosa	1			1(100%)	ì	1(100%)	17
S. maruescens	î			1(100%)	-		1(
INTRA-ABDOMINAL							
S. aureus(R)	_				1		1(
S. epidermidis	1	1(100%)			ī		1(
S. intermedius	4	4(100%)			ī	1(100%)	-1
S. mitis	ĩ	1(100%)			2	2(100%)	
S. morbillorum	2	2(100%)				2(1004)	
Strep. (Group A)	-	2(100%)			2	2/100%	
Strep. (Group B)	_				1	2(100%)	
S. viridans	3	2(67%)		1(33%)	_	1(100%)	
S. faecalis		2(0/%)		1(33%)	=		
	<del>-</del>	1 (1 00%)			3	(33%)	2(
S. faecium	1	1(100%)			1	1(100%)	
S. bovis	1	1(100%)			-		
S. sanguis	1	1(100%)			-		
5. salivarus	-				-		
A. hydrophilia	~				1	1(100%)	
E. aerngenes	1	1(100%)			2	2(100%)	
E. cloace	-				1	1(100%)	
E. coli	14	11 (79%)		3(21%)	12	9(75%)	3(:

,,,,				PRIMAXIN				MOXALAC	TAM
		8,		OGICAL RESPONSE				BACTERIOLOGIAL	RESPONSE
INTRAABDOMINAL		ERAD	SUPP	NOT ERAD	NO.		ERAD	SUPP	HOT ERAD
Klebsiella spp.	1	1(10	O <b>X</b> )			1		1(100%)	
K. pheumoniae	4	4(10	<b>0%</b> )			4		4(100%)	
P. multocida	1	1(10	O%)			_			
M. morganii	1807					2		2(190%)	
P. mirabilis	1	1(10				3		2(67%)	1(33%)
P. vulgaris	Ť.	1(10							
P. aeruginosa	2	2(10	<b>0%</b> )			4		2(50%)	2(50%)
Bifidobacterium									
spp.	-					1		1(100%)	•
Clostridium spp	9	9(10	<b>C%</b> )						
C. pertringens	2	2(10	0%)			3		3(100%)	
Eubacterium spp	2	2(10	C%()			3		2(67%)	1(33%)
Peptococcus spp	1	1 ( ).0	O%)						
Reptostrept # :cous									
spp	4	4(10	O%)			3		3(100%)	
Bacteroides spp.	5	5(10	C%)			7		7(100%)	
B. fragilis	12	12(10	O%)			13		12(92%)	I(8%)
Fusobacterium spp.	5	5(30				4		4(100%)	
V. parvula	1	1(10	OX)						

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	Moxilactam
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

<del></del>	~		PRIMAX	IN	
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Diairhea	6(2.8%)	2(0.9%)	3(1.4%)	I(0.5%)	
Nausea	1(0.5%)		1(0.5%)		
Vamiting	6(2.8%)	2(0.9%)	3(1.4%)	1(0.5%)	
Pruritus	1(0.5%)	1(0.5%)			

SYSTEMIC	SIDE	EFFECTS

		PR IMAXIN							
		PROBABLY	POSS IBLY	PROBABLY	DEFINITELY				
	NO.	NOT RELATED	RELATED	RELATED	RELATED				
Rash	3(1.4x)		1(0.52)	1(0.5%)	1(0.5%)				
Urticaria	1(0.5%)			1(0,5%)					
Faver	2(1.0%)	1(0.57)	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(0.52)			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								
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY					
	NO.	NOT RELATED	RELATED	RELATED	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%)							
Serva Sickness	1(0,5%)				1(0.5%)					
Epistexis	1(0,5%)		1(0,5%)							
Hemoperitoneum	1(0.57)			1(0.5%)						
GI hemorrhage	1(0,5%)			1(0.5%)						
Dysuria	1(0,5%)	1(0.5%)								
Urinary frequency	1(0.5Z)	1(0,5%)								
Abdominal pain	1(0.5Z)	1(0.5%)								
Respiratory										
insufficiency	1(0.5%)	1(0.5%)								
Headache	1(0.5%)	1(0,5%)								
Convulsive disorder	1(0.52)	1(0,5%)								
Alcohol intolerance	1(0.5%)		1(0.5%)							
Somnolence	1(0.5 <b>Z</b> )		1(0.5%)							
Vaginal discharge	1(0.5%)			1(0,5%)						
Myocardial infarction	1(0.5%)	1(0.5%)								

## LOCAL SIDE EFFECTS

			PRIMAX:	IN	
Shlebitis/	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Thromboohlebitis Infused vein pain Infused vein	12(5.5% 1(0.5%		12(5.5%)	1(0.5%)	
infection	1(0.5%	)	1(0.5%)	•	
			MOXALAC	CTAM	
I.V. site	NO.	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
hemorrhage Infused vein pain Phlebitis/	1(0.5%)	1(0.5%)		1(0.5%)	
Theombophic bitis	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

TESI'	FRIMAXIN	MOXAL ACTAM	
Hemoglobin	(D) 1	(D) 8	
Hematocrit	(D) 2	(D) 6	
WBC	(D) <b>3</b>	(D) 4	
Neut.rophils	(D) 1	(D) 1	•
Eosinophils	(I)17	(1)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	(1)14	
Bilirubin	(1) 2	(I) 1	
Alk. phosphatase	(I) 6	- (1) 6	
Serum sodium		(D) 1	
Serum potassium	0	(D) 1	4 10 to 10 t
Serum chloride	(I) 1	(D) 1	
Urine protein	(I) 3	(1) 2	
Urine WECs	(I) 4	(I) 2	
Urine RBCs	(I) 3	(I) 3	
Urine casts	(I) 2	(I) 1	
f. difficile			
Toxin assa (stool)	2	0	

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

TOTAL NO. OF PATIENTS	PRIMAXIN 21
Age Range (years)	21 - 78
Sex Male Female	13 8
EVALUATION	
EFFICACY	
No. of Cases Evaluable No. of Sites of Infection	19
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%)	<del>6(6</del> 7%)	$\overline{1(11\%)}$		
BONE/JOINT	1		1(100%)	_ ,,		
LOWER RESPIRATORY	2	1(50%)	•	1(50%)		
UTI(Uncomplicated)	1		1(100%)	_ ,,,		
INTRA-ABDOMINAL	6		5(83%)	J (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%)

		BACTERIOLÓGIC RESPONSE	
ORGANISM	NO.	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 3	1(100%)	
Bacteroides spp	3	3(100%)	
B. fragilis	1	1(100%)	
<b></b>			
BONE/JOINT			
S. faecalis	1	1(100%)	
P. mirabilis	1		1(100%)
P. stuartii	1		1(100%)
P. aeruginosa	1		1(100%)
A OWED DECEMBER OF			
LOWER RESPIRATORY	•	. ( )	
K. pneumoniae	1 1	1(100%)	
E. hafniae			1(100%)
P. aeruginosa	1		1(100%)
HTT (Ibo emplished and			
UTI (Uncomplicated) E. coli			1 ( 1 0 0 0 )
E. COII	1		1(100%)
INTRA-ABDOMINAL			
5. faecalis	1	1/100%)	
E. coli	1	1(100%)	1 / 770 \
P. mirabilis	3 1	2(67%)	1(33%)
K. pneumoniae	2	1(50%)	1(100%)
P. aeruginosa	1	• •	1(50%)
. • derdâtinas	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

Commence of the second of the	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

		DEFINITELY
	NJ.	RELATED
Candidiasis	T(4.8%)	<u> </u>
Diarrhea*	1(4.8%)	1

\*This patient's diarrhea was associated with a positive  $\underline{\text{C.}}$  difficile toxin assay.

Two patients who had non urug-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 cied 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. phrsphatase	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.

7. 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 wall 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

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.

concentration assays).

# Overall Summary of Studies Conducted Under Protocol No. 11

	Primaxin	Clindamycin/Ge	ntamicin		
Total No. of Patients	13	13	1-10-10-10-10-10-10-10-10-10-10-10-10-10		
Age Range (yrs)	24 - 95	26 - 7	3		
Mean Age	50.5	49.0			
Sex Male Female	9 4	10			
EVALUATION					
EFF ICACY					
No. of Cases Evaluable No. of Sites of Infection Evaluable No. of Cases Unevaluable  Primaxin 8 5 No. of Sites of Infection Evaluable 8 5 8					
REASONS CASES UNEVALUATION OF PRE-treatment paths Treatment course too organism resistant to Inadequate bacteriolog Concomitant effective	ogen short study drug jical cultures	3 1 - 1	4 2 1 -		
DOSE	Primaxin 500 mg q 6 h	Clindamycin 300-600 mg q 6 h	<u>Gentamicin</u> 1.0 <del>-1.7 mg/kg</del> q 8 h		
DURATION OF TREATMENT (days) 5 - 14	8 patients	5 patients	5 patients		

# RESULTS

INFECTION SKIN & SKIN STRUCTURE (Wound infection, abscess)	NO:		IMAXIN RESPONSE IMP.	FAIL	<u>NO.</u>	CLINDAMYCI CLINICAL CURE	N/GENTAMIC RESPONSE IMP.	FA.
LOWER RESPIRATORY (Pneumonia, bronchopneumonia)	2	1(50%)	1(50%)		2		1(50%)	1(5

10		•		٠.
(Con	L.	LNI	Jea	)

(Continued)							
			MIXAMI		1	CLINDAMYCIN	/GENTAMICIN
			RESPONSE		•	CLINICAL	RESPONSE
INFECTION	<u>NO.</u>	CURE	IMP.	FAIL	NO.	CURE	IMP. FF
UTI (Complicated)	1			1(100%)		<del></del>	<u> </u>
(Pyelonephritis)							
<del>-</del>							
INTRA-ABDOMINAL	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)
(Peritonitis, abscess,						• • • • •	_(,,
cholangitis)							
		PR:	IMAXIN		(	CLINDAMYCIN	/GENTAMICIN
		BACTERI OLO	OGJC RESPO	NSË		BACTERIOLOG	
ORGANISM	NO.	ERAD	NOT ERA	5	NO.	ERAD	
SKIN & SKIN STRUCTURE		**************************************		-			HO! LIV
5. viridans group	1	1(100%)					
Streptococcus spp	1	1(100%)					
S. faecalis	1	1(100%)					
E. coli	1	1(100%)					
Peptococcus spp	ī	1(100%)					
Bacteroides spr	2	2(100%)					
addicated opp	-	2(100%)					
LOWER RESPIRATORY							
H. influenzae	1		1(100%)				
E. coli	1	1(100%)	1(100%)		-,	1 / 1 000	
Enterobacter spp	_	1(100%)			1	1(100%	
P. aeruginosa	_				1	1(100%	
r. acraginosa	-				1		1(100%)
INTRA-ABDOMINAL							
S. aureus(S)	_					1/10/00/	`
Strep (Group A)	1	1(100%)			1	1(100%	,
Strep (Group D	*	1(100%)			~		
enterococci)	1	1(100%)					
S. viridans group	1	1(100%)			_		
Beta-hemolytic Strep	1	1(100%)			-		
E. coli	2	2(100%)			-	1 ( 1 0 0 0 )	
E. cloacae	1				1	1(100%	)
	_	1(100%)			-		
K. pneumoniae	1	1(100%)			-		
P. aeruginosa		1(100%)					
Peptococcus spp.	1	1(100%)			-	-	\ <u></u>
Peptostreptococcus spp	1	1(100%)			-		
B. fragilis	<del>-</del>				2	2(100%	
Bacteroides spp.	4	4(100%)			1	1(100%)	)
Fusobacterium spp.	2	2(100%)			-		
litt (Compliants)							
UTI (Complicated)	,		1/1000				
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 clirdamycin/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:
-Eradination of the etiologic pathogen(s)

Unfavorable bacteriologic outcome:

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

<u>Investigators</u>: 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 4-14	No. Patients
4-14	366
15-29	98
30-49	41
61	1

# RESULT.

and distribution — the		CLINI	CAL RESPONSE	
INFECTION GKIN & SKIN STRUCTURE	NO. 129	CURE 67(51.9%)	TMPROVE 56(43.4%)	$\frac{\text{FAIL}}{6(4.7\%)}$
(Wound infection, abscess, callulitis, carbuncle/furunc decubitus and other skin ulc	le ers)			
BONE/JOINT (Osteomyslitis, pyogenic	53	27(50.9%)	21(39.6%)	5(9.4%)
arthritis)	100	45(41.7%)	48(44.4%)	15(13.9%)
LOWER RESPIRATORY (Pneumonia, empyema, lung abscess, bronchitis)	108	4)(*1,/*/		·
UPPER RESPIRATORY (Peritonsillar abscess, tracheitis)	2		1(50%)	1(50%)
OTITIS	3	1(33.3%)	1(33.3%)	1(33.3%)
GYNEODLOGIC	49	36(73.5%)	10(20.4%)	3(6.1%)
(PID, endometritis, tubo-ovarian abscess, pelvic abscess)				-:: F#\
1NTRA-ABDOMINAL (Peritonitis, abscess, liver abscess, cholangitis cholecystitis)	,	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%)	15(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%)		

	BACTERI	OLOGIC RESPONSE
ORGANISM	NO.	ERADICATE
SKIN & SKIN STRUCTURE	T REAL PROPERTY.	H 4
Corynebacterium spp.	4	4(100%)
S. aureus(S)	9	8(88.9%)
S. aureus <sup>(R)</sup>	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%)
Acine cobacter spp.	1	1(100%)
Acinetabacter calcoaceticus	Δ	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 marcescers	5	4(80%)
Eikenella spp.	1	1(190%)
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%)
Veillopella parmila	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%)

(courtuded)	D.A.O.774*** D.#	
	BACIERI	OLOGIC RESPONSE
ORGANISM	NG.	EPADICATED
S. facecalis	2	2(100%)
Aceinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	1	1(100%)
Enterobacter aerogenes	3	3(10C%)
Enterobacter cloacae	6	6(100%)
Escherichia coli	2	1(50%)
Morganella morganii	2	2(100%)
Proteus species	3 6 2 2 1 2 3	Q
Proteus vulgaris	2	1(50%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	21	19 (90, 5%)
Serratia marcescens	1	1(100%)
Gaffkya anaerobia	ī	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%)
1 dooddccciidii opp.	1	I(IUUA)
LOWER RESPIRATORY		
5. aureus (5)	2	0(1008)
S. aureus(R)	6	2(100%)
S. epidermidis		6(100%)
	1	0
S. pneumoniae	20	20(100%)
Group A Streptococci	1	1(100%)
Group D Streptococci	,	0 ( 7 - 1 )
(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(1.00%)
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%)
Sarratia marcescens	5	3(60%)
Branhamella catarrhalis	1	1(100%)
Eikenella corrodens	ī	1(100%)
	-	4(100.0)

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1		ነቸ ጎ	n	æd)	
•				JC U /	

		COLOGIC RESPONSE
DRGANISM	NO.	ERADICATED
UPFER RESPIRATORY		
S. aureus (R)	1	٥
Streptococcus spp.	1	1(100%)
Enterobacter aprogenes	1	1(100%)
Klebsiella pneumoniae	1	1(100%)
Pentostreptoconcus 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-hamolytic Streptococci	3	3(100%)
Group B Stieptococci	13	13(100%)
Croup D Streptococci		(
(Enterococci)	13	11(84.6%)
S. faecalis	3	3(100%)
Other Streptodoccus species	6	6(100%)
Adinetobacter dalabaceticus	1	1(100%)
Citrobacter diversus	2	2(100%)
Citrobacter freundii	····· 1	1(100%)
Enterobacter merogenes	2	2(100%)
Escherichia coli	16	15(93.6%)
Klebsiella pneumoniae	5	5(100%)
Morganella morganii	1	1(100%)
Proteus mirabilis	3 1	2(66.7%)
Pseudomonas aeruginosa		0
Biridobacterium spp	2	2(100%)
Clostridium perfringens	1	1(100%)
fkya anaerobia	1	1(100%)
tococcus spp	·· · - 1. · · · · · · · · · · · · · · · · · ·	1(100%)
Persitreptococcus spp	6	6(100%)
Bacteroides spp	22	20(90.9%)
Bacteroides fragilis	7	6(85.7%)
Gardnerella vaginalis	3	3(100%)
Veilionella parvula	<u> </u>	1(100%)
inger og en er		

INTRA-ABDOMINAL		
S. aureus(R)	1	1(100%)
Group D Streptococci		
(Enterococci)	7	5(71.4%)
5. faecalis	1	0
Streptococcus viridans group	6	6(100%)
Other Streptogoccus species	8	8(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter species	2	2(100%)

		OLOGIC KESPONSE
ORGANISM	NO.	ERADICATED
Citrobacter freundii	T	1(100%)
Enterobacter aerogenes	2 3	2(100%)
Enterobacter cloacae	3	1(33.3%)
Escherichia coli	25	20 (80%)
Klebsiella oxytoca	3	3(100%)
Klebsiella pneumoniae	6	6(±00%)
Morganella morganii	6 2 <b>3</b> 5	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(190%)
Propionibacterium acnes	3	3(100%)
Peptococcus spp	2	2(100%)
Peptostreptococcus spp	3 2 2	1(50%)
Bacteroides spo	4	4(100%)
Bacteroides fragilis	19	18(94.7%)
Fusobacterium spp	2	2(100%)
	_	= (1.55.0)
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%)
	_	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(100%)
Providencia stuartii	3	1(33.3%)
Proteus rettgeri	3 3 3	2(66.7%)
Enterobacter cloacae	7	6(85,7%)
Klebsiella pneumoriae	_ <u></u> 5	5(100%)
Klebsiella oxytoca	ĺ	1(100%)
Pseudomonas aeruginosa	35	31(88.6%)
Serratia species	1	1(100%)
Serratia marcescens		1(100%)
Bifidobacterium spp	ī	1(100%)
Peptococcus spp	1	1(100%)
, op cooper opp		T ( TO()/0 )

(Continued)	DACTEDIO	LOGIC RESPONSE
	NO.	FRADICATED
ORGANISM	NU.	- LADICA ICD
BACTERIAL SEPTICEMIA	2	2(100%)
5. aureus (5)	2 9	8(88.9%)
S. aureus(R)	<i>)</i>	
S. epidermidis	1 7	1(100%)
S. pneumoniae	,	7(100%)
Group D Streptococci	•	0(100%)
(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 3 1 1	1(100%)
Klebsiella pheumoniae	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(190%)
Flavobacterium spp	1	1(100%)
Salmonella (Group D)	1	1(100%)
N. gonorrhoeae	ī	1(100%)
Corynebacterium acnes	ī	1(100%)
Clostridium bifermentans	ī	1(100%)
Bacteroides fragilis	3	2(66.7%)
Bacteroides Tragins		2(0007.07
BACTEREMIA		
S. aureus(S)	1	1(100%)
S. aureus (R)	2	2(100%)
S. epidermidis	1	1(100%)
S. pneumoniae	3.	1(100%)
Group D Streptococci		
(Enterococci)	1	1(100%)
H. influenzae	1	1(190%)
Escherichia coli	7	7(100%)
Enterobacter cloacae	1 7 3 1	3(100%)
Citrobacter diversus	1	1(100%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	4	4(100%)
Bacteroides bivius	1	1(100%)
Dag teroraco birrio		
ENDOCARDITIS	1	1/100%)
S. aureus(S)		1(100%) 5(100%)
S. aureus (R)	5	
Streptococcus spp	1	1(100%)
S. pneumoniae	1	1(100%)
Streptococcus viridans group	1	1(100%)
BRAIN ABSÇ <u>EŞS</u>		
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.

### SAL TY

Total No. of Patients: 717

No. of Patients with Systemic Side Effects: 81(11.3%) No. of Patients with Local Side Effects: 13(2.5%)

mer or construct while branches arrects.

SYSTEMIC SIDE EFFECTS					
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Nausea	$16(\overline{2.2\%})$	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 colitie	s* 3(0.4%)			3(0.4%)	
Heartburn	1(0.1%)		1(0,1%)		
Pruritus	2(0.3%)		1(0,1%)	1(0.1%)	
Pacial edema	1(0.1%)		• ,	1(0.17)	
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%)	
<b>Palpitations</b>	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.%)			

SYSTEM	IC	SIDE	EFFECTS

11010	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
NO.	NOT RELATED	RELATED	RELATED	RELATED
1(0.1%)	1(0.1%)	tenii Taranollia iliy ayon ne		
1(0.1%)		1(0.1%)		
1(0.1%)		1(0.1%)		
CTS 50- 16(2.2%)		2(0,3%)	12(1,7%)	2(0.3%)
	NO. 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%)  CTS 00- 16(2.2%)	PROBABLY NO. NOT RELATED 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%)  CTS	PROBABLY FOSSIBLY  NO. NOT RELATED  1(0.1%)  1(0.1%)  1(0.1%)  1(0.1%)  1(0.1%)  CTS  DO-  16(2.2%)  PROBABLY FOSSIBLY  RELATED  1(0.1%)  1(0.1%)  2(0.3%)	PROBABLY FOSSIBLY PROBABLY  NO. NOT RELATED RELATED  1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%)  CTS  16(2.2%)  PROBABLY PROBABLY  RELATED  1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%) 1(0.1%)

<sup>\*</sup>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-clouic 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 wass 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. Trestment 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 '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 thours during which time neurologic evaluation demonstrated a 24 hours during which time neurologic evaluation demonstrated a normal CT scan of the head, EEG, and LP (except for an increased CSF 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	(D) 4
Hemoglobin	(D) 4
Hematocrit	(D)11
MBC	(D) 3
Neutrophils	$-\frac{1}{(1)}\frac{1}{2}$
Monocytes	(1)27
Eosinophils	(1)12
Platelets	(p) 6
Positive Coombs' test Prothrombin time BUN Creatinine Bilirubin SGOT (AST)	16 (1) 2 (1) 2 (1) 1 (1) 3 (1) 26

## Abnormal Laboratory Tests

Test	
SGIT (ALT)	(1)25
Alkaline phosphatase	(I)23
Serum chloride	(I) 3
Urine protein	(I) l
WBCs in urine	(1) 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 10) 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 84/66 (97%) bacterial septicemia, and in 9/9 (100%) patients with endocarditis.

As shown in the table depicting the bacteriologic response to Primaxin treatment, the exadication 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 mycclonus occurred in 1.5% of the patients.

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

The most cummonly 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 stude 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 SKIN & SKIN STRUCTURE (cellulitis)	NO.	CLINICAL RESPON	NSE IMPROVE	FAIL
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%)	

		BACTERIOLOGIC RES	Ponse
ORGANISM	NO.	ERADICATED	NOT ERADICATED
SKIN & SKIN STRUCTURE		and the same a state of the same and the same as the s	800.
Corynebacterium spp S. aureus(R)	1	1(100%)	
S. acreus (R)	1 1	1(100%)	
E. coii	1	1(100%)	
BONE /JOINT			
S. aureus(R)	2	2(100%)	
Streptococcus spp	1	1(100%)	
E. coli	2	2(100%)	
M. morganii	2 1 2 1 2	1(100%)	
P. mirabilis		1(50%)	1(50%)
P. aeruginosa	4	3(75%)	1(25%)
남. fragilis	1	1(106%)	
B. vulgatus	1	1(100%)	
LOWER RESPIRATORY			
E. coli	1	1(100%)	
P. mirabilis	1		1(100%)
P. aeruginosa	1 2 1	1(50%)	1*(50%)
S. marcescens	1	1(100%)	
UTI (Uncomplicated)			
E. coli	1	1(100%)	
UTI (Complicated)			
Strep. (Group B)	2	2(3.00%)	
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 EFF	EUIS				
	<del></del>	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Fever	1(5%)	1(5%)			<del></del>
Abdominal pain	1(5%)	1(5%)			
Diarrhea	1(5%)		1(5%)		

LOCAL	<u>NO.</u>	NOT RELATED	RELATED	PROBABLY RELATED	DEFINITELY RELATED
Phlebit is	1(5%)		1(5%)		
Abnormal Labor Hemoglobin	atory Tests	(D)1			

Abnormal Laboratory Tests	
Hemoglobin	(0)1
Hematocrit	(D)1
WBC	(D)1
Eosinophils	(I)1
Platelets	(D) I
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 imipenen 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.

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 to sted 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 LOWER RESPIRATORY INTRA-ABDOMINAL BACTERIAL SEPTICEMIA SKIN & SKIN STRUCTURE	NO. 8 2 1 2		ESPONSE IMPROVE 5(62.5%) 2(100%) 1(100%) 1(50%)	FAIL 2(25.0%) 1(50%)
ORGANISM LOWER RESPIRATORY Acinetobacter calcoacelicus P. aeruginosa P. maltophilia S. marcescens	NO. 3 6 1	BACTERIOLOGIC ERADICATED 2(66.7%)	C RESPONS	E NOT ERADICATED 1(35.3%) 6(100%) 1(100%) 1(100%)
INTRA-ABDOMINAL P. aeruginosa P. fluorescens	2 1	2(100%)		1(100%)
BACTERIAL SEPTICEMIA P. aeruginosa	1	1(100%)		
SKIN & SKIN STRUCTURE Strep (Group D enterococci) Enterobacter cloacae P. aeruginosa	2 1 2	1(50%)		1(50%) 1(100%) 2(100%)
SAFETY  NO. OF PATIENTS: 40  NO. OF PATIENTS WITH LUCAL S	STOF FFFF	"CTS> - 2(5¥)		

NO. OF PATIENTS WITH LOCAL SIDE EFFECTS: 2(5%)

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS: 8(20%)

#### SIDE REFERIS

SIDE LITEUIS					
		PROBABLY	POSSIBLY	PROBABLY	DOFINITELY
	NO	NUI RELATED	RELATED	RELATED	RELATED
LOCAL	<del>(1</del>				
Erythema I.V.					
site	1(2.5%)	1(2.5%)			
Phlebitis/thro	mbo-				
phlebitis	1(2.5%)			1(2.5%)	

2 OF 3 NDA: 50-587 SPONSOR: MERCK SHARP & DOHME TRADE: PRIMAXIN GENERIC: IMIPENEM

disorder

SIDE EFFECTS				•	
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
SYSTEMIC			***********		14271720
Chills	1(2.5%)	1(2.5%)			The second of th
Nausea	2(5%)	1(2.5%)	1(2.5%)		
Dysuria	1(2.5%)	1(2.5%)	_ ,,		
Nystagmus	1(2.5%)	1(2.5%)	The transmission of the tr	THE STATE OF STREET STATE STATE OF STREET	Section 1995 Albert St. Land St. Company and Company Section 1995 Annual Section 1995
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	- (= (=, )	2,241-0,			

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

1(2.5%)

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.

1(2.5%)

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

2(5%)

# 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 take 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, Cacn, 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 Alberts, Edmonton, Alberta, Canada.

# Summary of Studies Conducted Under Protocol No. 514

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

#### EVALUATION

EFFICACY		
NO. OF 04555 PM. 1451 P	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
COSE (Evaluable Cases)	250 mg q 6 h	2g q 6 h
DURATION OF TREATMENT (Days)	6-15	5-14
(Evaluable Cases)		

#### RESULTS

	***************************************	CLINICAL R			CEPHAL	TESPONSE
INFECTION SKIN & SKIN STRUCTURE	NO.		IMP. FAIL	NO.	CURE	IW.
(Abscess)	-					
LOWER RESPIRATORY	7	5(71X)	2(29%)	· · · · • 5	4(80%)	1(20%)
(Bronchitis, pneumonia, empyema)	)					
SEPTICEMIA	3	3(100 <del>K)</del>			3(75%)	1(25%)
UTI (UN:OMP)	4	4(100%)		1	1(100%)	
(cystitis, pyeinnephritis)						
UTI (Complicated)		1(100%)			1(100K)	
(pyeloriephritis)						

		ndu				C MIA	LOTHER	
		MACTER TO LOC	TC RESPONSE	:		DACTER TOLO	GIC HES PONS	<b>1</b>
ORGANISM	10.	ERAD	SUPP	NOT ERAD	10.	TIME	SUPP	E TOR
SKIN & SKIN STRUCTURE	_				-		-	
S. aureus(S)*	1	1(100%)			-			
LOWER RESPIRATORY								
K. phuemoniae	-	· · · · · · · · · · · · · · · · · · ·			1	1(100%)		
P, multocide	1	1(100%)			-	- •		
K. oseence	1	1(100%)			_			
T. colf		1(1007)	and the second	and the state of t				
S. pneumonime	2	2(100%)			1	1(100%)	A STATE OF THE PARTY OF THE PAR	
P. seruginosa	1	1(100%)			_			
H. influensee	2	2(100%)			3	3(100%)		
SEPTICENIA								
E. coli	1	1(100%)			2	2(1001)		
B. fragilis	1	1(100%)						
S. pneumoniae		1(100%)			1	1(100%)		
P. mirabilis	-				1	1(1002)		
UTI (Uncomp.)								
E. coli	4	4(100Z)			1	1(100%)		
UTI (Complicated)								
K. pneumonime	1	1(190%)			_			
E. coli					1	1(100%)		

In the Primarin treated group, 1 patient with an empyema developed a reinfection with a revistant P. seruginous strain. In the Cephalothin treated group, 1 patient with urinary tract infection developed a reinfection.

SAFETI	PRIMARIN	CEPHALOTHIN
TOTAL MO. OF PATIENTS	47	38
NO. OF PATIENTS WITH LOCAL SIDE REFECTS	2(4%)	4(10.5%)
NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS		
SISTEMIC STAR PALECTS	1(44)	1(32)

#### TACAL SIDE PERCTS

\*(\$) = Sensitive

<u> </u>	PRIMAXIN
	PROBABLY
<u> </u>	RELATED
Pain on infusion 1(2.13)	<b>14 1</b> 4
Phlebitis/thrombo-	4,4,46)
phlebitis 1(2.1%)	1(2,1%)
• • • • • • • • • • • • • • • • • • • •	The state of the s

	NO.	CEPHALOTHIN PROBABLY RELATED
Pain on infusion Fhlebitis/thrombo-	1(2.62)	1(2,6%)
phlebitis	1(2.67)	1(2.6%)
Venous intolerance	1(2.6%)	1(2,6%)
Erythema, IV Site	1(2.6%)	1(2.6%)

#### SYSTEMIC SIDE EFFECTS

Pruritus 1 PRIMAXIN DEFINITELY RELATED 1(2.12)

#### 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	PR DYAXXN	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
LDB	I/1	0

#### Summary and Conclusions

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

A total of 47 patients, 28 males and 29 females, ranging in age from 19 to 68 years were enrolled in the Primarin 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.

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

Clinical cure or improvement occurred in 14/15 (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 Primarin 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 Primarin 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 cosinophilis (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 eosinophilis, 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 Primaxiz 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, Randomised Study of the Comparative Efficacy, Safety, and Tolerance of Intravenously Administered Primaxin and Cefotaxine in the Treatment of Rospitalized Patients with Infectious Caused by Susceptible Bacteria."

Study Design: This was an open, active, drug-controlled, rendemized, multiclinic study to compare the efficacy, safety, and tolerance of Primaxin and Cefotaxine in the intravenous treatment of hospitalized patients with infectious caused by becteria 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 Primarin or the Cefotaxine group.

Each patient in the Primaxia group received a total daily dose of 1.5 g administered in three equal coses as an intravenous infusion over 30 minutes every 8 hours.

Patients in the Cefotaxine 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 otudy, 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

Daikse, G., "King Paul" Hospital, University of Athens Medical School, Athens, Greece

Glauser, H., 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 Hospital Winnipeg, Cenada

Stamboulian, D., British Rospital of Buenos Aires, Buenos Aires, Argentina

Stille, W., Klinixum A. J. W. Goethe-Universitant, Frankfurt, West Germany

Ten Napel, C., Hospital 'Ziekenworg', Enschede, Holland Veriava, Y., Coronation Hospital, Johannesburg, South Africa Wittmann, D., Allgemeines Krankenhaus Altona, Hamburg, West Germany

Yourssawsky, E., Hospital Brugmann, Brussels, Belgium

# Overall Summary of Studies Conducted Under Protocol 513

	PRIMAXIN	CEFOTAXDE
TOTAL NO. OF PATIENTS	123	111
AGE RANGE (Years)	16 <b>-8</b> 0	18-81
HEAN AGE (Tests) SEX	52.6	54 9
Male	78	65
Fenale	45	46

#### EVALUATION

#### EFF ICACT

	PRIMAKIN	CEFOTAXINE
NO. OF CASES EVALUABLE	69	69
NO. OF SITES OF IMPRICTION		
EVALUABLE	48	84
NO. OF CASES UNEVALUABLE.	54	42
REASONS CASES UNEVALUABLE		
No pretreatment pathogen	24	19
Organism rewistant to study drug	1	0
Clinical diagnosis not clear	2	1
Imedequate bacteriologic cultures	8	13
Effective concomitant antibiotic	4	2
Trestment course too short	15	6
Infection not included in claims	-	1

500 mg q 8 h 2 g q 8 h	DOSE	MADALIH SOO OR 9 8 h	CEPOTATION TERMS
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# DURATION OF TREATMENT (Days)

(Evaluable Cases) 5-14

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

3( 26X)

24 18(752)

3(12.58) 3(12.58)

#### RESULTS

<u> </u>		GDIG	DATE TO SE			CHICK	THE ROLL	
INFECTION  IKIN I SKIN STRUCTURE  (Variet infection)	16	73( <u>873</u> )	2(13%)	I(W)	13.	10(672)	)(202)	2(138)
cellulitie, erysipei	18)							

LOWER MESPHEATORY 19 (Frenchitis, poetmonia, bycachopasumonia, supyesa, 11(58%) 3(162) lung abscess)

(Continued)			DIAXTN			<u>arou</u>		
INTECTION HEDIAST DILLIS	NO.	CURE 1(100X)	DIP.	FAIL	₩O. 1	CULK CULK 1(100%)	MP.	PAIL
SEPTICEMIA	28	26( 93X)		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, pyelonephr perinephric abscess		2(1 <del>00</del> %)			2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess cholangitis, cholec		6( 40 <b>%</b> )	5( 33%)	4(27%)	11	10(912)	1(9%)	

		PR DIAL BACTER TOLOG		R7		CEFOTA BACTERIOLOG		,
CA CAN ISM	NO.	Bub	SUPP	KOT FRAD	NO.	FRAD	SUPY	NOT ER
SKIN & SKIN STRUCTURE								
S. aureus(5)	1	1(1002)			1	1(100%)		
S. sureus(R)	6	5(83%)		1(172)	4	4( 100%)		
Strep (Group A)	2	2(100%)			2	2(100%)		
Strep (Group D)	1	1(1007)						
Alpha-bom strep	1	1(100%)						
S. intermedius	1	1(100%)						
S. faccalis	-				1			1(100
I. closeas	-				3	3 <del>( 100%</del> )		*
A. calcomestious	1	1(100%)				-		
A. odorana	1	1(100%)						
E. colí	6	6(1007)			2			2( 100
I. pasumonies	1	1(100%)			ĺ	1(100%)		•
M. morganii	2	I(50I)		1(50%)	1	1(100X)		
P. mirabilia	1	•		1(100%)				
P. vulgeris	-				1			1(100
7. seruginosa	1	1(100%)			1	1(100%)		
5. marcescens	1	1(100%)			2	2(100Z)		
Peptococcus sp.	2	3(100%)			1	1(100%)		
Poptostrap sp.	3	3(100%)				•		
3. fragilia	4	4(100%)			1			1(10

(Continued)	
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(

(CODELEUGA)		PRIMA	TN.			CEFOT	. <b>*</b> ?***	
	DACTERIOLOGIC RESPONSE					BACTER TOLO		
OR CAN ISH	MO.	EIAD	SUPP	NOT ENAD	NO.	ERAD	SUPP	NOT ERA
LOVER RESPIRATORY			<u> </u>					-
S. aureus(R)	_				1	1(100%)		
5. bovis	1	1(1001)			_			
S. pneumoniae	4	4(100%)			9	9(100年)		
Bets-bem-strep	-				1	1(1007)		
Non-hem-strep	-				1	1(100%)		
E. closcae	-				1	1(100%)		•
E. cali	3	3(1002)			4	2(50%)		2(50%)
H. influentee	5	4(80I)		1(20%)	6	6(100%)		
H. pardinfluenzae	1	1(1002)			1	1(100%)		
K. pneumonise	1	1(100%)			2	2(100%)		
P. mirabilis	3	1(33%)		2(67%)	1	1(100%)		
F. seruginosa	2			2(100%)				
MEDIASTINITIS								
S. aureus (X)	1	1(100%)						
S. mercesceus	~				1			1(100)
SEFTICENIA								
S. aureus(S)	-							
S. sureus(R)	5	4(80%)		1(20%)	4	1(100%)		
S. pneumonise	3	3(100%)			1	1(100%)		
E. closcae	2	2(100X)			-	•		
A. calcosceticus	-				1	1(100%)		
C. diversus	-	·			1	1(100Z)		
E. coli	11	10(913)		1(92)	15	13(87%)		2(137
M. influenzac	1	1(100X)						
K. preumonies	3	3(100%)			1	1(1003)		
E. oxytoca	-				1	T(TGGZ)		
M. morganii	1	1(1062)			3	3(1002)		
P. mirabilis	_				1	1(10 <b>0X</b> )		
P. vulgaris	_				2	2(10 <b>0</b> %)		•
S. marcascens	-				2	2(100%)		
Serratia spp.	1	1(100%)						
Meningococcus (Group B)		1(100%)						•
I. fragilis	_1_	1(1002)						
UTI (Uncomp.)								
E. coll	1	1(100%)			2	2(100%)		
S. faccalis	1	1(190\$)			· · ·			
E. closcae	1	1(100%)			-			

f	Con	24	(beur	

(00001000)		PLDIAX				CEFOTA		
ORGANISM	NO.	BACTER IOLOG ERAD	SUPP	NOT ERAD	NO.	BACTER LOLOG		
UTI (Complicated)	<u></u>			NO. BOD	<u></u>	ERAD	SUPP	KIJE
S. Aureus(R)	-				1	1(100%)		
E. coli	4	2(50%)		2(50%)	3	3(100%)		
P. mirabilis	1	1(100%)			2	1(100%)		
-P. vulgaris	1			1(100%)	-		•	
S. faecalis	1	1(100%)		-	-			
K. pneumonise	1	1(100%)			-			
C. freundii	1			1(100%)	-			
C. diversus	_			, ,	1	1(100%)		
P. aeruginosa	3	2(67%)		1(33%)	1	•		1(1001
INTEA-AB DONINAL								
5. apidermidis	1	1(100%)			-			
8. mitis	~				1	1(100%)		
Strap (Group D)	2	2(100%)			-	-		
S. Raccalis	7	5(71%)		2(29%)	2	2(100%)		
E. closes	1	1(100%)		* *	1			1(1003
E. coli	8	5(62.5%)		3(37.5%)	7	7(100%)		
K. paesaoniae	3	2(67%)		1(33%)	1	1(100%)		
M. morganii	-	, ,			4	3(75%)		1(25%;
P. mirabilia	2	1(50X)		1(507)	2	2(100%)		
P. atruginosa	6	2(33%)		4(67%)	1	• •		1(100
Bifidobacterium		1(100%)						
Lectobecillus	1	1(100%)			_			
Peptontreptococcus	-	- 7			1	1(100%)		
B. fragilis	-				3	3(100%)		
B. melaninogenicus	1	1(1002)			_	-,,		
B. ruminicola	ī	1(1007)			_			**
Veillenalla	ī	1(100%)						
Veillumalla	1	1(100X)			-			

In the Primarin group, one patient with a chronic symbologyphritis due to P. aeruginose, E. coli and S. faecalis improved, and all organisms were eredicated. Rosever, 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 pyelosephritis due to E. coli developed a reinfection with a different E. coli strain.

Three patients in the cefotakine group, one with an injected ulcer due to M. notganii, and two with complicated urinary tract infections due to E. coli relepted during the follow-up period.

Superinfection developed in 3 patients in the Primaxia group and in 4 patients in the cefotaxian group.

SAFETY TOTAL NO. OF PATIENT NO. OF PATIENTS WITH	•	effects	PR THAKIN 123 8(6.5%)	CEFOTAXIME 111 3(3Z)	
NO. OF PATIENTS WITE EFFECTS	SYSTEMIC S	DE	13(10.5%)	9( 8%)	
LOCAL SIDE EFFECTS					
		TO 0 1 1 1 2	PR IMAXIN		
	NO.	PROBABLY NOT	Poss Ibly	DE CEASON V	NEE INTERV
Infused vein	<u> </u>	1101	IVSS LBL1	PROBABLY	DEF INITELY
infection	1(0.8%)	1(0.8%)			
Infused vein pain	3(2,4%)	1(0.8%)		1(0.87)	1(0.8%)
Phlebitis/thrombo-	-	•		` '	., ,
phlebitis	6(4,8%)			3(2.4%)	3( 2, 4%)
			CEFOTAXINE		
Phlebitis/thrombo-					
phlebitis	3(2,7%)		1(0.92)	1(0.9%)	1(0.9%)
SYSTEMIC SIDE EFFECT	<u>s</u>		PRIMAXIN		
		PROBABLY			
••	<u> 110.</u>	NOT	Poss Ibly	PROBABLY	DEF DETELT
Nauses Voniting	2(1.6%)			1(0.82)	1(0.82)
Glossitis	2(1.6%) 1(0.8%)				2(1.6%)
Pover	2(1.6%)			1(0.8%)	1(0.87)
Flushing	1(0.83)			1(0.0%)	1(0.8X) 1(0.8X)
Rech	1(0.3%)		1(0.8%)		1(0.00)
Sounolence	3(2.4%)		1(0.8%)	2(1,6%)	
- Heada che	1(0.8%)	1(0.82)		=(5,0=/	
Hypotensica	1(0.8%)			1(0.8%)	
Oliguria/anuria	1(0.8%)			1(0.8X)	
Polyuria	1(0.81)			1(0.8%)	
Meningitis	1(0.82)		1(0,6%)	, ,	
Pullness in ears	1(0.82)	1(0.67)		<u></u>	
			CEPOTATINE		
7omiting	_1 <del>(0.9%)</del> _			1(0.9%)	
Diarrhos	<del>3(2,7%)</del>		2(1.8%)		1(0.9%)
Mucous in feces	1(0.9%)		1(0,9%)		and the second s
(C. difficile posi	•				
Constipation	1(0.9%)				1(0,9%)
Pever	2(1.5%)		1(0,9%)	1(0. <b>%</b> )	
Pruritus	1(0.9%)		1(0,9%)		
Rach	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	PR IMAXIN	CEFOTAXIME
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
RBC	· · · <del>-</del>	(D) 1
<b>VBC</b>		(D) 2
<b>Eccinophils</b>	(I) 5	(I) 3
Platelets	(I) 5	(1) 1
	(D) 1	<b>, , , ,</b>
Blood Urea	(I) 3	(I) 2
bun	(1) 3	(I) 2
Creatinine	(I) 1	(1) 1
SGOT (AST)	(I) 6	(I) 4
SGPT (ALT)	(I) 6	(1) 5
Bilirubin	$(\mathbf{I})$ 2	$(\vec{1})$ $\vec{1}$
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 lime	_	(I) I
4 - Artistanto Peliki		<u>+ -/ -</u>

Summary and Conclusions

This was an open, randomized, controlled multicenter study comparing Primarin 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 Primarin 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  $\underline{P}$ . 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 Primarin 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" bocause of treatment failure.

Results of this study demonstrate that both Primaxin and cefotaxine 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 cefotaxine.

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 Bacteris."

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

Precedure: 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.1.d.) adjusted according to serum concentration access.

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 vas 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 bactariologic 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, Swedan
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	GENTANICIN/CLINDAMYCIN
	102	
AGE RANGE (Years)	15-79	
MEAN AGE (Years)	48. <del>9</del>	50.4
SEX		The second secon
Male	64	57
Female		55

#### evaluat ion

#### EFF ICACY

	PR IMAXIN	CENTAMICIN/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	s emperatus salabarans reconstruit i vor	O NECESSAR UNITE UNITERENTALISMO DE L'ESCA, NO 1
Treatment course too short	10	4
Organism resistant to study drug	1	1
Inadequate bacteriologic cultures	2	3

DOSE500	ng q 6 h 1.5 mg/kg q 8 h	600 mg q 6 h
DURATION OF TREATMENT (Evaluable Cases)	(days) Painaxin	CENTAMICIN/CLINDAMYCIN
4-14	65 patients	77 patients
15-20	5 netients	3 martants

GENTAMICIN

#### RESULTS

		PR	MAXIN	(	ENTAMICIN/CI	LINDAMYCIN	
		CLINICAL	RES PONSE		CLINICAL	RESPONSE	
INFECTION SKIN & SKIN STRUCTURE (Wound infection, absce	NO.	9(64.3%)	1MP. 5(37.7%)	FAIL NO.		D(P. 4(23.5%)	2(11.8%)
cellulitis, carbuncle furuncle, ulcers)	1						
(Pneumonia, empyema,	12	11(91.7%)	1(8,3%)	21	16(76.2%)	4(19.0%)	1(4.8%)
lung abacess)			· · · · · · · · · · · · · · · · · · ·				
SEPTICEMIA	10	10(1002)		<b>11</b>	8(72,7%)	1(9.12)	2(18.2%)
UTI (Uncomplicated)	_ 3	2(66.7%)	1(33.3%)		2(66.7%)	1(33.3%)	
(Cystitis, pyelo- nephritis)						and the same of th	
UTI (Complicated) (Cystitis,	8	5(62.5%)	3(37,5%)		2(100%)		
pyelonephritie)							
INTRA-ABDOMINAL (Peritonitis, abscess,	20	16(80%)	2(10%)	2(10%) 24	14(58.3%)	8(33,3X)	2(8.3%)
cholangitis, cholecys	titi:						

CLINDAMYCIN

and the state of t

		PA	DHAXIN		Œ	STAMICIN/C	LINDAMYCIN	
		CLINICA	L RESPONSE			CLINICA	L RESPONSE	
INFECTION	NO.	CURE	IMP.	FAIL	NO.	CURE	IMP.	FAIL
GYNEODLOGIC	8	6(75X)	2(25%)		5	5(100%)		
(Endometritis, PTD, ovarian abscess)	tubo-							
BONZ/JOINT	1	1(100%)			1			1( 100Z
-(Infectious arthrit	is,							

		FRIMA BACTERIOLO		Ned		GENTAMICE		
organism	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	GIC RESPON	NOT ERA
SKIN & SKIN STRUCTURE					<u> </u>		3011	WI EUR
		-·						
S. sureus(S)	1.	1(100%)			2	2(100%)		
S. aureus(R)	5	3(60%)		2(40X)	10	9(90%)		1(10%)
S. epidermidis	2	2(100%)			•			_,,
Strep (Group A)	2	1(50%)		1(50%)	5	5(100%)		
5. pyogenes	-			• •	1	1(100%)		
Beta-hem-strep	-				1	1(1002)		
5. faecalis	1			1(100%)	4	2(50%)		2(50%)
E. coli	1	1(100%)		- •	2	1(50%)		1(50%)
P. mirabilis	1	1(100%)				1(50%)		1(50X)
Klebsialia app.	1_	1(100%)			_	_(,		2(342)
E. agglomerane	1	1(100%)						
Pseudopones spp.	1	1(100%)			-			
P. aeruginosa	1			1(100%)	1			1(100%
Bacteroides spp.	1	1(100%)						of same
B. fragilia	ī	1(100%)			1	1(100%)		
Peprostreptococcus	· 1	1(1002)			······ <del>-</del> ·	1(1000)		
Anserobes, Mixed	- <u>-</u>	2(100%)		:	_			
	-	_(,						
LOWER RESPIRATORY			5 1 200 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1					
	-					man and an analysis	100000000000000000000000000000000000000	***************************************
S. aureus(R)	-				1	1(1002)		
S. pneumoniae	5	5(100%)			11	10(90.9%)		1(9.17
Alpha-hem-strep					2	2(100%)		-,,-,-
Straptococcus app	_				1	1(100%)		
H. influenzae	6	6(100%)			6	4(66.7%)	1(16.6%)	1(16.6
H. perainfluentee	·				ĭ	1(1002)	_(10.04)	7(70.0
E. coli	-				<u> </u>			1(100%
Gren-neg-rods	1	1(100%)						
P. mirabilis			<del></del>		1	1(100%)		
Enterobecter spp.								

	MDA 50-587		- 106 -						<del></del>
	(Continued)		PR DIAXI	7N			@NTANICIN	/CLINDAHYCI	<u> </u>
	A Committee of the Comm		BACTER 10 LOGI	TC RESPON	<b>32</b>		BACTER TOLO	CIC RESPONS	<u> </u>
I	OR GAN ISM	NO.	ERAD	SUPP	NOT LRAD	NO.	ERAD	SUPP	NOT ER
1	Klebsiella spp.	1	1(100%)	<del></del>			<del></del>	<del></del> -	-
l	B. catarrhalis	1	1(100%)			-			
i	S. marcescens	-				1	1(100%)		
i	M. meningitidis	1	1(100%)			1	1(100%)		
	B. fragilis						1(100%)		
i	- Fusobacterium	-				ı	1(100%)		
ı	•								
sure control of the second	ro como de macion <mark>SEPTICENTA</mark> qualque de proceso de accomo de se	40.001942-01942-1-014-6	and one way that the state of	and what is the second	AND THE SECOND STREET STREET, STREET STREET, STREET STREET, ST	Jan Carrest Manager	2017 S. C. STANSON 1975 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.	A REPORT OF THE PERSON OF THE	
ı		1	1/1007)			1	1(100%)		
i	S. aureus(S)	1 2	1(100%) 2(100%)			_	4( *****		
i	5. aureus(R)	4	2( 100 m /			1	1(100%)		
ı	S. epidermidis	-	1/100%			ī	1(100%)		
ı	Alpha-hem-strep	1	1(100%)			1	1(1002)		
L	S. pneumonise	T	1(100%)				11		<del>-</del>
1	S. bovis	<u>1</u>	1(100%)			6	4(66.7%)		2( 33, 3
	B. coli		4(100%)			1	1(100%)		
	Klebsiella spp					1	1(100%)		
	P. mirabilia	-	**********			<u> </u>	4/ 4V		
I	Salmonella (Group B)	1	1(100%)			1	1(100%)		
I	Bacteroides spp	1	1(100%)			=	1( 100-,		
I	B. fragilis	1	1(100%)			-			
ı	B. melaninogenicus	1	1(100%)			_			
l	B. corrodens	1	1(100%)			_			
	UTI (Uncomp.)				1(33,32)		2(66.71)		1(33.
 I	E. coli	3	2(66.7%)		4/ 33, 50,				
l 2									
µ. €	UTI (Complicated)				1(33.3X)		2(100%)		
<b>I</b>	5. coli	3	2(66.7%)		1(33.32)		41 44		
I	P. mirabilis	1 1			1(100%)	-			
	P. stuartii	<u>1</u>	~ < 4 (M)\$/		7(700-)				
1	Pseudomonas spp	- 4	2(100%)						
1	P. aeruginosa	1	1(100%)					<del></del> -	_
	INTRA-ASDOKINAL								
						<del></del>			
ı	S. aureus(8)	-			<b>-</b> -	1			
ľ	S. aureus(R)	2	1(50%)		1(50%)	2			***
<del> </del>	S. epidermidis		· · · · · · · · · · · · · · · · · · ·		·····		2(50X)	<del></del>	2( 50X )
I	Streptococcus spp	-				1	1(100%)		
1	Alpha-hem-Strep	. 1	1(100%)			-			
	Nets-hem-Strep		1(100%)					1(100%)	
	S. faecalis					4	3(75%)		1(25%)
I	A. calcoaceticus	1				-			
f	K. pneumoniee	2	2(100%)			2	1 (50%)		1( 50%)
	•								
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<u> </u>									
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I			and a tripue		· · · · · · · · · · · · · · · · · · ·		·		
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=									

(Continued)						* * * * * * * * * * * * * * * * * * * *	tree or make as a	
<del>reformation</del>		PR IMAX BACTER IOLOG	IC RESPONSE			GENTAMICIN/ BACTER IOLOG	LUDAMCI	
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAL
Haemophilus spp	1	1(100Z)			-			
Citrobacter app	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. hafnise	1	1(100%)			1	1(100%)		•
E. coli	10	10(1001)			14	12(85.7%)		2(14.32
P. mirabilis	-				1			1 1002)
P. rettgeri	-				1	1(100%)		/
M. morganii	-				1	• /		1(100%)
Pseudomonas spp	-				1			1(100%)
P. aeruginosa	1	1(100%)			1			1(100%)
Serratie spp					1	1(100%)		
C. perfringens	. 1	1(100%)			1	1(100%)		
C. butyricus	_		the state of the same of the s		ī	1(100%)		
C. histolyticum	_				ī	1(100%)		
S. typhi	1	1(100%)			_	-//		
S. choleraesuis	1	1(100%)			_			
Peptococcus spp	2	2(100%)			1	1(100%)		
Peptostreptococcus spp	ī	1(100%)			_	7(7004)		
P. granulosum	-	_(			1	1(100%)		
E. lentum	1	1(100%)			-	2(2004)		
Lactobacillus	<u> </u>	1(100%)			-			
Bacteroides spp		2(100%)			2	2(100%)		
B. fragilie	3	3(100%)			<del>-</del>		1(14, 32)	2020 41
B. bivius	í	1(100%)			<u>'</u>	4( J/ . IK)	1(14,34)	4(40.0)
B. meleninogenicus	_	~( ~~~ )			ī	1/10041		
B. ruminicola				er en en en en en en en en en	1	1(100%)		
	_			***	1	-1(100X)		
CINECOLOGIC								
S. aureus(R)	-	•			1	the more security of		1(1002
S. epidermidis	1	1(100%)			-			• • • • •
Strep (non-hem)	1	1(100%)			-			1.75
Alpha-hem-strep	-					1(100%)		
Bets-hem-strep	-				1	1(100%)		
E. coli	1	1(100%)			1	, , ,		1(1007
E. agglomerans	1	1(100%)					yr rener new allegan and a	
H. influenzse	1	1(100%)			-			
E. pheumonise	1	1(100%)			-			
P. mirabilis	1	1(100%)						
P. aeruginosa					1	1(100%)		
N. gonorrhoese		*** *** *******************************			<del></del> -	1(100%)		

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(Continued)		7 T T T T T T T T T T T T T T T T T T T						
		PEDIA	C) N			CENTANICIN,	CL DID MY	CIN
		BACTER TOLOG	IC RESPONS	<b>2</b>		BACTER TOLO		
OR CANISM	NO.	DAD	SUPP	NOT ELAD	<b>30.</b>	ERAD	SUPP	HOT ELLE
P. granulosum	T	1(100x)		سيسيس				
Peptococcus app	1	1(100I)			1	1(100%)		
Peptostreptococcus app	-				1	1(1007)		
Bacteroides app	1	1(100%)			-	•		
B. fragilis	1	1(100%)			1	1(100%)		
BONE / JO INT								
5. pyogenes	1	1(100%)			-			
B. fragilis	da	- • • • • • • • • • • • • • • • • • • •			1			1(100%)
ENTER IT IS								
Campylobecter	1	1(100%)			1	1(100%)		
Salmonella Type B	1	_(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		1(100%)	•	1(1004)		

Two patients in the Primarin group and seven in the Gentanicin/Clindenycin 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/Clindarycin group.

SAFETY

	PR IMAXIN	CI.INDAMYCIN/GENTAMICIN
TOTAL NO. OF PATIENTS	102	112
NO. OF PATIENTS WITH LOCAL SIDE		
<b>D</b> FRCTS	6(5,9%)	5(4,52)
NO. OF PATIENTS WITH SYSTEMIC	••	
SIDE EFFECTS	17(16.7%)	25(22,3 <b>%</b> )

#### LOCAL SIDE EFFECTS

		FEOBABLY	PRIMATIN		en e
Phlebitis/thrombo-	NO.	NOT	Poss Idly	PROBABLY	DEFINITELY
phlebitis	6(5.9%)	1(1,02)		3(3.0%)	2(1.9%)
			ENTANICIN/CLIM	AMTCIN	
Infused wein pain	2(1.8%)			2(1.8%)	the second second second second second
Vein induration Phlebitis/thrombo-	1(0.9%)			1(0,9%)	
phlebitis	2(1.8%)			1(0.91)	1(0,9%)

#### SYSTEMIC SIDE EFFECTS

			PRIMIXIN		
	NO.	PROBABI Y	**************************************	DEAD 451 M	
Nausea	$7(\overline{7.0}x)$	NOT	POSSEBLY	PROBABLY	DEFINITELY
			4(4)	3(3%)	
Vowiting	3(3.0%)		2(2%)	1(17)	
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(1,0Z)	1(1%)	•		
Chest discomfort	1(1.07)	1(1%)			
Hypotension	1(1.0%)			1(1%)	
Vaginal candidiasis	1(1,0%)		1(1%)	•	
Hemoptysis	1(1,0%)	1(1%)	7 .		
Anxiety	1(1,0%)	1(1%)			
		G	ENTAMICIN/CLIND	amycin	

Nausea	1(0.9%)	1(0.9%)			
Vomiting	1(0.9%)	1(0.9%)			
Diarrhea	10(8.9%)	6(5.3 <b>Z</b> )	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%)	-		= fra a alax
Headache	2(1.8%)	2(1.8%)			
Dizziness	1(0.9%)	As an assessment of the second		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 diarrhes had positive C. difficile toxin in the

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.

#### Absormal Laboratory Tests

TEST	PR IMAXIN	GENTAMICIN/CLINDAMYCIN
RBC	(D) 1	(D) 3
Hemoglobin	(D) 2	(D) 2
Hematocrit	(D) 1	(D) 1
WBC.	(D) 1	\-, - -
Eosinophila	(I) 2	(I) 1
Platelet count	• • • • • • • • • • • • • • • • • • •	$(1)$ $\overline{2}$
Platelet estimate	(I) 4	(D) 1
Positive Coombs' Test	` 2	2
BUN	$(1)$ $\overline{1}$	(I) <sup>2</sup>
Blood urea	(I) 1	(1) 2
Creatinine	(I) 4	(1) 22
Serum uric scid	(-, -	(1) 6
SGOT (ASAT)	(I) Y	(1) 10
SGPT (ALAT)	(I) 12	(1) 11
Bilirubin	(I) 1	(I) I
Alk. phosphatase	(I) 7	(I) 6
Serum potassium	(I) I	(1) 2
• • • • • • • • • • • • • • • • • • • •	$(\tilde{\mathbf{D}}) \stackrel{-}{1}$	(D) 1
Serum chloride	(D) 1	(D) 4
Urine protein		(1) 5
Urine WBCs	(I) 3	(I) 8 ···
Urine RBCs	(I) I	(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 makes 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/clindarycin 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 Primaxic 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 B. coli, H. influenzae, and Enterobacter species.

Clinical Studies (Foreign)

#### II. Uncoptrolled

#### 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 grass (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, rensl, 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

Transment course too short

Inadequate bacteriologic cultures

Effective concomitant antimicrobial therapy

Diagnosis not clear

# DURATION OF TREATMENT (Evaluable cases)

DAYS	MO. OF	PATIENTS
5-14	1.	59
15-30		6

#### RESULTS

#### CLINICAL RESPONSE

Invection	NO.	CURE	<b>IMPROVE</b>	PAIL
SKIN & SKIN STRUCTURE	44	34 (77.3%)	8 (18, 21)	2 (4,5%)
(Wound infection, abscess, cellulitis,		••	* * * * * * * * * * * * * * * * * * *	
carbuncle/furuncle,				
decubitus & other skin ulcers				

NDA 50-587	- 113	-		
(Continued)				
BONE/JOINT (Pyogenic arthritis)	1	1 (100%)		
IOWER 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 R	es ponse	
UTI (Uncomplicated) (Cystitis, pyelonephritis)	NO.	CURE 5 (100%)	IMPLOVE	PAIL
UTI (Complicated) (Cystitis, pyelonephritis renal abscess)	35	19 (54.3%)	16 (45.72)	
INFECTION BACTERIAL SEPTICEMIA	19	18 (94,7%)	1 (5.3%)	
ORGANISM SKIN & SKIN STRUCTURE	NO.		ACTERIOLOGIC RES	Ponse
Genolia 8. aureus	<u> </u>		1 (100%) 5 (100%)	
S. aureus <sup>R</sup> S. epidermidis	9		8 (89.9%) 3 (75%)	
Streptococcus spp.	2		2 (100X)	
Streptococcus (Group A)	- 3		3 (100%)	
Streptococcus (Group C)	1		1 (100%)	
Streptococcus (Group D) Enterococci)	6		4 (66.72)	
Streptococcus faccalis	2		2 (100%)	
Streptococcus viridans Beta-hemolytic streptococci	3		2 (100%) 3 (100%)	

(Continued)	10.	BRADICATED
•	<del></del>	Conference of Proper Land
Acinetobacter spp.	1	0
Enterobacter spp.	4	3 (75%)
Enterobacter serogenes	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 seruginosa	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Peptococcus spp.	3	3 (1002)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	3	3 (1002)
Fusobacterium spp.	1	1 (1002)
Acidaminococcus fermentans	1	1 (100%)
organ ism		BACTERIOLOGIC RESPONSE
BONE/JOINT	NO.	ERADICATED
S. aureus <sup>R</sup>	1	1 (100%)
INTRA-ABDOMINAL		
S. aureus <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	3 3	3 (100Z)
S. epidermidis	Ĭ.	4 (100%)
Streptococcus app.	i	1 (100%)
Streptococcus (Group D) Enterococci)	3	3 (100%)
Streptococcus faecalis	•	1 /1008\
	1 5	1 (100%)
Streptococcus viridans Non-hemolytic		5 (100%)
	2	2 (1007)
streptococci	-	
Citrobacter freundii	2	1 (50X)
Enterobacter app.	1	1 (100%)
Enterobecter cloucse		1 (100%)
Escherichia coli	27	24 (88.91)
Klebsiella pneumoniae	2	2 (100%)
Lictobacillus	1	1 (100%)
Morganella morganii	3	2 (66.7%)
Proteus mirabilis	2	2 (100%)
Proteus vulgaria	3	2 (66.7%)
Providencia rettgeri	1	1 (100%)
Pseudomonas app.	1	1 (100%)
Pseudomonas aeruginosa	2	1 (50%)
Serratia liquefacions	1	1 (100%)
Clostridium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
	_	• • • • • • • • • • • • • • • • • • • •
Propionibacterium app.	<b>J</b>	1 (100%)
Propionibacterium spp. Peptostreptococcus spp.	1	
		1 (100%) 1 (100%) 5 (83.3%)

LOWER RESPIRATORY	NO.	ERADICATED
S. aureusS	4	4 (100%)
S. aureus <sup>R</sup>	2	2 (1002)
S. epidermidis	1	0
Streptococcus app.	1	1 (100%)
S. pneumonise	2	2 (100%)
Streptocaccus (Group D)	3	2 (66,7%)
Enterococci)		
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%)
Pentostreptococcus 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.

GYNECOLOGIC	NO.	ERAD ICATED
treptococcus (Group D) Enterococci)	1	1 (100%)
Sacherichia coli	7	5 (71.4%)
roteus Vulgaris	1	1 (100%)
Neisseria gonorrhoeae	and the second s	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides app.	2	2 (100%)
UTI (Uncomplicated)	1	, ,
UTI (Uncomplicated)	1	2 (100%)  1 (100%)  1 (100%)
TI (Uncomplicated)  . aureusR  treptococcus (Group D  Enterococci)	2 1 1	1 (100%)
TI (Uncomplicated)  . aureus <sup>R</sup> treptococcus (Group D Enterococci) scherichia coli	1 1 4 1	1 (100%) 1 (100%)
UTI (Uncomplicated)  S. aureus <sup>R</sup> Streptococcus (Group D	2 1 1 4 1	1 (100%) 1 (100%) 4 (100%)

UTI (complicated)	NO.	ERADICATED
S. aureus <sup>R</sup>	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 <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	2	2 (100%)
S. epidermidis	2	2 (100%)
Streptococcus pneumoniae	1	1 (100%)
Streptococcus (Group D	1	1 (100%)
Enterococci)		
Streptococcus faecalis	1	1 (100%)
Acinetobacter app.	1	1 (100%)
Enterobacter aerogenes	1	1 (100%)
Escherichia coli	6	6 (100%)
Riebsiella 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 tobramyclu and piperacillin.

#### SAFETY

NO. OF PATIENTS WITH SYSTEMIC SIDE EFFECTS ---- 24 (10.3%)
NO. OF PATIENTS WITH LOCAL SIDE EFFECTS ----- 27 (11.5%)

SIDE EFFECTS SYSTEMIC	<u></u>	Probably	Possible Related	Probably Related	Definitely Related
	No.	Not Related	VETATER	METTER	
			2 (0.8%)	δ (2.6%)	3 (1.3%)
Diarrhea	11 (4.7%)			5 (2.1%)	3 (1.3%)
Nausea	10 (4.3%)		2 (0.8%)	2 (0.8%)	3 (1.3%)
Vomiting	6 (2.6%)		1 (0.4%)	1 (0.4%)	3 (2:54)
Heartburn	1 (0.4%)		- (0 (8)	1 (0.4%)	
Abdominal pain	1 (0.4%)		1 (0.4%)	2 (1 28)	
Brown tongue	3 (1.3%)	ran i e e e e e e e e e e e e e e e e e e	NAME OF THE STREET, THE STREET	3 (1.3%)	***
Allergic	1 (0.4%)			1 (0.4%)	
dermatitis	, ,				
Pruritus	1 (0.4%)			1 (0.4%)	4 (0 (9)
Rash	1 (0.4%)				1 (0.4%)
Dizziness	3 (1.3%)			1 (0.4%)	
	1 (0.4%)			1 (0.4%)	
Hypotension	1 (0.4%)		1 (0.4%)		
Dyspnes	1 (0.44)		•		
LOCAL					
	9 (3.8%)	4 (1.7%)	3 (1.3%)	1 (0.4%)	1 (0.4%)
Pain		*	4 (1.7%)	•	
Induration	11 (4.7%)		6 (2.5%)		
Erythema	12 (5.1%)		4 (1.7%)	1 (0.4%)	)
Phlebitis/	5 (2.1%)		7 (11/2/	_ \- \- \- \-	·
thrombo-					
phlebitis					

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	(1) 8	
Eosinophils	(I) 6	
Basophils	(I) 3	
Prothrombin time	(I) 2	
Positive Coombs' test	2	
Creatinine	(I) 1	
SGOT (AST)	(I6	
SGPT (ALT)	(I) 11	
Albeline 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**

### EFF ICACY

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	214	115 (53.7%)	72 (33,6%)	27 (12.6%)	
(Pneumonia, empyema, lung abscess)					
URINARY TRACT -					
UNCOMPLICATED (Cystitis, pyelonephritis)	41	38 (92.7%)	2 (4.9%)	1 (2,4%)	
URINARY TRACT -					
(Cystitis, pyelonephritis) renal or perinephric	139	90 (64.7%)	42 (30.2%)	7 (5.1%)	
abacesa)					

ſ

	INTRA-ABDOMINAL	NO.	CURE	IMPROVE	FAIL
	(Abscess, peritonitis,	156	112 (71.8%)	32 (20.5%)	12 (7.7%)
	cholecystitis, cholangitis,				
	liver abscess,				
	-perirectal				
•	abscess)				
	ENTERITIS		1 (1002)	Application of the second of the second	and the state of the state of the same
	GYNECOLOGIC	95	75 (78.9%)	16 (16.8%)	4 (4.2%)
	(Endometritis, pelvic				, ,
	cellulitis, pelvic				
	inflammatory disease, tubo-overian abscess,		en en la companya de		_
	pelvic abscess	the second second second second second			
	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	72	32 (44.4%)	35 (48.6%)	5 (6.9%)
	Infectious arthritis, osteomyelitis)				
	SKIN & SKIN STRUCTURE	328	204 (62.2%)	110 (33.5%)	14 (4.3%)
	(Wound Infection,				
	abscess, cellulitis, carbuncle/furuncle,	_			
	infected decubitus and				
	other skin ulcers)				
=	OTITIS	<b> 4</b>	2 (50%)	1 (25%)	1 (25%)
	UPPER RESPIRATORY	2		1 (50%)	1 (50%)
	MEDIASTINITIS	1	1 (100%)		
	BRAIN ABSCESS		1 (100%)		
				<u> </u>	

ORGANISM		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	NO.	ERADICATED
S. aureus <sup>S*</sup>	··· 7	7 (100%)
S. aureus <sup>R**</sup>	9	9 (100%)
S. epidermidis	2	0
S. pneumoniae	49	49 (100%)
Streptococcus (Group A)	. <b>2</b>	2 (100%)
S. viridans group	1	1 (100%)
Beta-hemolytic streptococcus	2	2 (100%)
not Group A S. bovis	•	The state of the s
<del>-</del>	1	1 (100%)
Other streptococcus species	7	9 (100%)
Group D streptococcus (enterococcus)	,	4 (57%)
Branhamella catarrhalis	<b> 2</b>	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 (100%)
E. aerogenes	3	2 (67%)
E. cloacee	10	9 (90%)
E. agglomerans	1	I (100X)
Hafnis alvei	1	0
Providencia stuartii	1	1 (100%)
P. multocida	2	2 (100%)
Citrobacter freundii	1	0
Citrobacter spp.	1	1 (100%)
P. seruginosa	54	18 (33,3%)***

\*\*\* Penicillin-sensitive \*\*\* 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 patient
had failed previous courses of antibiotic therapy.

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

OKGANISM		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	No	ERADI (GATE)
Pseudomonas spp.	1	1 (100%)
A. hydrophilia	1	1 (100%)
S. marcescens	6	4 (67%)
Alcaligens spp.		1 (100%)

NO.   RADICATED	(Continued) ORGANISM		BACTER TOLOGIC RESPONSE
A. calcoaceticus 4 4 (100%) Acinetobacter spp. 2 (100%) Corynebacterium acnes 1 1 (100%) Peptostreptococcus spp. 3 3 (100%) Pusobacterium spp. 1 1 (100%) Bacteroides spp. 3 3 (100%) Eikenella corrodens 1 (100%)  Eikenella corrodens 1 (100%)  ORGANISM NO. ERADICATED  URINARY TRACT  (UNCOMPLICATED)  S. auraus 1 1 (100%)  S. auraus 2 1 (100%)  S. faecalís 1 1 (100%) Centerococci) S. faecalís 1 1 (100%) P. wigaris 2 2 (100%) K. pneumonise 2 2 (100%) K. pneumonise 2 2 (100%) K. coxytoca 1 1 (100%) Euterobacter spp. 1 1 (100%) Euterobacter spp. 1 1 (100%)  URINARY TRACT  COMPLICATED)  S. auraus 2 5 (83%) S. epidermidis 4 (100%) Coroup B Streptococcus 2 (100%) S. faecalís 2 1 (50%) S. faecalís 2 1 (50%		NO.	
Acinetobacter spp. 2 2 (100%) Corymebacterium acnes 1 1 (100%) Peptostreptococcus spp. 3 3 (100%) Fusobacterium spp. 1 1 (100%) Bacteroides spp. 3 3 (100%) Eikenella corrodens 1 1 (100%)  CORGANISM NO. ERADICATED  URINARY IRACT  (UNCOMPLICATED)  S. aureus 1 1 (100%)  Group B Streptococcus 1 1 (100%)  E. coli 32 29 (91%) P. wilgaris 2 2 (100%) E. p. wilgaris 2 2 (100%) E. colacae 2 2 (100%) E. colacae 2 2 (100%) Enterodacter spp. 1 1 (100%) F. aeruginosa 1 1 (100%)  URINARY TRACT  COMPLICATED  URINARY TRACT  COMPLICATED  S. aureus 2 2 (100%) Enterodacter spp. 1 1 (100%) F. aeruginosa 1 1 (100%)  URINARY TRACT  COMPLICATED  S. faecalis 4 4 (100%) Group B Streptococcus 10 9 (90%)  Group B Streptococcus 10 9 (90%)  Group B Streptococcus 10 9 (90%)  F. aeruginosa 1 1 (50%) E. coli 43 26 (60%) F. mirabilis 12 6 (50%) F. wilgaris 1 0 F. ertegeri 3 2 (60%) F. rettgeri 3 2 (60%) F. rettgeri 3 3 (100%) K. pneumoniae 8 7 (67,5%) K. oxytoca 1 1 (100%) E. cloacae 7 (685,7%) Enterobacter spp. 1 1 (100%) E. cloacae 7 (685,7%) Enterobacter spp. 1 1 (100%) E. cloacae 7 (685,7%) Enterobacter spp. 1 1 (100%) E. cloacae 7 (685,7%) Enterobacter spp. 1 1 (100%)			
Corprebacterium acnes			
Peptoatreptococcus spp. 3 3 (100%)			
Puscobacterium spp. 1			
Bacteroides spp.   3   3 (100%)			· · · · · · · · · · · · · · · · · · ·
BACTERIOLOGIC RESPONSE			· · · · · · · · · · · · · · · · · · ·
RACTERIOLOGIC RES FONSE			
ORGANISM   NO.   ERADICATED	Eikenella corrodens	1	1 (100%)
ORGANISM   NO.   ERADICATED			T I ATTOM TAY CORD IN THE POLICE
URINARY   TRACT	OR CANTSM	NO	
CUNCOMPLICATED			ERADICALED
S. aureus   S. faecalis			
Group D Streptococcus (enterococci)  S. faecalis 1 1 (100%) E. coli 32 29 (91%) P. mirabilis 3 3 (100%) P. vulgaris 2 2 (100%) K. preumonise 2 2 (100%) E. cloacae 1 1 (100%) E. cloacae 2 2 (100%) E. cloacae 2 2 (100%) E. cloacae 3 1 1 (100%) P. aeruginosa 1 1 (100%)  URINARY TRACT COMPLICATED)  S. aureus 6 5 (83%) S. epidermidis 4 4 (100%) Group B Streptococcus 10 9 (90%) (enterococci) S. faecalis 2 1 (50%) E. coli 43 26 (60%) P. mirabilis 12 6 (50%) P. vulgarie 1 0 P. rettgeri 3 2 (67%) M. morganii 3 3 (100%) K. pneumoniae 8 7 (87.5%) K. oxytoca 1 1 (100%) E. cloacae 7 (67.5%) E. cloacae 7 6 (85.7%) Enterobacter spp. 1 (100%) Enterobacter spp. 1 (100%)	Validating)		
Group D Streptococcus (enterococci) S. faecalis E. coli S. faecalis I I I (100%) E. coli S. faecalis I I I (100%) E. coli S. faecalis I I I (100%) I I I I I I I I I I I I I I I I I I I	S. aureus <sup>S</sup>	1	1 (100%)
(enterococi) S. faecalis I. (100%) E. coli 32 29 (91%) P. mirabilis 3 (100%) P. vulgaris 2 (100%) K. pneumonise 2 (100%) K. oxytoca 1 (100%) E. cloacae 2 (100%) E. cloacae 2 (100%) Enterobacter app. 1 (100%) Enterobacter app. 1 (100%)  E. aeruginosa 2 (100%)  Group B Streptococcus 2 (100%) Group B Streptococcus 10 (9 (90%)  (enterococci) S. faecalis 2 (100%) E. coli 43 (26 (60%) P. wilgaris 1 (100%) P. rettgeri 3 (2 (60%) P. vulgaris 1 (100%) E. rettgeri 3 (100%) K. pneumoniae 8 (7 (87.5%) K. oxytoca 1 (100%) E. aerogenes 1 (100%) Enterobacter app. 1 (100%) Enterobacter app.	Group D Streptococcus		
E. coli 32 29 (91%) P. mirabilis 3 3 (100%) P. vulgaris 2 2 (100%) K. pneumonise 2 2 (100%) E. cloacse 1 1 (100%) E. cloacse 2 2 (100%) Enterobacter spp. 1 1 (100%)  URINARY TRACT COMPLICATED)  S. aureus 6 5 (83%) S. epidermidis 4 (100%) Group B Streptococcus 2 (100%) Group D Streptococcus 10 (100%) Group D Streptococcus 10 (100%) E. coli 43 (100%) E. coli 43 (100%) F. mirabilis 1 (100%) F. rettgeri 3 (100%) M. morganii 3 (100%) K. pneumonise 8 (76%,5%) K. oxytoca 1 (100%) E. cloacse 7 (685,7%) Enterobacter spp. 1 (100%) E. cloacse 7 (685,7%) Enterobacter spp. 1 (100%)			<b>↓</b> = =, <b>↓</b>
E. coli 32 29 (91%) P. mirabilis 3 3 (100%) P. vulgaris 2 2 (100%) K. pneumonise 2 2 (100%) K. oxytoca 1 1 (100%) E. cloacse 2 2 (100%) Enterobacter spp. 1 1 (100%) P. aeruginosa 1 1 (100%) URINARY TRACT COMPLICATED)  S. aureus 6 5 (83%) S. epidermidis 4 4 (100%) Group B Streptococcus 2 2 (100%) Group B Streptococcus 10 9 (90%) (enterococci) 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. pneumonise 8 7 (87.5%) K. oxytoca 1 1 (100%) E. cloacse 7 (87.5%) Enterobacter spp. 1 (100%)	S. faecalis	1	1 (100%)
P. vulgaris 2 2 (100%)  K. pneumonise 2 2 (100%)  K. oxytoca 1 1 (100%)  E. closcae 2 2 (100%)  Enterobacter spp. 1 1 (100%)  P. aeruginosa 1 1 (100%)  URINARY TRACT  COMPLICATED)  S. aureus 6 5 (83%) S. epidermidis 4 (100%)  Group B Streptococcus 2 (100%)  Group D Streptococcus 10 9 (90%)  (enterococci)  S. faecalis 2 1 (50%) E. coli 43 26 (60%)  P. wilgaris 1 0 P. rettgeri 3 2 (67%)  M. morganii 3 3 (100%)  K. pneumoniae 8 7 (87.5%)  K. oxytoca 1 1 (100%)  E. cloacae 7 6 (85.7%)  Enterobacter spp. 1 1 (100%)	E. coli	32	
K. pneumonise   2	P. mirabilis		3 (100%)
R. oxytoca   1	P. vulgaris		2 (100%)
Enterobacter spp. 1 1 (100%)  P. aeruginosa 1 1 (100%)  URINARY TRACT  COMPLICATED)  S. aureus	K. pneumonise	2	2 (100%)
Enterobacter spp. 1 1 (100%)  P. aeruginosa 1 1 (100%)  URINARY TRACT  COMPLICATED)  S. aureus		1	1 (100%)
P. aeruginosa   1			The state of the s
URINARY TRACT  COMPLICATED)  S. aureus <sup>R</sup> S. epidermidis  4 4 (100Z)  Group B Streptococcus  10 9 (90X)  (enterococci)  S. faecalis  2 1 (50Z)  E. coli  43 26 (60X)  F. mirabilis  12 6 (50X)  P. vuigaris  1 0  P. rettgeri  3 2 (67Z)  M. morganii  3 3 (100Z)  K. pneumoniae  K. oxytoca  1 (100Z)  E. aerogenes  1 (100Z)  E. cloacae  7 6 (85.7%)  Enterobacter spp.		- <del>-</del>	
S. aureus   S. aureus   S. epidermidis   A. (100%)	P. aeruginosa	1	1 (100%)
S. aureus   S. aureus   S. epidermidis   A. (100%)	IID TNADV TO ACT		
S. aureus 6 5 (83%) S. epidermidis 4 (100%) Group B Streptococcus 2 2 (100%) Group D Straptococcus 10 9 (90%)  (enterococci) 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. pneumonise 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%)			
S. epidermidis       4       4 (100%)         Group B Streptococcus       2       2 (100%)         Group D Streptococcus       10       9 (90%)         (enterococci)       8       1 (50%)         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%)		the world and the second	
S. epidermidis       4       4 (100%)         Group B Streptococcus       2       2 (100%)         Group D Streptococcus       10       9 (90%)         (enterococci)       3       1 (50%)         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. pneumonise       8       7 (87.5%)         K. oxytoca       1       1 (100%)         E. aerogenes       1       1 (100%)         E. closcae       7       6 (85.7%)         Enterobacter spp.       1       1 (100%)	S. aureus <sup>R</sup>	6	5 (83%)
Group B Streptococcus       2       2 (100%)         Group D Streptococcus       10       9 (90%)         (enterococci)       3       1 (50%)         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%)	S, epidermidis		
Group D Streptococcus       10       9 (90%)         (enterococci)       2       1 (50%)         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 (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%)		<b>2</b>	
(enterococci)       3. faecalis       2       1 (50Z)         E. coli       43       26 (60Z)         P. mirabilis       12       6 (50X)         P. vulgaris       1       0         P. rettgeri       3       2 (67Z)         M. morganii       3 (100X)         K. pneumoniae       8       7 (87.5X)         K. oxytoca       1       1 (100X)         E. aerogenes       1       1 (100X)         E. cloacae       7       6 (85.7%)         Enterobacter spp.       1       1 (100X)		10	
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. pneumonise 8 7 (87.5%)  K. oxytoca 1 1 (100%)  E. serogenes 1 1 (100%)  E. cloacae 7 6 (85.7%)  Enterobacter spp. 1 (100%)	(enterococci)		·
P. mirabilis       12       6 (50%)         P. vulgaris       1       0         P. rettgeri       3       2 (67%)         M. morganii       3 (100%)         K. pneumonise       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%)	S. faecalis	2	1 (50%)
P. vulgaris 1 2 (67%) P. rettgeri 3 2 (67%) M. morganii 3 3 (100%) K. pneumonise 8 7 (87.5%) K. oxytoca 1 1 (100%) E. serogenes 1 1 (100%) E. cloacae 7 6 (85.7%) Enterobacter spp. 1 (100%)	E. coli		26 (60%)
P. rettgeri       3       2 (67%)         M. morganii       3       3 (100%)         K. pneumonise       8       7 (87.5%)         K. oxytoca       1       1 (100%)         E. serogenes       1       1 (100%)         E. cloacae       7       6 (85.7%)         Enterobacter spp.       1       1 (100%)			6 (50%)
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%)	<b>~</b>		
K. pneumonise       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%)			
K. oxytoca       1       1 (100%)         E. aerogenes       1       1 (100%)         E. cloacae       7       6 (85.7%)         Enterobacter spp.       1       1 (100%)			
E. serogenes 1 1 (100%) E. cloacae 7 6 (85.7%) Enterobacter spp. 1 1 (100%)			
E. cloacae 7 6 (85.7%) Enterobacter spp. 1 1 (100%)		. <u>.</u>	
Enterobacter spp. 1 (100%)		Ţ	The state of the s
		<i>'</i>	
Frovidencia stuartii 4 1 (25%)		1.	, _ •
	Frovidencia Stuartii	4	1 (45%)

		BACTERIOLOGIC RESPONSE	
ORGANISM	NO.	ERADICATED	
URINARY TRACT			
COMPLICATED)			
Providencia spp.	1	o	
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 (1007)	
Peptococcus spp.	1	1 (100%)	
INTRA-ABDOMINAL			
S. aureus <sup>S</sup>	3	3 (100%)	
S. aureus <sup>R</sup>	6	5 (83%)	
S. epidermidis	6	6 (100%)	
Streptococcus (Group A)		1 (100%)	
S. viridans group	15	14 (93%)	
Alpha-hemolytic	1	1 (100%)	
streptococus	<b>-</b>	1 (2002)	
Beta-hemolytic	2	2 (100%)	
streptococcus	~	2 (100%)	
Non-hemolytic	2	2 (100%)	
streptococcus	•	2 (100%)	
S. intermedius	4	4 (100%)	
S. mitis	ĭ	1 (100%)	
S. salivarius			
S. sanguis	1	1 (100%)	
S. morbillorum	<del>-</del>	1 (100%)	
	. 2	2 (100%)	
S. bovis	1	1 (100%)	
S. faecium	1	1 (100%)	
Other streptococus spp.	12	9 (100%)	
Group D streptococcus  (enterococcus)		11 (85%)	
S. faecalis	10	7 (70%)	
Haemophilus spp.	1	1 (100%)	
E. coli	89	74 (83%)	
P. mirabilis	9	6 (67%)	
P. vulgaris	Ž.	3 (75%)	
P. rettgeri	1	1 (100%)	
M. morganii	- 5	4 (80%)	
K. pneumoniae	20		
K. oxytoca	3	18 (90%)	
		3 (100%)	
Klebsiella spp.	1	1 (100%)	t the .

5		BACTER IOLOGIC RESPONSE
ORGANISM INTRA-ABDOMINAL	NO.	ERADICATED
MIAA ADDONING	MO.	ERAD I CATED
Enterobacter aerogenes	3	3 (100%)
E. cloacae	6	4 (67Z)
Enterobacter spp.	1	1 (100%)
Enterobacter agglomerans	2	2 (100%)
Rafnia alvei	1	1 (100%)
P. multocids	1	1 (100%)
Citrobacter diversus	1	1 (100%)
Citrobacter freundii	3	2 (67%)
Citrobacter spp.	3	3 (100%)
Acinetobacter	2	2 (100%)
calcoaceticus	_	. (2004)
P. aeruginosa	18	12 (67%)
P. alcaligenes	1	1 (100%)
Pseudomonas spp.	î	1 (100%
Salmonella typhi	î	1 (100%)
Salmonella choleraesuis	i	1 (100%)
Serratia liquefaciens	1	1 (100%)
Lactobacillus	3	3 (100Z)
Bubacterium lentum	1	1 (100Z)
Eubacterium spp.	··· • 2 · · · · · · · · · · ·	
	3	2 (100%)
Propionibacterium acnes		3 (100%)
Propionibacterium spp.	1 4	1 (100%)
C. perfringens	•	4 (100%)
Clostridium spp.	22	22 (100%)
Bifidobacterium	1	1 (100%)
adolescentis	•	1 (1008)
Bifidobacterium spp.	1	1 (1007)
Peptococcus app.	6	6 (100%)
Peptostreptococcus spp.	9	8 (89%)
Bacteroides spp.	21	20 (95%)
B. fragilis	35	34 (97%)
B. melaninogenicus	1	1 (1002)
B. ruminicola	1	1 (1002)
B. bivius	1	1 (100%)
Fusobacterium spp.	<b>9</b>	9 (100%)
Veillonella parvula	1	1 (1002)
Veillonella spp.	1	1 (100%)
ENTERITIS	and the second s	
Campylobacter spp.	1	1 (100%)
Salmonella type B	î	0
nermanerre file n	4	<b>▼</b>

		BACTERIOLOGIC RESPONSE
ORGANISM		
GYNE COLOGIC	NO.	ERADICATED
S. aureusS*	3	3 (100%)
S. aureus R*	8	7 (88%)
5. epidermidis	17	17 (100%)
Alpha-hemolytic	3	3 (100%)
streptococus		` ,
S. viridans group	2	2 (100%)
Non-hemolytic	3	3 (100%)
streptococcus		, ,
Group B streptococcus	20	20 (100%)
Other streptococcus spp.	7	7 (100%)
Group D streptococcus	14	12 (86 <b>Z</b> )
(enterococcus)		•
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 serogenes	2	2 (100%)
Enterobecter cloacae	1	1 (100%)
Enterobacter agglomerans	1	1 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter freundii	1	1 (100%)
Acinetobacter	1	1 (100%)
calcoaceticus		= (====,
Pseudomonas aeruginosa	1	0
N. gonorrhoese	<b>3</b>	3 (100%)
Propionibacterium	1	1 (100%)
granulosum		•
Propionibacterium spp.	1	1 (100%)
Clostridium perfringens	1	1 (100%)
Bifidobacterium spp.	3	3 (100%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	<b>5</b>	5 (100%)
Peptostreptoco is 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%)

ORCANTOM		BACTERIOLOGIC RESPONSE
ORGANISM BACTERIAL SEPTICEMIA	NO.	<b>ውዕ ል</b> ስ ተራልማኝ ስ
DAULATAL DELITORITA	10.	ERADICATED
S. aureus <sup>S</sup>	7	7 (100%)
Micrococcus	1	1 (100%)
S.aureus <sup>R</sup>	21	19 (90%)
S. epidermidis	6	6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic .	1	1 (100%)
streptococcus		, ,
Beta-hemolytic	1	1 (100%)
streptococcus		• •
Group A streptococcus	1	1 (100%)
Streptococcus sanguis	1	1 (100%)
Streptococcus bovis	1	1 (100%)
Other streptococcus app.	10	10 (100%)
Group D streptococcus	4	4 (100%)
(enterococus)		, ,
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	ī	1 (100%)
K. pneumonise	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	ĩ	1 (100%)
Citrobacter freundii	ī	1 (100%)
Acinetobacter	1	1 (100%)
calcoaceticus		
Acinetobacter spp.	2	2 (100%)
Yersinia enterocolitica	<u>1</u>	1 (100%)
Pseudomonas aeruginosa	3	3 (100%)
Serratia marcescens	6	5 (83%)
Serratia spp.	1	1 (100%)
N. gonorrhoeae	$ar{f 1}$	1 (100%)
Salmonella spp.	<u>.</u> 3	3 (100%)
Clostridium bifermentans		1 (100%)
Clostridium spp.	1	
Corynebacterium acnes	ī	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilian	6	5 (83%)
Bacteroides corrodens	1	1 (100X)
Bacteroides	i	1 (100%)
melaninogenicus	-	- (+00%)
Bacteroides spp.	4	<del>4 (100Z)</del>
Fusobacterium spp.	2	2 (100%)
Flavobacterium spp.	1	1 (100%)
ereannecrarium shh.		7 (100%)

		BACTERIOLOGIC RESPONSE	
ORGANISM BACTEREMIA	NO.	<b>ERADICATED</b>	
- 5	_		
S. aureus <sup>S</sup>	1	1 (100%)	
S. aureus <sup>R</sup>	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 <sup>S</sup>	1	1 (100%)	
S. aureus <sup>R</sup>	6	6 (100%)	
S. pneumoniae	1	1 (100%)	
S. sanguis	<b>1</b>	1 (100%)	
Streptococcus spp.	1	1 (100%)	
S. viridens group	1	1 (100%)	
BONE / JO INT			
S. aureus <sup>S</sup>	8	8 (100%)	
S. aureus R	23	22 (96%)	
S. epidermidis	5	5 (100%)	
S. pyogenes	1	1 (100%)	
Beta-hemolytic		2 (100%)	
streptococcus			
Streptococcus spp.	12	12 (100%)	
Group D Streptococcus	5	5 (100%)	
(enterococci)	_		
S. faecalis	<u> </u>	5 (100%)	
E. coli	5		
P. mirabilis	8	<del>5 (63<b>%</b>)</del>	
P. vulgaria	2	1 (50%)	
M. morganii	3	3 (100%)	
Proteus spp.	1	0	
Providencia stuartii	1	0	
Enterobacter aerogenes	3	3 (100%)	
Enterobacter closcae	6	6 (100 <b>%</b> )	
Citrobacter diversus	1	1 (100%)	
Acinetobacter	1	1 (100%)	
calcoaceticus		•	
P. aeruginosa	28	22 (79%)	
The commence of the commence o			

on a wrav		BACTERIOLOGIC RESPONSE
ORGANISM BONE/JOINT	NO.	ERADICATED
	2	
Serratia marcescens	3	1 (33%)
Gaffkya anaerobia	1	1 (100%)
Peptococcus spp.	3	3 (100%)
Pertostreptococcus spp.	1	1 (100%)
Bacteroides fragilis	6	5 (93%)
Bacteroides app.	3	2 (67%)
Fusobacterium spp.	1	1 (100%)
SKIN & SKIN STRUCTURE		
Gemella _	1	1 (100%)
S. aureus <sup>S</sup>	<b>2</b> 5	21 (84%)
S. aureus <sup>R</sup>	116	98 (84%)
S. epidermidis	23	18 (78%)
Alpha-hemolytic streptococcus	11	11 (100%)
S, viridans	3	3 (1007)
	24	3 (100X)
Seta-hemolytic	24	22 (92%)
atreptococcus	20	24 (828)
Group A streptococcus	28	26 (93%)
Group B streptococcus	13	11 (85%)
Group C streptococcus	1	1 (100%)
S. intermedius	1	1 (100%)
Streptococcus app.	38	35 (92%)
Group D streptococcus	30	24 (80%)
8. faecalis	22	19 (86%)
Corynebacterium app.	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%)
d. morganii	14	12 (86%)
K. pneumoniae	11	9 (82%)
K. oxytoca	12	11 (92%)
Klebsiella spp.	· · <b>2</b> · ·	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 app.	5	4 (80%)
Gitrobacter freundii	4	4 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter spp.		2 (100%)
Acinetobacter	6	6 (100%)
UCTURFORRCERT	U	0 (100%)

		BACTERIOLOGIC RESPONSE
ORGANISM		
SKIN & SKIN STRUCTURE	NO.	ERADICATED
Acinetobacter app.	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 anserobia	1	1 (100%)
Clostridium p fringens	ī	1 (100%)
Peptococcus spp.	22	22 (100%)
Peptostreptococcus spp.	13	13 (100%)
Eubacterium spp.	1	1 (100%)
A. eriksonii	î	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	•
Eikenella spp.	î	1 (100%) 1 (100%)
A. fermentans	1	
Fusobacterium spp.	5	1 (100%)
Fusobacterium rusii	1	5 (100%)
		1 (100%)
Veillonella parvula Mixed anaerobes	2 2	2 (100%)
mixed anaerobes	2	2 (100%)
OTITIS		
S. pneumoniae	1	1 (100%)
UPPER RESPIRATORY		
S. aureusR	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 <sup>R</sup>		i (100%)
	-	+ (1004)

BRAIN ABSCESS	NO.	ERADICATED
S. aureus <sup>R</sup> SAFETY	1	1 (100%)
NO. OF CASES EVALUABLE		1,696
NO. OF PATIENTS WITH LOCA	AL SIDE EFFECTS -	79 (4.7%)
NO. OF PATIENTS WITH SYST	TEMIC SIDE EFFECTS	181 (10.7%)
LOCAL SIDE EFFECTS		

	NO.	Probably Not	Possibly	Probably	Definite
Infused vein pain	17 (1.0)	<b>(0,3%)</b>	4 (0.2%)	5 (0.3%)	3 (0.2)
Infused vein induration	11 (0.6)		4 (0.2%)	5 (0.0%)	3 (0.2
Infused vein infection	3 (0.2		1 (0.12)		
Erythema I.V. site	13 (0.8		6 (0.4%)		
Phlebitis/	56 (3.3)		24 (1.42)	22 (1.3%)	7 /0 /
thrombophlebitis	JU (3.3/	5 (0.2%)	24 (1.4%)	22 (1.3%)	7 (0.4
SYSTEMIC SIDE EFFECTS					
Anxiety	1 (0.0	5%) 1 (0.05%)			
Confusion	4 (0.2	<b>3</b> (0.15%)	1 (0.05%)		
Seizures	11 (0.6	<b>4</b> (0,2%)	3 (0.15%)	4 (0.2%)	
Encephalopathy	1 (0.0		• • • • • • • • • • • • • • • • • • • •	1 (0.05%)	
Dizziness	6 (0, 3)		1 (0.05%)	1 (0.05%)	3 (0.1
Vertigo	2 (0.13	•	2 (0.1%)	. (,	- (
Headache	5 (0,3)		2 (0.1%)		
Myoclonus	2 (0.13			2 (0.1%)	
Meningitis	1 (0.0		1 (0.05%)	~ (=	
Intracerebral hemorrhage	1 (0.0			<u> </u>	
Paresthesia	1 (0.0				1 (0.
Somnolence	3 (0,1	5%)	1 (0.05%)	2 (0.1%)	
Nystagmus	1 (0.0				
Asthenia/weakness	2 (0.1)		1 (0.05%)	the second of th	1 (0.
Chest discomfort/pain	4 (0.2)		1 (0.05%)		_ ( - (
Syncope	1 (0.0		- (,		
Hypotension	10 (0.6	•	3 (0.15%)	3 (0.15%)	
Palpitation	2 (0.1		2 (0.1%)	0 (0,125//)	
Tachycardia	1 (0.0		1 (0.05%)		
Apnea	2 (0.1		_ (======		
Dyspnea	2 (0,1		1 (0.05%)		
Hyperventilation	1 (0.0		- (		1 (0.
Hemoptysis	1 (0.0				_ \
Respiratory distress	1 (0.0				
syndrome	_ (***	= (			

SYS	TEMIC	SIDE
-		

EFFECTS		Probably	Possibly	Probably	Defiri
	NO.	Not		·	
Cyanosis	1 (0.05%)		1 (0.05%)		
Septic Shock	2 (0.1%)	2 (0.1%)	_ (******/		
Flushing	1 (0.05%)	_ ( - ( )			1 (0.
Fever	10 (0.6%)	2 (0.1%)	5 (0.3%)	1 (0.05%)	2 (0.)
Chills	2 (0.1%)	2 (0.17)	- (-,-,/	2 (0.05%)	2 (0.
Hyperhydrosis	2 (0.1%)	1 (0.05%)	1 (0.05%)		
Facial edema	1 (C.05%)	, , ,	- (	1 (0.05%)	
Pruritus	6 (0.3%)	1 (0.05%)	J (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%)			* (A.TW)	1 (0.
Polyarthropathy	1 (0.05%)		1 (0.05%)		× (0.
Thoracic spine pain	1 (0.05%)		- (0.00%)		1 (0.
Pharyngeal pain	1 (0.05%)			1 (0.05%)	1 (0.
Increased salivation	1 (0.05%)			1 (0.05%)	
Glossitis	1 (0.05%)			1 (0.03%)	1 (0,
Brown tongue	3 (0.2%)			3 (0.2%)	1 (0,
Heartburn	2 (0.1%)		1 (0.05%)	1 (0.05%)	
Hiccups	1 (0.05%)	1 (0.65%)	Z (0,00m)	1 (0.05%)	
Neusea	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%)	3 10
Pseudomembranous colitis	3 (0.15%)	1 (0.034)	z (0.05%)	3 (0.15%)	
Hemorrhagic colitis	1 (0.05%)			1 (0.05%)	
Oral candidiasis	1 (0.05%)			* (0.00#)	1 ((
Vaginal candidiasis	1 (0.05%)		1 (0.05%)		* /,
Pruritus vulvae	1 (0.05%)	-	1 (0.05%)		
Menorrhagia	1 (0.05%)	1 (0.05%)	- (01000)		
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%)		~ (U.UJA)	
Hearing loss	3 (0.15%)	2 (0.1%)	1 (0.05%)	<u> </u>	
Tinnitus	1 (0.05%)		1 (0.05%)	Committee an arms are a second on the second	
A TOTAL CONTROL OF THE CONTROL OF TH		Definitely	Probably	Probably	

	NO.	Definitely Not	Probably Not	Probably
DRATHS	£8 (5,3%)	83 (5.0%)	4 (0.2%)	1 (0.1%)

#### Abnormal Laboratory Tests

	1		
Dect eased RBCs	.1.	(0.17)	
Decreased hemoglobin	17	(1.07)	
-Decreased hematocrit	14	•	
Decreased WBC	22	(1.37)	
Decreased neutrophils	10	(0.67)	
Increased lymphocytes	2	(0.17)	
Increased monocytes	- <b>13</b>		
Increased eosinophils	69	The state of the s	the second of the second of the second of
Increased basophils	3	(0.27)	
Increased platelets	27	(1.67)	
Decreased platelets	12	(0.72)	
Prothrombin time (abnormal)	13	(0.82)	
Increased BUN	10	(0.61)	er ere i de la cale de
Increased blood urea	4.	(0.27)	The second secon
Increased creatinine	13	(0.8%)	
Increased bilirubin	13	(0.87)	
Increased AST (SGOT)	76	(4.52)	
Increased ALT (SGPT)	83	(4.97)	
Increased alkaline phosphatase	61	(3.6Z)	
Increased LDH	6	(0.47)	
Increased blood glucose	<b>2</b> _	(0,17)	_
Increased potassium		(0.12)	
Decreased potassium	1	(0.17)	
Increased chloride		(0.2X)	
Decreased chloride	* *** **** * * * * * <b> </b>	(0.17)	**
Positive Coombs' test	33	(1.97)	The first of the second
Urine protein		(0.42)	
Urine RBCs	6_	(0.42)	
Urine WBCs	9	(0.5Z)	
Urine epithelial cells		(0.17)	
Urine casts		(0.37)	<u>andra and an ann an an</u>
Urine bilirubin	3	(0.27)	
Urine urobilinogen		(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

			DRUG RELATIONSHIP					
		Probably	Possibly	Probably	Definit			
-	NO.	Not						
LOCAL SIDE EFFECTS								
Infraion site ulcer	1 (0,07%)			1 (0.07%)	2 (0.1			
Intused vein induration	1 ((0.07%)			1 (0.07%)	2 (0.1			
Erythema I.V. site	5 (0.4%)	3 (0,22%)	2 (0,15%)	1 (0,074)				
Phlebitis/	53 (3.9%)	12 (0.9%)		21 /7 545	7 (0 5			
thrombophlebitis	23 (3,98) ·	12 (0.34)	13 (1.0%)	21 (1.5%)	7 (0.5			
SYSTEMIC SIDE EFFECTS								
Nervousness	1 (0.07%)			1 (0.07%)				
Insomnia	1 (0.07%)		the same of the same of the same of	1 (0.07%)				
Disorientation	1 (0.07%)		1-(0,07%)	~ ( 3707 M )				
Tremor	2 (0.15%)		2 (0.152)	The same of the sa				
Hallucinations	1 (0.07%)		1 (0.072)					
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%)	J . J . J . J . J	1 (0.07%)	2 (0.012),				
Hemiplegia	1 (0.07%)	1 (0.07%)	1 (0.0/A)					
Vertigo	1 (0.07%)	1 (0.07%)						
Heada che	3 (0,22%)	2 (0.15%)		1 (0,07%)				
Chest discomfort	1 (0.07%)	1 (0.07%)		1 (0,0/2)				
Asthma	1 (0.07%)	1 (0.07%)						
Pulmonary embolism	1 (0.07%)	1 (0.07%)						
and infarction	1 (0.0/%)	T (OLOIN)						
Cardiac arrest	1 (0.07%)	1 (0.07%)						
Cardiogenic shock	1 (0.072)	1 (0.07%)						
Tachycardia		T-(0-0/A)	the state of the s					
	2 (0.15%)	1 (0 078)	1 (0.07%)	1 (0.07%)				
Atrial fibrillation	1 (0.07%)	1 (0.07%)		And the second second				
Transient ischemic shock	1 (0.07%)	1 (0.07%)						
Myocardial infarction	1 (0.07%)	1 (0.07%)		The state of the	-			
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%)			<del>2 (0.15%)</del>				
Petechiae		1 (0.07%)						
Pruritus	7 (0.5%)		2 (0.15%)	5 (0.42)				
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 (0.072)		, - ,,	1 (0.07%)	- \			
	1 (0.07%)	to the contract of the contrac		1 (0.07%)				
Skin inflammation	+ ( V + V / H )							

					DRU	G RELATION	SHIP			
			1	robably	Po	ossibly	Pr	obably	Def:	nitely
SYSTEMIC SIDE EFFECTS	NO	·		Not						
Pharyngeal discomfort	1 (0	.07%)			1	1 (0.07%)				
Dry-mouth	2 (0	.15%)				2 (0.15%)				
Glossitis	2 (0	.15%)					2	(0.15%)		
Heartburn	1 (0	0.07%)						(0.072)		
Nausea	38 (2	.8%)	1	(0.07%)	13	(0.9%)		(1.72)	1	(0.07%
Vomiting	19 (1	. 4%)		(0.07%)		(0.4%)		(0.97)		(0.07%
Diarrhea	38 (2	.8%)		(0.67)		(1.2%)		(0.87)		(0.15%
Gastroenteritis	1 (0	0.07%)				(0.67%)		, , ,,	_	(
Abdominal cramps	2 (0	15%)				, ,	1	(0.072)	1	(0.07%
Abdominal pain	5 (0	.4%)	2	(0.15%)	1	(0.07%)		(0.15%)	_	
Pseudomembranous colitis	2 (0	15%)						(0.071)	. 1	(0.07%
Oral candidiasis		37)						(0.37)	_	<b>1</b> - • - • · ·
Taste perversion	4 (0	3%)	1	(0,07%)	2	(0.15%)		(0.072)		
Visual disturbance	1 (0	.07%)				(0.07%)		<b>\</b> = <b>\</b> - \ \ - \ \ \ \ - \ \ \ \ \ \ \ \ \ \		-
Paralytic lens		.07%)			-	· ·	1	(0.071)		
Tooth discoloration	7	0.07%)	1	(0.07%)			_	<b>,</b> - <b>,</b> - , - , - ,		
<b>Hematuria</b>	-	15%)		(0.07%)	1	(0.07%)				
Abnormal arine color	•	22%)		(0.07%)		(0.07%)	1	(0.07%)		

Adverse Exper	iences in	133 Patients	(usually one	dose

	_				
		Probably	Possibly	Probably	Definitel
SYSTEMIC SIDE EFFECTS	NO.	Not			
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 (0,3%)	
Hyperhydrosis	2 (1.5%)			2 (1.5%)	** * * * ** *** * * * * * * * * * * * *
Urticaria	1 (0.8%)		1 (0.8%)		
Taste perversion	1 (0.8%)	<del> </del>	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. Ecsinophils 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 MORMAL RANGE POST NOA SAFETY UPDATE 1369 PATIENTS

	, <b>∤</b> ¶.	Prob.					
	Mot	<u>Hot</u>	Poss.	Prob.	Def.	Total	
• • . ' .							
Hemoglobin decrease	2	4	1	1	0	8	.58
Humatocrit decrease	1	5	2	0	0	8	.58
MBC decrease	3	2	6	3	ì	15	1.1
MBC increase	4(1)	4	1	0	0	9(1)	. <b>6</b> 6
Neutrophils decrease	0	0	1	0	0	1	.07
Seg. Neutrophils decrease	1	1	4	5	0	11	.60
Lymphocytes decrease	0	3	0	0	0	3	.22
Monocytes increase	2	1	4	1	0	8	.58
Eosinophils increase	1	4	21	13	2	47	3.4
Atypical Lyc	0	1	0	0	0	4	.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 Norph. 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)		0	27(6)	2.0
Bilimbin increase	4	5(1)	_	1	0	12(1)	.86
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	•	0	65(1)	4.7
<b>GCT</b>	0	0	0	1	0	1	-07
81. Glucose	1(1)	1	n	0	0	<b>S(1)</b>	. 15
S. Lectate	0	1(1)	b	0	0	1(1)	.07
S. Uric Acid	1	0	0	0	0	)	-07
S. Sedium	1	0	0	0	Đ	1	.07
S. Potassiem	2(1)	5(1)	2	0	0	9(2)	
S. Chloride	0	1	4	1	0	6	.44
Magnesium	1(1)	0	0	0	0	1(1)	.07
Counts (+)	1	1		17	0	27	2.0
Urine Protein	1	S	4	1	0		.58
Urine teles					<u> </u>	11	.80
Urine RECs	<b>5</b>		0	0	<u>0</u>	<u> </u>	.66
Urine Epithelial Cells	2	0	0	. 0	0	2	. 15
Urine Casts	0	-	1				.07
MBC Casts	0	0		<b>-</b>	-0		.07
Calcium Oxalate Crystals	0	3,	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-cualified 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:

- 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 (penicilinase producing strains), Group D streptococci
  (enterococci), E. coli, Klebsiella species, Enterobacter species, Proteus
  vulgaris, Providencia rettgeri, M. morganii, P. seruginosa.
- 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. epidermidia, 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

The proposed package insert for Primaxin was discussed with representatives Review of Package Insert 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).

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

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

Page 12, under Skin and Skin Structure Infections, underline Peptococcus and Peptostreptococcus.

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 Conclusions.

MSDRL should be notified of the above labeling revisions.

Merceles 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

2945

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# Drug Control Review Notes #3

In ectable combination of imipenem and cilastatin sodium NDA #50-587

Dosage Form:

Submissions Reviewed:

Original dated: May 3, 1984 Amendments dated: August 22, 1985

c. Providing for: Draft Labeling

### Names:

imipenem and cilastatin Trade: Primaxin

1- The applicant has completed labeling deficiencies by submission of an adequate draft package insert, dated May 3, 1984. This submission adequate draft package insert, the manufacturing controls viewmoint arovides adequate labeling from the manufacturing controls. adequate draft package insert, dated may 3, 1984. Inis submission provides adequate labeling from the manufacturing controls viewpoint. provides adequate labeling from the manufacturing controls viewpoint.

All outstanding microbiological issues concerning spectrum, the statements susceptibility testing breakpoints have been rectified and the statements in the labeling are satisfactory. Remarks:

2- A satisfactory (GIP evaluation was received, dated July 26, 1985. in the labeling are satisfactory.

3- The certification monographs have not been negotiated with the ine 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 on proceeding and controls provided by the applicant concrusions: the manufacturing and controls provided by the applica are approvable, pending su coessful negotiation of a proposed draft and controls commitments. James R. King, 9/12/85

certification monograph.

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

### 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 Staphylococcus aureus.

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

### EFF ICACY

		CLINICAL	RESPONSE			
INFECTION	NO	CURE	IMPROVE	FAIL		
Endocarditis	14	11 (79%)	2 (14%)	1 (7%)		
·		BACTERIOLOGIC RESPONSE				
Organism S. aureus(S)		ERADICATED	NO	ERADICATED		
S. aureus(S)	3	3 (100%)	5			
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 Endocarditis	No. 21	Cure 18 (86%)	<u>Improve</u> 1 (9%)	Faii 1 (5%)
Organism	No.	Bradicated	<u>.</u>	
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.





### Drug Control Review Notes #2

Form 5 # 50-587

Rx thienanycin derivative/ dihydropentidase inhibitor

Applicant: Merck, Sharp, & Dohme Research Laboratories

West Point, PA 19486

### Submission Reviewed:

a. Original Dated: May 3, 1984b. 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 "mission should be deleted from the original draft package insert submitted May 3, 1984. As a large limit 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:

Pseudomonas aeruginosa ATC 27853

Breakpoints 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.

3-

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.

### 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.
- 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.

Junes- R. King 3/15/85

James R. King, 1/10/85

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

	DRUG CONTROL REVIEW HOTES		I. TYPE		2. NS. 50-587
	SPONSOR	,			S. SUBMISSIONS
	Merck, Sharp & Dohme Research Labo	pratories			A DRIGINAL DATED
4.	ADDRESS			<del> </del>	May 3, 1984
٧	lest Point, PA 19486				CSTAG STHEMONEMA .
Se.	PROVIDING FOR				
6.	a. TRADE				
İ					
į	Primaxin A. NON-PROPRIETARY	<del></del> ;			
l	a. Henry near 2 range				
ļ	imipenem and cilastatin				
ĺ	G. CHEMICAL N-formimidoyl thienamyci	n monohydra	ate and [	Z,7(R), 2	(S)]-7- ((2-amino-2-
=	carboxyethyl)thio]-2-[[(2,2-dime	thylcyclop	ropyl) car	rbony]]am	ing -2-heptanoic a
NAME (S)	d. ESTAB	7. STRUCTUR			monasodium salt.
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ĺ	e. USAN	C#3 -	CHTI	)-SCH	L-CH2-NHCH=NHL
į	imipemide/none designated		- J K!	$\neg$	·H20
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	none designated	CACH		the said	EX. P
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<u> </u>	ASLATED NOA. INC. MF. FORM 5'3	1	·		
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12.	REMARKS				
				<u> </u>	
13	CONCLUSIONS				
	Manufacturing and Controls are in	adequate.			

- 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	1 y =	$\sim 1$ (	1	1/-
6/13/84	James 2	King .27	142 /1	1:41-6	128/34
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and the second of the second o			HFN-815	/JRKing/6/2	25/94/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 "lay 31, 1984.

5- Laboratory Controls

Adequate for in-house release

1- Components and Composition	Adequate	
2- Source and Synthesis	<u>Adequate</u>	
??.		9.00
	en e	
√ 3- Raw Materials	Adequate	
	The state of the s	<u>C 30</u>
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Adequate for a shelf-life of 18 months

<u>Adequate</u>

Inadequate

Control Numbers

Stability

8- Labeling

a- Draft vial and carton labels

Adequate draft vial and carton labels were filed.

b- Package Insert

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

Streptococcus agalactiae (Group B) -Streptococcus Group C · Streptococcus Group G

Salmonella spp.

Citrobacter spp. Enterobacter agglomerans

Mafnia alvei Yersinia enterocolitica Yersinia pseudotuberculosis Bordetella bronchiseptica

Shouldget C. vorg. nalis ms. C. 4p. Haemophilus parainfluenzae Con Gardnere la spp.

·Campylobacter spp.

-Acinetobacter spp.

Achromobacter Alcalinenes spp. Moraxel 3 spp.

# NEW ANTIBIOTIC APPLICATION Merck Sharp & Dohme Research Laboratories

PRIMAXIN for Injection (Imipenem and Cilastatin Sodium, MSD)

Section 3a

3a. Name and location of each plant conducting the operations.

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**1**,

Bacteroides asaccharolyticus
B. bivius
B. disiens
B. distasonis
B. ovatus
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

<u>Adequate</u>

Bacteroides asaccharolyticus

B. bivius

B. disiens

B. distasonis

B. ovatus

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

# AA

### REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 50-587 (Original Submission)

Date Review Completed: 6/18/85

Applicant: Merck Sharp & Dohme

Drug: Primaxin<sup>R</sup> (Imipenem/Cilastatin Sodium; MK 789/MK-791)

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

### Chemical Names:

Imipenem: [5 R - [5 a, 6a (R\*)]] -6-(1-hydroxyethy1) -3- [[2-liminomethy1)] amino] ethyl] thio] -7-oxo-1+ azabicyclo [3,2,0] tept-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 [PrimaxinTM (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<sub>3</sub> \* 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 formanidine derivative of thienamycin via the NH3 <sup>†</sup> 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." 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;
- if coadministered with imipenem, a substantial increase in urinary recovery of the antibiotic (intact);
- 3. virtually no influence on plasma level (systemic availability) of impenem;

- 4. blockage of the metabolism of the drug by two routes: (a) glomerular filtration, and (b) tubular excretion (secretion?)\*;
- 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;
- 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 <u>in vitro</u> or <u>in vivo</u> 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 ha 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 mankey.

# 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 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 the ephrotoxicity of cephaloridine.
- 2. The D(-) isomer of constatin has no enzyme-inhibiting activity, but is still capable of preciting nephrotoxicity of both imipenem & cephaloridine by blooming their entry into the tubular epithelial cells. The metabolism of appenem 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 & 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 Tack 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. ( an inhibitor prevents the formation of this metabolite. It is not considered to be nephrotoxic. The identity of metabolite II is unknown. It 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 Imipener

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 14C-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 (14c & 35s) 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 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 14C-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, Y-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 35S-RA vs. 14C-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. J. 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 RP 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

NDA 50-587 Page 8

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, iminenem 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 nice 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, HP, recommon 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/Cilastatir 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 LN50 values for imipenem in both species ranges approx. 1500 to greater than 2000 mpk with no sexor 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 LD50 values in mice & rats are greater than 10 gm/kg. IV LD50 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 LD50 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.
- 8. 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 F1 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 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 malliple-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" custion of this review.

The protective effect of cilastatin on iminenem-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 incutation 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 & nigher 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. 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. 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 Mat, "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 F1 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. <u>Drug Interaction</u>: 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.
- P. 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.

cc: Orig. NDA - 1/16/85 HFN-815/110

CSO HFN-340 HFN-815/LBuko/smc/8/27/85 R/d init.by:JMDavitt 0045p Lorant Buko, D.V.M., M.Sc.

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### Statistical Review and Evaluation

Date:

AUG 29 1985

NDA #: 50-587/Drug Class: 16

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. (HFH-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 and 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 ethologic 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, 1.8%).

### 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 favon 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 baseling when the exception that Primaxin patients had a significantly greater in the diagnostic therapy procedures, polymicrobial infections and 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 dyration of therapy for Primaxin evaluable patients was 9.5 days whereas that for Cefazolin patients was 8.9 days.

### Conclusions

I. 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.

Yames 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

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Table 1 Summary of Results for Evaluable Patients - All infectious organisms

Diagnosis		Drugs	Z	# Pathogens	Eradicated	Clinically Improved	Duration of Therapy (days)
Skin & Skin Structures Gynecologic Lower Respiratory Intra-Abdominal	(29%) (18%) (16%) (8%)	Primaxin Moxalactam	153	303 208	89.4% 92.3%	944 80%	11.0 8.8
Intra-Abdominal Lower Respiratory Skin & Skin Structures Genitourinary Tract Bloodstream	(31%) (22%) (20%) (20%) (11%)	Primaxin Gent./Clind.	89	112	91.12 81.24	98% 89% (p=0.02)	11
Intra-Ardomiral Infections	- 3	Primaxin Gent./Clind.		61	98% 74% (p=0.002)		
Septicemia Pneumonia Wound infection Bronchopneumonia Intra-Abdominal	(2000) (2	Primaxin Cefotaxime	70	128 102	80.5% 88.2%	84 84 80 80 84 8	:
Skin & Skin Structures Lower Respiratory Upper Urinary Tract	(60%) (14%) (9%)	Primaxin Cefazolin	108	177	88.18 91.8%	94% 96%	တာ ထ ကေတာ

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	882
Cefotaxime	55	93%
Primaxin	67	388
Cefazolin	68	3001

# 

Imipenem/Cilastatin Sodium
Injection (I.V.)
Sterile Powder (250 mg & 500 mg)
Form 5 50-587;030885
Reviewer: Raja Velagapudi, Ph.D.
Wang

Merck Sharp & Dohme Submission Dated: March 8, 1985

FEB 14 S86

### 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

Fild fillactor fields Lyal autitor branch

RD Initialed by J.P. Hunt FT Initialed by J.P. Hunt

cc: Form 5 50-587 Orig., NEW-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

G. References	<b>V</b> OLUME	STARTING PAGE
1. Annotated Package Circular.	2.84	IV=00086
<ol> <li>A Preclinical Evaluation of MK-0787, a broad Spectrum Antibiotic, and MK-0791, an Inhibitor of the Metabolism of the Antibiotic. Section D - Biochemical, Metabolic, and Pharmacological Studies.</li> <li>Wise, R., Andrews, J. M., and Patel, N. N-Formimidoyl-thienamycin a powel Selector.</li> </ol>	2.84	IV-00126
with other 8-lactam antibiotics. J. Antimicrob. Chemother. 7, 521-529 (1981).	2.85	IV-00417
4. An open, single-dose tolerance and pharmacokinetic study of thienamycin-formamidine in healthy volunteer subjects. A. M. Geddes, M.D., Study #501.	2.85	IV-00426
5. An open, single-dose, tolerance and pharmacokinetic study of thienamycin-formamidine (TF; MK-787) in healthy volunteers. F. Follath, M.D., Study #503.	2.85	IV-00539
formamidine (TF; MK-787) to study the variability in postrenal metabolism between subjects and between occasions within subjects and to determine the effect of probenecid on blood concentrations and urinary excretion of MK-787. S. R. Norrby, M.D., Study #504.	2,85	IV-00615
7. A double-blind, single, rising-dose, placebo-controlled study to determine a) the safety and tolerability of MK-787, and b) the pharmacokinetic profile of doses of 250, 500, 750, and 1000 mg of MK-787 given intravenously to 12 healthy volunteers. F. G. McMahon, M.D., Study \$1.		
	2.86	IV-00740
8. An open, multiple-dose study to investigate the toler- ability of MK-787 (thiensmycin-formamidine) in healthy volunteers. S. R. Norrby. M.D., Study #505.	2.86	IV-00885
<ol> <li>A double-blind, placebo-controlled, dost-ranging study in healthy male volunteers to investigate the tolerability of single and multiple doses of L-642,957.</li> <li>P. J. DeSchepper, M.D., Study #506.</li> </ol>	2.86	IV 35
10. An open, two-treatment, single-dose study in healthy volunteers to determine the metabolic disposition of MK-787-Cl administered alone and in combination with MK-791. S. R. Norrby, M.D., Study #545.		
	2.86	IV-01032

NDA: 50-587 SPONSOR: MERCK SHARP & DOHME 3 OF 3 TRADE: PRIMAXIN GENERIC: IMIPENEM

# Biopharmaceutics Summary

### List of Attachments

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		PAGE
11. At open, randomized, three-treatment, single-dose study in healthy volunteers to investigate the metabolic disposition of MK-791-14C administered alone and to	e para ser apopa a resapensa e apopera serse.	eri ge geran a on san met voqean a vykon oppga ong sagem
sition of MK-791-14C administered alone and in combination with MK-787. S. R. Norrby, M.D., Study #612.	2.87	IV-01206
12. An open study to determine the tolerability, safety, and pharmacokinetic properties of single doses of MR-787 and MK-787 plus L-642,957 (Dehydropeptidese Inhibitor; DHI)		رو به مساور استان و مساور استان و استان استان استان اس
in healthy volunteers. S. R. Norrby, M.D., Study \$507.	2.87	IV-01351
13. In open, randomized, single-dose, within-subject dose titration study in healthy volunteers to determine the phermacokinetic properties of combinations of MK-787 and MK-791. S. R. Korrby, M.D., Study #515.	2.88	IV-01631
14. A double-blind, placebo-controlled study to investigate		
the safety and tolerability of multiple doses of MK-787 (1000 mg) administered concomitantly with MK-791 (1000 mg) for 10 days. G. Drusano, M.D., H. C. Standiford		
M.D., Study #42.	2.89	IV02081
15. A double-blind, parallel, multiple-dose, placebo- controlled study to determine the safety and tolerability of multiple doses of MK-787 (250 mg) administered con- comitantly with MK-791. F. G. McMahon, M.D., Study \$2.	2,89	IV-02332
16. A double-blind, parallel, multiple-dose, placebo- controlled study to determine the safety and tolerability of multiple doses of MK-787 (500 mg) administered core		
comitantly with MK-791 (500 mg). F. G. McMahon, M.D., Study #4.	2.90	JV-02452
17. An open, randomized, single-doso pharmacokinetic study to		
determine the effect of probenecid on plasma concentra- tions and urinary excretion of MK-787 and MK-781		
following the concomitant administration of MK-787/MK-791/Probenecid. D. S. Reeves, M.D., Study #526.		
	2.90	IV-02578
18. An open study to determine the pharmacokinetics of single 1.v. doses of MK-787 and MK-787 plus MK-791 given concomitantly in patients with varying degrees of renal in-		
surriciency and in subjects with normal renal function.	Marian and San San Alberta San San San San San San San San San Sa	e also e estat de la cataloga de la
M. Z. DeBroe, M.D., G. A. Verpooten, M.D., L. Verbist, M.D., Study #513.	2.91	IV-02886

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IV-03688

# Biopharmaceutics Summary

# STARTING VOLUME STARTING VOLUME PAGE 19. An open, single-dose, crossover study to determine the pharmacokinetics of dehydropeptidase inhibitor (MK-791) given concomitantly with thienawycin forwamidine (MK-787) in a 1:1 ratio versus dehydropeptidase inhibitor (MK-791) given alone in healthy subjects and patients with verying degrees of renal failure. T. P. Gibson, H.D., Study \$5. 20. An open, multiple-dose study of the safety, tolerance, and efficacy of thienawycin formamidine/potentiator (MK-787/MK-791) in the parenteral therapy of urinary

(MK-787/MK-791) in the parenteral therapy of urinary tract infections in 20 hospital sed patients. W. L. George, M.D., Study #19.

21. MK-787 Bioassay Procedure.

22. EPLC method for the determination of MK-787 in plasma.

MPLC method for the determination of MR-787 in urine.
 Analytical procedure for the determination of MK-791 free acid in plasma, stabilized urine, and stabilized infusion solutions.

4-10-04 Antibiotic Cortification Anguest Labeling withe Submission MINA \$8-327 Norch Sharp and Bohne Research Laboratories Assotated Package Circular PEIMAZININ (Imipenes/Cilestatin Sodium, MED) PRIMAXINA (Laipenes-Cliartatia Sodium, 2020) is a fosmulative of imipenes. Cliartatia Sodium, 2020) is a fosmulative of imipenes, a thieramycia antibiotic and dipoptidase, dehydropoptidase I, with wedium bicarhonate added as a buffer. I PAIMAXIN is a patent broad spectrum antibecterial agent for intravances administration. Imipenes (M-forminidopthieramycia monohydrate) is a prysicalize derivative of thieramycia, online is produced by threshources sattlers. Its chemical name is [5 m [3 4 (m) ]] -6 (m) [1 - 4 (m) ]] -4 (m) [1 - 4 (m) [ Titem 2. Composition of the Brug (Vol. 7. Page 8000)

Stem 9:C.IV Controlled Clinical Studios - Entroduction Fiton 9.8.1 - Mirrobiological Studies, Rrepp. et el. 2966. Antisteropial Egonts and Chemoth 12 (6): 9+3-3000. hept-z-ene-z-earbysylic seld monohydrate. It is an super-come-z-carporayite seid monohydrate. It is an off-white, nonlygrotorpic erystelline compound with a nonleonier-weight-of 12137. It is sparingly soluble in-weight, and slightly soluble in methanol. Its its structural formula is (1,0) and Sites 2; Composition of the Brig (Val. 2.1 , page 8090) \_\_\_. Page\_\_\_\_\_\_\_\_\_\_ Fitom 9.A.1 - Chapical Structural Formula ATRAGEMENT OF MERCE & CO., INC. - Page 00417 COPYRIGHT 1984 MERCE & CO., INC. All rights reserved Antibiotic Cortification Soquest MOS 50-587 Morek Sharp and Dobne Hesearch Laboratories Associated Fookage Circular FRIMAXININ (Imipensa/Cilestatis Sotium, MES) Chinical PRANTACOLOGY
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15 (Vol. 2.84 , page 1V-00024 )
15 appendix IV, Biophermacouties Report, (Vol. 1.84 , page 17-00034 )
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Antibiotic Cortification Request

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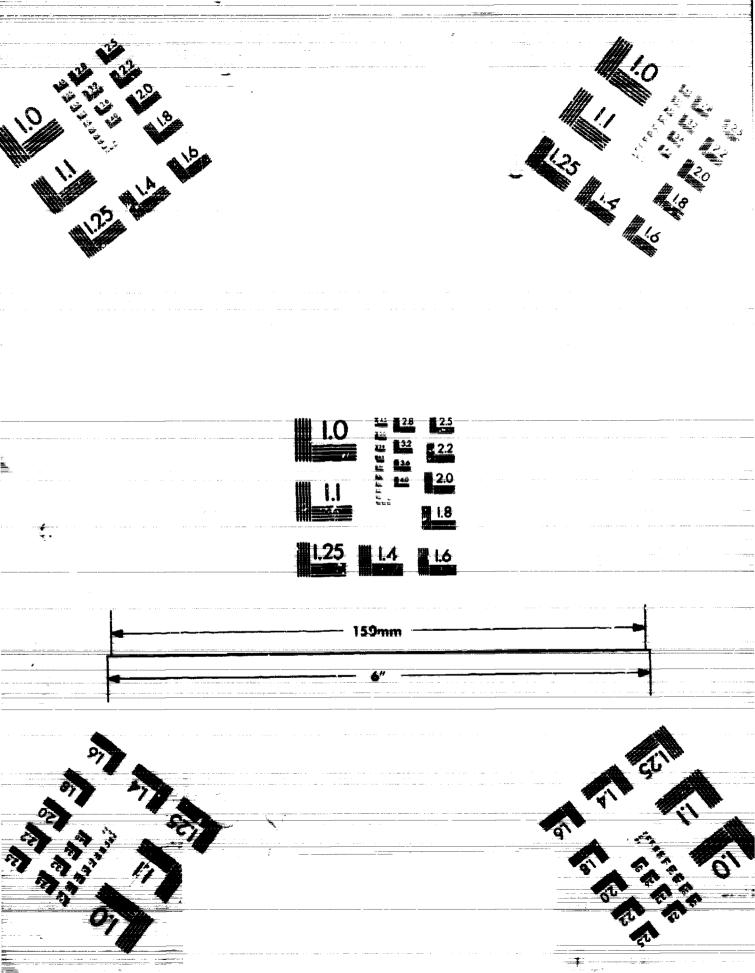
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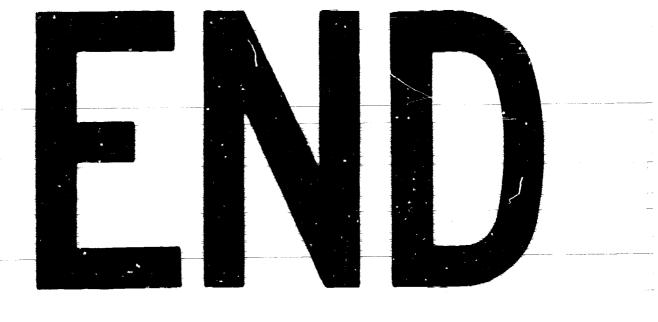
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### Addendum to Medical Officer's Reivew of NDA 50-587

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 Staphylococcus aureus.

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

### EFF ICACY

		CLINICAL	RESPONSE	
INFECTION	NO	CURE	IMPROVE	FAIL
Endocarditis	14	11 (79%)	2 (14%)	l (7%)
		BACTERIO	LOGIC RESPO	ONSE
Organism S. aureus(S)		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.

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M.O. Review #1

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-[5 $\alpha$ , 6 $\alpha$ , (R)]]-6-(1-nydroxyethyl)-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 MKO787, is the approved name (USAN) for N-formimidoyl thienamycin, a broad spectrum antibiotic.

<u>Cilaslatin</u>, also know as MKO791, 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.

Imipemide was transiently used to refer to N-formimidayl 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.

M.O. Review #1

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

(1) Generic: Imipenem and Cilastatin Sodium

(2) Trade: PRIMAXIN

(3) Chemical:

Imipenem [ $5R-[5 \propto , 6 \sim , (R)]]-6-(1-hydroxyethy!)-3-[[2-[(iminomethyl) amino] ethyl] thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate.$ 

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

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

Primaxin, also known as MKO787/MKO791, is a broad spectrum, antibiotic consisting of equal parts of imipenem and cilastatim.

### (4) Chemical Structure

### Imipenem

$$H_3CCH$$

$$SEG_2CF_2NHCH = NH2$$

$$CO_2$$

$$H_3C$$

### Cilastatin Sodium

### B) Pharmacologic Category

Imipenem is a new broad spectrum teta-lactam antibiotic.

<u>Cilastatin</u> 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 C3 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 tysis accounts for the bactericidal nature of thienamycin activity. Biochemical studies indicate thienamyc's 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 <u>P. aeruginosa</u>, 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 I and 2

TABLE 1

## AGAR DILUTION SUSCEPTIBILITY TEST MIC (mcg/nl) of

STRAIN (	105CFU)	IMIPENEM	TIM	CFX	CEF	CAB	GEN
0	2025	2 2			•		0.7.
S. aureus	2985	0.01	0.02	3.2	0.2	0.63	9.32
S. aureus	210	0.02	0.04	3.2	0.4	1.3	0.33
S. aureus	2874	0.02	0.04	3.2	0.2	1.3	0.13
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	44280	20.0	40.0	>100	>100 25 °	80.0	5.0
Enterococcus	2864	0.63	1.3	> 100	25.0	40.0	10.0
Enterococcus	2362	1.3	2.5	>100	25.0	40.0	20
Enterococcus	2863	40.3	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	0.03	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 <b>.</b> 63	25.0	>100	08 <	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	2647 <sup>C</sup>	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	<i>-</i> 100	20.0	0.63
Enterobacter spp.	2903	0.63	1.3	<b>&gt;</b> 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.ບ	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	<b>&gt;</b> 20
Klebsiella spp.	2888	0.63	1.3	>100	>100	10.0	1.3
Klebsiella spp.	2890	13	1.3	2100	> 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	$\frac{1}{2.5}$
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, thlemanycin, CFX, cefoxitin, CEF, cephalothin, CAB, caroenicillin; GEN, gentamicin
- b) Methicillin resistant
- c) Beta-lactamase-negative nutant derived from parent strain 2645

#### TABLE 2

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

STRAIN	(105CFU)	IMIPENEM	THM	CAB	GEN	AMK	ΡΙΡ
40 2824		1.6 0.63 2.5	3.1 0.63	5.0 30 80	50 2.5 5.0	6.3	3.1
2835 3350 <sup>h</sup> 3286 3287 <sup>c</sup>		10 2.5 2.5	20 10 10	> 80 80 80	> 20 5.0 5.0	6.3	6.3
3288 <sup>d</sup> 4293 4294		20.0 6.3 12.5	40 25 50	80 100 1.30	5.0 12.5 25	25 50	6.3 6.3

- a) Antibiotic abbreviations: THM = thienamycin; CAB= carbenicillin; GEN = gentamicin; AMK = Anikacin; PIP = piperacillin.
- b) Strain 3350 bears plasmid nediated 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 <u>Pseudononas</u> species. On the average, imipenem shows a two-fold advantage over thienamycin for the entire range of species. Isolates exhibiting beta-lact mase 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 imipenen, 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  $(0.25~mc_3/ml)$  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. fragil's Scrains to Imipenem and Three Reference antibiotics MIC (mcg/ml)

		For 50%	For 90%
Compound	Range	of Strains	of Strains
Imipenem	0.13 to 1.0	0,25	1.0
Thienamyc'n	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 0/13 were judged resistant to carbenicillin (Table 4). Two inoculum levels, 105 and 107CFU, 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)

	10 <sup>5</sup> CFU Inoculum For % Strains			10 <sup>7</sup> CFU Inoculu For % Stra			
Compound	Range	50	90	Range	50	90	
Imipenem	0.8 - 12.5	3.1	6.3	3.1 - 25	6.3	12.5	
Thimamycin	1.6 - 50	6.3	25	3.1 <b>-</b> 50	12.5	25	
Moxalactam	12.5 -> 50	25	50	50 - 50	- 50	30	
Cefotaxime	12.5 - 7 100	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 - 250	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 Susceptionility 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	$\sim 0.06$ 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<sup>5</sup> and 10<sup>7</sup>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)

	10 <sup>5</sup> CFU Inoculum  For % Strains			10 <sup>7</sup> CFU Inoculu For % Stra		
Compound	Range	50	90	Range	50	90
Imipenem	0.8 - 12.5	3.1	6,3	3.1 - 25	6.3	12.5
Th <b>k</b> namycin	1.6 - 50	6.3	25	3.1 - 50	12.5	25
Moxalactam	12.5 -> 50	25	50	50 <b>-</b> > 50	- 50	50
Ceforaxime	12.5 - 7 100	25	100	50 <b>-</b> >100	~100	>100
Carbenicillin	50 - 400	100	400	100 - > 400	2 🕒	~ 400
Piperacillin	3.1 -> 100	6.3	25	25 <b>- →1</b> 00	100	~ 100
Gentamicin	1.6 - 50	6.3	50	6.3 <b>-</b> ~50	6.3	- 50
Amikacin	1.6 - 50	6.3	25	6.3 - 50	12.5	50

NDA 50-587

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 (103 and 105CFU per microtiter well), imipenem is bactericidal at its MIC. At the high inoculum level(107CFU), 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 MKO787 WITH BETA-LACTAM AND AMINOGLYCOSIDE ANTIBIOTICS

TABLE 5	GRAM POSITIVE ORGA	NISMS			
	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4			GEOMETI MIC	RIC MEAN mg/ml
ORGANISM	ANTIBIOTIC	Ī	11	50%	20%
STAPH. AUREUS	MK0787	14	379	≤ 0.04	≤0.06
	CEFOTAXIME	9	150	2.1	<b>3.</b> 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	MK0787	8	163		0.44
EPIDERMIDIS	CEPHALOTHIN	5	105	<b>≤</b> 0.16	1.2
	CEFTAZIDIME	1	12	8.0	32.0
	MOXALACTAM	3	40	16.6	<b>≥</b> 45.0
	PENICILLIN G	6	117	0.69	5.8
	TOBRAMYCIN	1	18	0.25	> 32.0
STREPTOCOCCUS	MK0787	11	265	≤ 0.02	≤ 0.04
SPP.	CEPHALOTHIN	6	136	$\leq 0.16$	<b>≤</b> 0.03
	MOXALACTAM	6	215	2.6	4.9
	OXACILLIN	3	32	0.13	0.21
	PENICILLIN G	9	170	<b>≤</b> 0.02	≤ 0.05
	PIPERACILLIN	2	95	≤0.06	$\leq 0.2$
	TOBRAMYCIN	2	35	>32.0	> 32.0
ENTEROCOCCUS	MK0787	9	307	1.17	2.1
	AMPICILLIN	3	94	1.15	I. • 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	ī		<b>≻32.</b> 0	>32.0
	VANCOMYCIN	1	2.9	1.0	2.0

I = # OF INVESTIGATORS N = # OF STRAINS EXAMINED

TABLE 5 (cont'd)	ABLE 5 (cont'd) GRAM NEGATIVE ORGANISMS				
<del></del>		_ <del></del> -		· -	RIC MEAN
				MIC	Ç
ORGANISM	ANTIBIOTIC	<u>_T</u>	$\overline{N}$	<u>50%</u>	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
	CEFTAZ ID IME	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
	CEFTAZ ID IME	1	34	0.5	16.0
	MOXALACTAM	7	313		0.76
	CARBENICILLIN	4	106		47.0
	PIPERACILLIN	6	171		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.	MK078?	11	315		0.47
	CEFO TAX IME	4	139	0.02	0.09
	CEFOXITIN	4	48	2.7	4.8
	CEFTAZ ID IME	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		1.3
	CEFOTAXIME	4	102	0.26	2.0
	CEFOXITIN	4	47	•	55.0
	CEFTAZ ID IME	1	30	9.25	0.25
	MOXALACTAM	6	77 <b>7</b> 2	-	2.J
	CARBENICILLIN	2	70	<del>-</del>	578.0
	GENTAMICIN	3	47	4.2	51.0

TABLE 5 (cont'd)	GRAM NEGATIVE ORGAN	ISMS			
					RIC MEAN
				MIC	mg/nı
ORGANISM	ANTIBIOTIC	Ī	N	<u>50%</u>	<u>30</u> .
ESCHERICHIA COLI	MK0787	9	446	0,16	0.35
	CEFOPERAZONE	2	80	0.13	2.5
	CEFOTAXIME	4	160	0.05	0.10
	CEFOXITIN	3	97	3.5	t. • 4
	CEFTAZ ID IME	1	60	0.12	C.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
	CEFTAZ ID IME	i	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	2 <b>7</b>	0.5	0.73
KLEBSIELLA SPP.	MK0787	11	315		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	Հţ	102	0.26	2.0
	CEFOXITIN	4	47	20.0	55.0
	CEFTAZ ID IME	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)				SEDMET	RIC MEAN
ORGANISM	ANTIBIOTIC	Ī	<u> </u>	MIC 50%	
PROTEUS MIRABILIS	MKO787 CEFOPERAZONE CEFOTAXIME CEFOXITIN CEFTAZIDIME MOXALACTAM CARBENICILLIN PIPERACILLIN TICARCILLIN TOBRAMYCIN	7 2 3 2 1 4 1 3 4 2	210 74 146 26 60 101 33 101 121 38	1.4 0.61 0.02 4.6 0.06 ≤ 0.12 0.78 ≤ 0.41 0.68 0.86	3.0 2.0 0.03 8.0 0.06 0.16 0.78 ≤ 1.33 _ 14.0 3.0
PROTEUS SPP. INDOLE (+)	MKO787 CEFOPERAZONE CEFOTAXIME CEFOXITIN CEFTAZIDIME MOXALACTAM PIPERACILLIN TICARCILLIN AMIKACIN	17 5 11 6 4 10 5 8	386 82 318 215 60 265 95 110 38	1.8 1.5 ≤ 0.04 4.3 0.12 0.11 0.77 ≥ 4.5 2.3	3.3 6.5 0.4 > 15.0 0.21 0.20 6.0 ≥ 48.0 5.8
PSEUDOMONAS AERUGINOSA	MKO787 CEFOPERAZONE CEFOTAXIME CEFTAZIDIME CEFTIZOXIME MOXALACTAM CARBENICILLIN PIPERACILLIN GENTAMICIN TOBRAMYCIN	12 5 7 1 1 8 4 4 5	590 254 372 59 100 389 198 230 237 138	1.5 3.9 12.2 2.0 64.0 13.0 75.0 5.2 2.3 1.4	4.9 22.4 243.4 4.0 64.0 242.4 563.0 19.6 211.0 10.2
BACTEROIDES FRAGILIS	MKO787 CEFOTAXIME CEFOXITIN MOXALACTAM CHLORAMPHENICOL CLINDAMYCIN METRONIDAZOLE	5 2 4 4 1 2 1	345 47 203 180 100 156 56	0.15 4.81 9.3 0.6 4.0 ≤ 0.47 0.5	0.4 225.0 20.2 4.8 8.0 1.6 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  MYCOBACTERIUM AVIUM - INTRACELLULARE  NOCARDIA ASTEROIDES	11 15 8	0.125 0.2(MIC 70) 1.56
AEROBES - GRAM-NEGATIVE		
ACINETOBACTER SPP ALCALIGENES SPP BRUCELLA MELITENSIS HAEMOPHILUS INFLUENZAE MORAXELLA SPP NEISSERIA GONORRHOEAE NEISSERIA MENINGTTIDIS SHIGELLA SPP YERSINIA ENTEROCOLITICA	64 33 98 173 28 111 93 22 10	0.24 2.0 2.0 1.9 0.125 0.13 0.04 0.20
ANAEROBES - GRAM-POSITIVE		
CLOSTRIDIUM DIFFICILE CLOSTRIDIUM PERFRINGENS CLOSTRIDIUM SPP EUBACTERIUM SPP PEPTOCOCCUS SPP PETOSTREPTOCOCCUS SPP	47 15 100 6 49 32	2.9 4.0 0.25 2.0 0.07 0.14
ANAEROBES - GRAM-NEGATIVE		
CAMPYLOBACTER FETUS SS. JEJUNI CAMPYLOBACTER FETUS SS. INTESTINALIS EIKENELLA CORRODENS FUSOBACTERIUM SFP VEILLONELLA SPP	36 4 28 57 23	0.03 0.19 0.25 0.5 0.25

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

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

	<u> </u>	N	GEOMETRIC MEAN MIC90 mg/ml
Gram-Positive			
Staphyloccus aureus (W.T.)	22	1063	<b>≤</b> 0.06
Staphylococcus aureus (Pen-R)	5	110	0.08
	20	795	1.58
Enterococci	3	45	2.66
Nocardia asteroides	2	22	0.48 (MIC <sub>70</sub> )
Mycobacterium avium	ī	12	12.5
Mycobacterium fortuitum	*		
Gram Negative			
Desidences coruginoss (W.T.)	31	2278	3.54
Pseudomonas aeruginosa (W.T.) Pseudomonas aeruginosa (A <sup>*</sup> -R)	9	317	3.80
Pseudomonas aeruginosa (A K)	22	1122	<u> </u>
Escherichia coli (W.T.)	4	41	<b>≤</b> 0.70
Escherichia coli (Gen-R)	14	436	0.47
Acinetobacter spp.	3	92	≤ 0.07
Campylobacter fetus	14	906	≤ 0.33
Bacteroides fragilis	14		

I = Number of independent investigators

N = Number of clinical isolates tested

<sup>\*</sup>A = Aminoglycosides, eg. Gentamicin, Amikacin, Tobramycin

TABLE 8

Comparative Activities Against Streptococcus faecalis Isolates (n = 89)

Antibiotic	<u>N</u>	Geometric Mean MIC90, mg/ml
MKO787 Piperacillin Cephalothin Cefotaxime Cefoperazone Ceftazidime Moxalactam Cefsulodin Ceftriaxone Ceftizoxime Cefuroxime Gentamicin	89 35 54 89 39 54 89 54 54 54 54	0.9 4.0 32.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0 > 128.0

TABLE 9

MKO787 Activity Against P. aeruginosa Isolates

Resistant to One or More Aminoglycosides or Penicillins

Antibiotic	No. of <u>Isolates</u>	MKO787 MIC <sub>90, mg/ml</sub>
Tobramycin (MIC ≥ 8) Gentamicin (MIC ≥ 8) Amikacin (MIC ≥ 32) Azlocillin (MIC ≥ 128) Ticarcillin (MIC ≥ 128)	15 65 26 28 29 163	8 4 8 4 8 5.4 (Geom. Mean)

TABLE 10

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

Antibiotic	GEN-S, n = 29 MIC <sub>90, mg/ml</sub>	GEN-R, $n = 34$ MIC <sub>90</sub> , mg/ml
MKO787 Gentamicin Amikacin Tobramycin Moxalactam Cetoperazone Cefotaxime Piperacillin	2 4 8 2 32 32 64 16	8 32 64 8 64 32 128 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
MK0787 Piperacillin Cefotaxime Moxalactam	20	95	100 20	60	80 20	85 75 5

TABLE 10

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

Antibiotic	GEN-S, $n = 29$ MIC90, mg/ml	GEN-R, $n = 34$ MIC90, mg/ml
MK0787	2	8
Gentamicin	4	32
Amikacin	3	64
Tobramycin	2	8
Moxalactam	32	64
Cefoperazone	32	32
Cefotaxime	64	128
Piperacillin	16	<b>3</b> 2

### TABLE 11

### Carbenicillin-R. <u>Pseudomonas aeruginosa</u> Isolates

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

Antibiotic	3.13	6.25	12.5	25	50	100
MKO787 Piperacillin Cefotaxime Moxalactam	90	95	100 20	60	80 20	85 75 5

TABLE 12 Comparative Activity Against Campylobacter fetus, supp. jejuni  $\frac{1}{1000} = \frac{1}{1000} = \frac{1}{1000$ 

Antibiotic	MIC90,mg/ml
MKO787 Ampicillin Moxalactam Cefotaxime Erythromycin Chloramphenicol	0.03 4.0 16.0 4.0 0.5 4.0
Rifampin Cefoperazone Vancomycin	> 128.0 > 128.0 > 128.0

TABLE 14

Comparative Activity Against Acinetobacter spp. n = 14

Antibiotic	MIC90,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  $n = \overline{100}$ 

Antibiotic	MIC <sub>90,mg/ml</sub>
MK0787	0.25
Moxalactam	4.0
Piperacillin	64.0
Mezlocillin	128.0
Carbenicillin	<b>&gt;</b> 256.0
Ticarcillin	<b>&gt;</b> 256.0
Azlocillin	<b>&gt;</b> 256 <b>.</b> 0
Cefoxitin	16.0
Cefotaxime	256.0
Cefoperazone	256.0
Cefamandole	<b>&gt;</b> 256.0
Clindamycin	1.0
Metronidazole	1.0
Chioramphenicol	4.0

TABLE 14 Comparative Activity Against Bacteroides fragilis Isolates  $n \, = \, 100$ 

Antibiotic	MIC90,mg/ml
MK0787	0.25
Moxalactam	4.0
Piperacillin	64.0
Mezlocillin	128.0
Carbenicillin	<b>&gt;</b> 256 <b>.</b> 0
Ticarcillin	<b>&gt;</b> 256.0
Azlocillin	> 256.0
Cefoxitin	16.0
Cefotaxime	256.0
Cefoperazone	256.0
Cefamandole	> 256.0
	1.0
Clindamycin	1.0
Metronidazole	4.0
Chloramphenicol	4.0

TABLE 15

Susceptibility Reference List of MK0787 (N-Formimidoyl Thienamycin)

Destantal Christa	Gram (+/-)	N	Geom. Mean	-
Bacterial Strain	(+/-)	N N	MIC <sub>50</sub>	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	<b>;</b>		
Acinetobacter calcoaceticus	alcalige es			
Aeromonas hydrophilia	<b>~</b>	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. melani	nogenicus			
Bacteroides oralis				
Bacteroides ruminocola brev	is			
Bacteroides thetaiotaomicro	n			
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 intesti	nalis	0.710		
Citrobacter/Salmonella	-	370	0.30	0.62
Citrobacter freundii				
Citrobacter diversus	• •			
(Arizona hinshawii include	•	2.2.2		
Clostridia spp.	+	292	0.31	1.14
Clostridium septicum				
Clostridium difficile				
Clostridium perfringens				
Clostridium bifermentans				
Clostridium botulinum				

	ram	N	Geom. Mean	
Bacterial Strain (	+/-)	N	MIC <sub>50</sub>	MIC <sub>90</sub>
			Geom. Mean	
Chi-tile two bounts		7	cidal level =	27.8
Chlamidia trachomatis		4	32.0	-32.0
Corynebacterium sp.	+			
E. coli	<del></del>	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			3,23	• • • •
Klebsiella spp.	_	952	0.18	0.41
Klebsiella pneumoniae		732	0.10	0,41
Klebsiella oxytoca	_	36	~ 0.08	0.11
Listeria monocytogenes	+		·	
Moraxella spp.	-	37	. 0.08	0.37
Moraxella osloensis		2.2		0.40
Mycobacterium avium intracellular	e -	22		0.48
		1.0	2 12	$(MIC_{70})$
Mycobacterium fortuitum	÷	12	3.12	12.50
Neisseria gonorrhoeae	-	387	0.10	0.30
Neisseria meningitidis		266	0.05	0.11
Nocariia spp.	+	45	1.13	2.66
Nocardia asterbides				
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	U.13
Staphylococcus epidermidis	+	50 <b>9</b>	0.09	1.33

TABLE 15 (CONT'D)

	Gram		Geom. Mean (mg/ml)		
Bacterial Strain	(+/-)	N	MIC <sub>50</sub>	MIC90	
			Geom. Mean		
Chlamidia trachematis		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	_	23	2.17	20.0	
	_	57	0.03	0.50	
Fusionacterium sp.	_	25	<b>0.</b> 03	0.50	
Gardnerella vaginalis	_	302	0.95	1.82	
Haemophilus influenzae			0.93 6 0.28		
Hafnia spp.	_	14	0.28	0.46	
Hafnia alvei		0.50	0.10	0.71	
Klebsiella spp.	-	952	C.18	0.41	
Klebsiella pneumoniae					
Klebsiella oxytoca		2.6	0.00	0.11	
Listeria monocytogenes	+	36	< 0.08	0.11	
Moraxella spp.		37	0.08	0.37	
Moraxella osloensis				- 4	
Mycobacterium avium intracellula	re -	22		0.48	
Musahaatawi um famtuitum	<u>.</u>	12	3.12	(MIC <sub>70</sub> ) 12.50	
Mycobacterium fortuitum	+	387	- 0.10	0.30	
Neisseria gonorrhoeae	_	266	0.05	0.11	
Neisseria meningitidis	-	45	1.15		
Nocardia spp.	+	43	~ X.IJ	2.66	
Nocardia asteroides		1.0	0.50	1 00	
Pasteurella multocida	-	10	•	1.00	
Peptococcus/Petostreptococcus	+	87	0,02	0.06	
Peptococcus asaccharolyticus					
Peptococcus magnus		1.5	0.12	0.05	
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 (+/-)	Ŋ	Geom. Mea MIC50	n (mg/ml) MIC90
Pseudomonas spp. Pseudomonas aeruginosa Pseudomonas acidovorans Pseudomonas putrefaciens Pseudomonas stutzeri Pseudomonas fluorescens	-	2278	1.57	3.54
Pseudomonas cepacia Pseudomonas maltophilia Rhodococcus spp.	-	40 118 11	4.5 > 64.0 _ 0.39	> 50.0 > 128.0 0.39
Serratia spp.	_	806	£ 0.76	1.93
Serratia marcescens Shigella sp. Streptococcus spp. (Grps. A,8 Streptococcus agalactiae Streptococcus pneumoniae Streptococcus durans Streptococcus pyogenes	- 3,C,G) +	33 1293	0.17 ≤ 0.03	0.27 ≤ 0.05
Streptococcus bovis Viridans streptococci Streptococcus faecalis (Grp. Streptococcus faecium Veillonella spp. Veillonella parvula	) + + + -	51 795 30 23	= 0.06 0.93 20.0 0.05	<pre>0.11     1.58 78.0     0.25</pre>
Yersinia spp. Yersinia enterocolitica Yersinia pseudotuberculosis	-	234	<b>≤</b> 0.23	0.44

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Outstanding in-vitro porency 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;

Occasionally, strains of <u>S. epidermidis</u> 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 Initenem in the cerebrospinal fluid (CSF) of rabbits with inflamed and uninflamed meninges. They also demonstrated that excellent bactericidal and inhibitory liters in plasma and CSF of rabbits are achievable against both methicillin-sensitive and methicillin-resistant clinical isolates of Staphylococcus aureus.

Dr. George McCracker, Jr., at the University of Texas Health Science Center in Dallas has confirmed this work.

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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 <u>S. aureus</u> isolated from endocarditis patients. This investigator also observed excellent activity of imipenem against a clinical isolate of <u>S. faecalis</u> 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 stively 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 (KI)<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 C3 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 liponilic 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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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 metabolited 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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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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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 chromalographic analysis indicated that greater than 95% of the human urinary radioactivity was associated with intact imipenem and Metabolite I.

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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,  $^{14}\text{C}$ -imipenem, 500 mg, was administered alone and with an equal dose of cilastatin sodium. In another,  $^{14}\text{C}$ -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 rilastatin 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 19U-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 I 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 I hour throughout the study. No accumulation of cilastatin was observed.

The results of two other studies, wherein  $250/250~\mathrm{mg}$  or  $500/500~\mathrm{mg}$  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 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 probenacid 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 $^2$   $\leq$  GFR  $\leq$  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/  $^{22}$  m<sup>2</sup> GFR  $\leq$  30 ml/min/1.73 m<sup>2</sup>). The plasma clearance of the  $^{2}$ r and ped to 83 ml/min, while the plasma half-life increased to 2

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 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 parients 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:

- 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 \( \leq \frac{30}{30} \) 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 Himor (mcg/ml)
25 minutes	95.2	3.66
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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## Imipenem Levels in Human Body Fluids and Tissues

## Imipenem Levels in Aqueous Humor After 1 CM 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)

			Time After	Levels
Tissue or Fluid	No. of Patients	Dose	Dose	(mcg/m1)
0.11	6	1 g	15 minutes	0.3
Saliva	U	500 mg	15 minutes	0.3
		1 g	15 minutes	0.6
		500 mg	20 minutes	0.3
		500 mg	1 hour	0.3
		_	20 minutes	<b>&lt;</b> 0.3*
		1 g	20 minutes	- 0.0
Sputum	5	1. g	30 minutes	2.5
D F II O III	(10 samples)		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	l hour	22.0
	_		/ 1 11	
Ileal Fluid	2	500 mg	6 hr collection	< 0.3*
Nasal Gastric Aspira	ate 3	l g	30 minutes	< 0.3*
			15 minutes	< 0.3
			30 minutes	< 0.3
	1	500 mg	15 minutes	0.6
Gastric Aspirate		Joo mg	1.5 hours	1.7
	(2 samples)		1.5 Hours	<b>.</b>
Abdominal Drain	1	500 mg	2 hours	9.8
Peritoneal Fluid	1	1 g	30 minutes	3.9
				(mcg/g)
Bone	6	1 g 6 h	_	0.52
bone	(9 samples)	1 g 6 h	_	4.05
	( = 5000 / 200 /	1 g 6 h	_	1.5
		l g	10 minutes	0.42
		1 g	1.5 hours	2.5
		l g	25 minutes	5.4
		1 g	20 minutes	3.9
		l g	_	1.6
		l g	-	1.3
		- 0		

<sup>\*&</sup>quot;ndetectable

#### 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	
9	,	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	
		•	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 parients)

rail A. Ulliu	rramed meninges (	22 partents)			
Mean Time	Mean Serum Con	centration (mcg/ml)	Mean CSF Conce	entration (mcg/m	11)
After Dose	Imipinem:	Cilastatin	lmipinem	Cilastatin	
(Hours)					
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: Infl.	amed 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	Skin Window Fluid
		(intermittent)	(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 <b>.</b> 8
6.0	0.8	0.6	3.7
AUC	79.05	29.8	48

<sup>\*</sup>Dr. Tan could not explain the discrepancy between continuous and intermittent during the 0.5 and 1 hour samples.

NOA 50-587

mipenem	Levers III con	in Compassionate T	Sample			Cilastin	. (шсв/шт.
	Treatment	Dose	Time	CSF	Serum	<u>CS F</u>	Serum
atient	Day						0.24
	2	3:45 p.m.	3:15 p.m.	0.6	0.3	0.10	0.24
1.	3	500 mg q 8 ii	4:30 p.m.	0.3	15.4	<del></del>	17.24
		Joo mg d o u	5:30 p.m.	2.2	5,2	0.74	4.25
			6:30 p.m.	2.0	1.1	0.80	0.43
			·	^ ^	0.3	0.80	0.34
	5	10.00 a.m.	9:30 a.m.	0.9	0.3	0.92	27.3
	٠,	500 mg q 8 h	11.15 a.m.	ე.8	26.6		7.43
		3 - 1 - 3 - 1	12.15 p.m.	0.6	7,5	0.53	
			1.15 p.m.	0.6	3.4		2.54
			<b>.</b> L	_	0.3	_	0.43
	8	1 g q 8 h	trough	2.6	21.7	0,22	32.31
(	day 1 of		1 hr post dose		7.0	0.45	8.16
ħ	igher dose)		2 hr post dose	4.1	2.4	-	1.37
			3 hr post dose	-	4,4		
			. •	0.5	0.4		0.43
	10	1 g q 8 h	trough		16.7	1.04	27.03
			1 hr post dose	1.0	-	-	7.32
			2 hr post dose	-			15.53
			3 hr post dose	-	14.6		<b>4</b> • • •
		2.	<b>.</b>	0.5	_	0.91	0.27
	12	1 g q 8 h	trough	1.2	25.4	0.98	_
			1 hr post dose	1 · 4	5.4	_	2.89
			2 hr post dose		3.1	0.35	1.14
			3 hr post dose	-	J. 1	0,00	
			trough	0.4	0.4	0.56	0.24
	17	1 g q 8 h		3.3	28.8	1.14	35.54
			1 hr post dose	-	-	-	-
			2 hr post dose 3 hr post dose	1.8	1.9	1.12	0.91
			5 p		2.0		0.93
4)	7		trough	-	0.8	-	69.91
2	,	1 g q 6 h	15 min p-dose	-	33.2	2	
		. g q v	5 h o-dose	3.7	16.9	3.	21.53
			<b>.</b>	_	0.3	_	0.22
	14	1 g q 8 ħ	trough		31.8		47.08
			15 min p-dose 2 h p-dose	2.6	15.5	2.26	25.41
			·		0.0		0.51
3		1 g q 6 h	trough	-	0.9	-	29.11
3		1	peak	***	27.8	-	
			5 h p-dose	3.7	-	4.02	-

#### Clinical Studies (Domestic)

#### I. Controlled (3 studies)

#### 1. Protecol No. 001

Title: "A Multicenter Study of the Comparative Efficacy, 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 II investigators treated patients under Protocol No. 001:

Investigators Richard E. Bryant, M.D.	Number Primaxin 3	of Patients Cefazolin 2
University of Oregon Health Science Center  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)

		of Patients	
Investigators John Mills, M.D. San Francisco General Hospital	Primaxin 7	<u>Cefazolin</u> 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

Total No. of Patients	Primaxin 161	Cefazolin 158
Age Range (yrs)	17 - 83	16 - 84
Sex Male Female	99 62	90 68

#### Evaluation

#### Efficacy

	Primaxin	Cefazolin
No. of Cases Evaluable	104	<sup>5</sup> '8
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	1.7	16
Inadequate cultures	9	11
Patient lost to follow-up	1	0
Organism resistant to study drug	0	3

## DURATION OF TREATMENT (days)

(Evaluable Cases)
5 14 93 patients 94 patients
14 11 patients 4 patients

(Continued)

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

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#### DURATION OF TREATMENT (days)

(Evaluable Cases)
5 - 14
93 patients
94 patients
11 patients
4 patients

•

### RESULTS

			IMAXIN L RESPONSE				RESPONSE	<u>سر</u>
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, cell ulitis, carbuncle/furu pyoderma, infected ulo	ıncle	CURE 48(71%)	IMP. 17(25%)	FAIL 3(4%)	NO. 70	CURE 48 (68%)	IMP. 20(28%)	<u>FAIL</u> (2(3%)
BONE/JOINT (Pyogenic arthritis, osteomyelitis)	5	2(40%)	3(60%)		4	2(50%)	2(50%)	
LOWER RESPIRATORY (Pneumonia, lung abscess, bronchiolitis	14 s)	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%)		

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## RESULTS

			IMAXIN L RESPONSE				AZOLIN RESPONSE	
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, cel- ulitis, carbuncle/fur- pyoderma, infected ul-	uncle	CURE 48(71%)	IMP. 17(25%)	FAIL 3(4%)	NO. 70	CURE 48(68%)	<u>IMP.</u> 20(28%)	FAIL( 2(3%)
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GYNECOLOGIC (Pelvic cellulitis)	1		1 (100%)		-			
SEPTICEMIA	16	14(88%)	2(12%)		5	4(80%)	1(20%)	
ENDOCARDITIS	1	1(100%)			-			
UT. (Uncomplicated) (Pyelonephritis)	7	6(86%)		1(14%)	5	5(100%)		
UTI (Complicated)	3	2(67%)		1(33%)	2	2(100%)		

	PRIMAXIN BACTERIOLOGICAL RESPONSE							EFAZOLIN .OGIAL RES	PONSE
INFECTION SKIN AND SKIN STRUCTURE	<u>NO.</u>	ERADI	SUPP <sup>2</sup>	NOT ERAD3	<u>NG.</u>		ERAD <sup>1</sup>	SUPP2	NOT ERAL
S. aureus(S)*	6	4(67%)	1(17%)			3	3(100%)		C
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. Group D Strep	5	4(80%)		1(20%)					
(enterococcus) Aeromonas	7	7(100%)				3	3(100%)		
hydrophilia	1	1(100%)				1	1(100%)		
Alcaligenes spp.	ì	1(100%)				_	1 (100.4)		
C. freundii	2	2(100%)				1	1(100%)		
Eikenella	-	2(100%)				_	_(		
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	上(50 <b>%)</b>	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 spo	1	1(100%)				-			
B. fragilis	5	5(10 <b>0%</b> )				1	1(100%)		
B. melaninogenicus	3	3(100%)				3	3(100%)		
B. bivius	1	1(100%)				_			
Peptococcus spp Peptostreptococcus	1	1(100%)				5	5(100%)		•
spn	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(J.0 <b>0%</b> )		

(Continued)

(CONCINUEU)		BACTE		IMAXIN CAL RESPONSE				EFAZOLIN DLOGIAL RESP	PONSE
INFECTION BONE/JOINT	<u>NO.</u>	ERAD1	SUPP2	NOT ERAD3	<u>NO.</u>		ERADI	SUPP <sup>2</sup>	NOT ERAC
S. aureus <sup>(R)</sup>	2	2(100%)				2	2(100%)		
Beta-hem-Strep	2	2(100%)				1	1(100%)		
(Group A)	1	1(100%)				1	1(100%)		(
Streptococcus spp E. coli	1	1(100%)					1(100%)		
P. aeruginosa	1	1(100%)		i(100%)		_			
S. marcescens	ī			1(100%)		_			
B. melaninogenicus	-			-(		1	1(100%)		
Enterobacter						_	-		
cloacae	_		,			Ţ	1(100%)		
P. mirabilis	-					1	1(100%)		
LOWER RESPIRATORY	1	1717.79							
S. aurues (s)	1	1(10.3%)				11	11(100%)		
S. pneumoniae	8	8(10 <b>0%</b> )		1(25%)		6	5(83%)		1(17%)
H. influenzae H. parainfluenzae	4	3(75 <b>%)</b> 1(100 <b>%</b> )		1(20.0)		_	J(0Ja)		1(178)
E. cloacae	1	1(100%)				_			
P. aeruginosa	1	1(100%)		1(100%)		_			
Klebsiella ozaenae				1(100%)		1		1 (100%)	
GYNECOLOGIC									
Streptococcus spp	1	1(100%)				_			
E. coli	1	1(100%)				_			
Peptostreptococcus	,	1/100%)							
spp	1	1(100%)				-			
Bacteroides spp	1	1(100%)				-			
SEPTICEMIA									
S. aureus <sup>(R)</sup>	3	3(100%)				_			
S. aureus (S)	ĺ	1(100%)				_			
Streptococcus spp	ī	1(100%)							
S. epidermidis	3	3(100%)				1	I(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%)				_	1/10001		
E. coli	-					1	1(100%)		
ENDOCARDITIS									
S. aureus (R)	1	1(100%)				_			

(Continued)

(60115711909)		BACTE		IMAXIN CAL RESPONSE				EFAZOLIN JLGGIAL RE	SPONSE
INFECTION	<u>NO.</u>	ERADL	SUPP2	NOT ERAD <sup>3</sup>	<u>NO.</u>		<u>ERAD</u>	SUPP <sup>2</sup>	NOT ERAU3
UTI (Uncomplicated E. coli	7	6(86%)		1(14%)		5	5(100%)		
UTI (Complicated) E. coli C. diversus	2	2(100%)		1(100%)		2	2(100%)		

\*(S) = Sensitive to penicillin \*\*(R) = Resistant to penicillin

1 = Eradicated

2 = Suppressed
3 = Not eradicated

In the Primaxin treatment group, one patient with procumonia 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	Cerazolin
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( <b>3%</b> )

#### LOCAL SIDE EFFECTS

LUCAL SIDE EFFEUTS			PRIMAX:	IN	
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Pain at I.V.site	$\overline{1(0.6\%)}$		$\overline{1(0.6\%)}$		<del></del>
Vein infection	1(0.6%)	1(0.6%)			
Phlebitis/thrombo-		_		_	
phlebitis	8(5.0%)	2(1.2%)	5(3,1%)	1(0.6%)	
			CEFAZOI	LJN	
Pain at I.V. site	i(0.6%)	1(0.6%)	<del>ب بن باد النس</del> ي ر		
Vein infection	1(0.6%)		1(0.6%)		
Phlebitis/thrombo+					
phlebitis	3(1.9%)	1(0.6%)	2(1.3%)		

(Continued)

Weakness

Thoracic spine pain

(33.12.1333)	<u>NO.</u>	PROBABLY NOT RELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
SYSTEMIC SIDE EFFECTS			PRIMAXI	N	
Vamiting	2(1.2%)		1(0.6%)		1(0.6%)
Diarrhea Pruritus	1(0.6%)	,		1(0.6%)	
Rash Dizziness	1(0.6%) 1(0.6%)				1(0.6%)
Apnea Chest pain/cough	1(0.6%) 1(0.6%)				
Hyperventilation	1(0.6%)				1(0.6%)
Parest.hesia	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%) 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%)

1(0.6%)

1(0.6%)

2(1**.3%**)

1(0.6%)

1(0.6%)

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	(b) 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) $I$
Platelets	(I) 2	(D) 1 (1) 3
Positive Coombs' Test	l	1
Glucose	(I) 2	(I) $I$
BUN	(I) 3	(I) $I$
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	$\overline{(1)}$ 2
Alk. phosphatase	(I) 9	(I) 1
LDH	(I) 5	(I) $I$
Serum potassium	0	(I) l
Urine protein	0	(I) l
Urine uric acid	0	(I) l
Urine WBC	(I) l	(I) 2
Urine RBC	(1) 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 eticlogic 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 Alan S. Berkeley, M.D.	Number Primaxin 18	of Patients  Moxalactam  16
Cornell Medical Center		
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. Onio 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)

	Number	r of Patients
Investigators Charles A. Kallick, M.D. Cook County Hospital	Primaxin 4	Moxalactam 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	.t
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

Total No. of Patients	Primaxin 218	Moxalact.am 223
Age Range (yrs)	14 - 91	14 - 96
Mean Age	48.9	48.4
Sex Male Female	109 109	99 124

## EVALUATION

## EFFICACY

No. of Cases Evaluable No. of Sites of Infection Evalua No. of Cases Unevaluable	Primaxin 145 ble 161 73	Moxalact.am 148 156 75
REASONS CASES UNEVALUABLE No pre-treatment pathogen Organism resistant to study drug Clinical diagnosis not clear Inadequate bacteriological cultu Treatment course too short Effective concumitant treatment Infection not included in claims	2 ires 11 11 3	42 4 1 10 11 4 3
<u>DOSE</u> (Evaluable Cases)	Primaxin 500 mg q 6 h (2 g/day)	Moxalactam 1-2 g q 8 h (3-6 g/day)
DUTATION OF TREATMENT (days)  (Evaluable Cases)  4 - 14  15 - 21  >21*	117 patients 18 patients 10 patients	7 patients

<sup>\*</sup>Four patients were treated for 41 days.

## RESULTS

			IMAXIN L RESPONSE				ACTAM RESPONSE	
INFECTION SKIN & SKIN STRUCTURE (Wound infection, abscertable) cellulitis, carbuncle/ furuncle, ulcers)	<u>NC.</u> 44 ≘ss	CURE 27(61%)	IMP. 16(36%)	FAIL 1(2%)	NO. 48	CURE 23(48%)	<u>IMP.</u> 17(35%)	$\frac{\text{FAIL}}{8(17\%)}$
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, tuboov abscess)	27 varian	23(85%)	3(11%)	1(4%)	27	21(78%)	5(18%)	1(4%)
SEPTICEMIA	2.2	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(:6%)
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%)	

		DACT"	PRIMAX				CXALACTAM LOGIAL RESP	KONICE"
INFECTION	NO.	ERAD	RIOLOGICAL SUPP	NOT ERAD	NO.	ERAD	SUPP	VIOT EPAD
SKIN AND SKIN								
STRUCTURE								
Bacillus spp.	-				1	1(100%)		
S. aureus(5)	2	1(50%)		1(50%)	5	5(100%)		
S. aureus <sup>(R)</sup>	17	13(76%)	1(6%)	3(18 <b>%</b> )	16	15(94%)		1,6%)
S. apidermidis	3	3(100%)			3	3(100%)		
Strep. (Group A)	5	5(1 <b>00%</b> )			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%)			$\overline{1}$	1(100%)		
P. mirabilis	5	1(20%)	1(20%)	3(60%)	12	11(92%)		1(8%)
P. vulgaris	2	2(100%)	2(20,0)	× (00,0)	2	1(50%)		1(50%)
P. stuartii	2	2(100%)			_	_ (- 0		= ( • • · · ·
Pseudomonas spp	-	2(100,0)			1	1(100%)		
P. aeruginosa	11	6(55%)	1(9%)	4(36%)	ā	5(62.5%	,	3(37.5%
Serratia spp.	1	1(100%)	1(//0/	, (50.0)	2	2(100%)	•	
S. marcescens	2	2(100%)			2	1(50%)	1(50%)	
Eubacterium spp.	_	2(1000)			Ī	1(100%)		
Gaffkya anaerobia	_				2	1(100%)		
Peptococcus spp.	2	2(100%)			4	4(100%)		
Bacteroides spp.	7	7(100%)			4	4(100%)		
B. fragilis	ĺ	1(100%)			i	1(100%)		
F. russii	Î	1(100%)			<u>.                                      </u>	1(100%)		
V. parvula	ī	1(100%)			Ĩ	1(100%)		
v. parvuru		1(100%)			-	1 (100.0)		
BONE/JOINT_								
S. aureus <sup>(R)</sup>	2	2(100%)			1	1(100%)		
S. faecalis	2	2(100%)			-			
E. coli	-				<u></u>	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%)			-			

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(Continued)			22.40	** * ·			TUNE BOTAL	
			PRIMAX				XALACTAM	DOLG:
	_		RIOLOGICAL				OGIAL RES	·
	<u>۸0.</u>	ERAD	SUPP	NOT ERAD	<u>NO.</u>	ERAD	SUPP	NOT ESA
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%)			_			
	i	1(100%)		1(100%)	_			
E. aerogenes	1	1(100%)		1(100%)	2	2(100%)		
E. cloacae	1				1	1(100%)		
E. coli	1	1(100%)	1/170/)			·		
H. influenzae	6	5(83%)	1(17%)		2	2(100%)		
H. parainfluenzae	i	1(100%)			Ţ	L(100%)		
K. oxytoca	1	1(100%)			2	2(100%)		1.7.1250
K. pneumoniae	2	2(10 <b>0%</b> )			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(10 <b>0%</b> )			5	L(20%)	2(40%)	2(40%)
S. marcescens	-				2	2(J <b>.00%)</b>		
B. catarrhalis	-				1	1(100%)		
Peptostreptococcus								
spp.	1	1(100%)						
Bacteroides spp.	3	3(100%)						
CYNECOLOCIC								
GYNECOLOGIC					,	1(100%)		
Corynebacterium spp		* / **= ** \	1 (05%)		1	1(100%)		. 1(05%)
S. aureus <sup>(R)</sup>	4	3(75 <b>%</b> )	1(25%)		4	3(75%)		1(25%)
S. intermedius	-				<u>l</u>	1(100%)		
Strep. (Group A)	-				1	1(100%)		
Strep. (Group B)	7	7(100%)			7	7(100%)		
S. viridans	2	2(100%)			2	2(10 <b>0%</b> )		
Strep								
(non-hemolytic)	2	2(1 <b>00%</b> )			<u>,</u>	1(100%)		
S. faecalis	8	7(8 <b>8%</b> )	1(12%)		2			2(100%)
A. calcoaceticus	-				<del>-</del>			1(100%)
Enterobacter spp.	-				1	1(100%)		
E. cloacae	I	1(100%)			±	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(190%)			i	1(100%)		
P. aeruginosa	_	,			1	, - ,		1(100%)
N. donorroheae $(-)^*$	2	2(100%)			<u>-</u>			- ( = 22/1/
N. gonorroheae (+)**	_	, , ,			1	1(100%)		
<u>ganaza on outo</u>					=	- (/		

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(Continued)

OTITIS MEDIA
S. pneumoniae

1(100%)

1

•								
GYNECOLOGIC	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
Bifidobacterium spr	1	1(100%)			••			
Propionibacterium								
spp	1	1(100%)			-			
Pertococcus spp	3	3(100%)			9	9(100%)		
Peptostreptococcus								
spp	1	1(100%)			-			
Bacteroides spp	5	5(100%)			4	4(100%)		
B. fragilis	Ĺ	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%)			-			
Velllonella parvula	1.	1(100%)			6	6(100%)		
(-)* = penicill	inase	negative						
(+)** = penicil								
• ,		_						
SEPTICEMIA								
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%)			-			
5. 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	~				l			1(100%)
-								

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(Continued)		CACTE	PRIMA RIOLOGICAL			MGXALAC BACTERIÓLUGIAL	TAM
INFECTION	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD SUPP	
OTITIS MEDIA S. pneumonias	J	1(100%)	<del>~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~</del>		_		
ENDOCARDITIS S. sanguis	1	1(100%)			-		
INFECTED VASCULAR GRAFT							(
S. aureus (R)	-				1	1(100%)	
UNCOMPLICATED UTI	3	3(100%)			8	7(87.5%)	1(12.5%)
E. cloacae	-				1	1(100%)	
P. miratilis	1	1(100%)			2	2(100%)	
S. marcescens	-				<u>l</u>	1(100%)	
P. aeruginosa	-				1 1	1(100%) 1(100%)	
Klebsiella spp. K. pneumoniae	2	2(100%)			1	1(100%)	
COMPLICATED UTI							
E. coli	2	1(50%)		1(50%)	3	3(100%)	
a. mirabilis	_	1(500)		1(30%)	ĺ	1(100%)	
E. aerogenes	1	1(100%)			_		
K. pneumoniae	-				1	1(100%)	
P. aeruginosa	ì			1(100%)			1(100%)
S. marcescens	1			1(100%)	-		
INTRA-ABDOMINAL					1		1 ( 100%)
S. aureus (R)	1	1 ( 1000%)			1		1(100%) 1(100%)
S. epidermidis S. intermedius	$\frac{1}{4}$	1(100%) 4(100%)			1	1(100%)	1 (100%)
S. mitis	1	1(100%)			2	2(100%)	
S. morbillorum	2	2(100%)				2(200.0)	
Strep. (Group A)	_	_,,,			.2	2(100%)	
Strep. (Group 8)	-				1	1(100%)	
S. viridans	3	2( <b>67%</b> )		1(33%)	•		
S. faecalis	-				3	1(33%)	2(67%)
S. faecium	1	1(100%)			1	1(100%)	
S. bovis	1	1(100%)			-		
S. sanguis S. salivarus	1	1(100%)			-		
A. hydrophilia	-				- :	1(100%)	
E. aerogenes	1	1(100%)			2	2(100%)	
E. cloacae	_	1(100%)			ī	1(100%)	
E. coli	14	11(79%)		3(21%)	12	9(75%)	7(25 <b>%</b> )

(Continued)	PRIMAXIN	1	MCXALACTAM	
	BACTERIOLOGICAL RE	SPGNSE	BASTERIOLOGIAL RE	SPONSE T ERAD
INTRAABDOMINAL Klebsiella spp. K. pneumoniae P. multocida	ERAD SUPP NOT E 1 1(100%) 4 4(100%) 1 1(100%)	RAD NO. ERAD 1 4 - 2	SUPP NO 1(100%) .(100%) 2(100%)	1 2-040
M. morganii	1 1(100%)	3	2(67%)	1(33%)
P. mirabilis P. vulgaris P. aeruginosa	1 1(100%) 2 2(100%)	4	2(50%)	2(50%)
Bifidobacterium	_	1	1(100%)	
spp. Clastridium spp C. perfringens Eubacterium spp Peptococcus spp	9 9(100%) 2 2(100%) 2 2(100%) 1 1(100%)	3 3	3(100%) 2(67%)	1(33%)
Peptostreptococcus spp Bacteroides spp. B. fragilis Fusobacterium spp. V. parvula	4 4(100%) 5 5(100%) 12 12(100%) 5 5(100%) 1 1(100%)	3 7 13 4	3(100%) 7(100%) 12(92%) 4(100%)	1(8%)

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

(Continued)

SYSTEMIC	SIDE	EFFECTS
21210110	3100	

SYSTEMIC SIDE ELL			PR IMAX1_	N	VITTIV
Rash	NO. 3(1.4%)	PROBABLY NOT RELATED	POSSIBLY RELATED 1(0.5%)	PROBABLY RELATED 1(0.5%) 1(0.5%)	DEFINITELY RELATED 1(0.5%)
Urticaria Fever	1(0.5%) 2(1.0%)	1(0.5%)	1(0.5%)		
Transient hearing loss Palpitation Tachycardia	1(0.5%) 1(0.5%) 1(0.5%)		1(0.5%) 1(0.5%) 1(0.5%)		
Respiratory distress syn. Pharyngeal pain	1(0.5%) 1(0.5%)	1(0.5%)		1(0.5%)	
Menorrhagia Hemorrhagic colitis	1(0.5%)	1(0.5%)		1(0.5%)	
Asthenia Hyperhydrosis	1(0.5%) 1(0.5%)		1(0.5%) 1(0.5%)		

#### SYSTEMIC SIDE EFFECTS

SYSTEMIC SIDE EFFECTS		PROBABLY	MOXALAC POSSIBLY	TAM PROBABLY RELATED	DEFINITELY RELATED
	NO.	NOT RELATED	RELATED 4(1.9%)	1(0.5%)	
	$9(\overline{4.32})$	4(1.9%)	1(0.5%)	1(0.3%)	
Nausea	1(0.5%)		2(1.0%)		
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%)	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%)	1(0.5%)			
Urinary frequency	1(0.5%)	1(0.5%)			
Abdominal pain	1(0.5%)	2(0.00)			
Respiratory	1(0.5%)	1(0.5%)			
insufficiency	1(0.5%)	1(0.5%)			
Headache Convulsive disorder	1(0.5%)	1(0.5%)			
Alcohol intolerance	1(0.5%)		1(0.5%)		
Somnolence	1(0.5%)		1(0.5%)	1(0.5%)	
Vaginal discharge	1(0.5%)			1(0.0%)	
Myocardial infarction	1(0.5%)	1(0.5%)			

#### LOCAL SIDE EFFECTS

			PRIMAXIN		
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Phlebitis/					
Thrombophlebitis	12(5.5%		12(5.5%)		
Infused vein pain	1(0.5%	)		1(0.5%)	
Infused vein					
infection	1(0.5%)	)	i(0.5%)		
	MOXALACTAM				
		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
		INODADEI	1 0001051	1110011001	DEL THE LEET
	NO.	NOT RELATED	RELATED	RELATED	RELATED
I.V. site	NO.	NOT RELATED	RELATED	RELATED	RELATED
I.V. site hemorrhage		NOT RELATED	RELATED	RELATED	RELATED
I.V. site hemorrhage Infused vein pain	NO. 1(0.5%) 1(0.5%)	<del></del>	RELATED	RELATED 1(0.5%)	RELATED
hemorrhage	1(0.5%)	<del></del>	RELATED		RELATED

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) I	(D) 8
Hematocrit	(D) 2	(D) 6
WBC	(D) 3	(D) 4
Neutrophils	(D) l	(D) l
Fosinophils	(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) l
Creatinine	(I) 2	(I) 6
GGT (AST)	(I) 7	(I)12
JAG (ALT)	(I)10	(1)14
t i f m	(I) 2	(I) l
rathat ase	(I) 6	(I) 6
451	0	1 (d)
· #"1	0	(D) I
	(I) 1	(D) 1
	(1) 3	(I) 2
	(T) 4	(I) 2
	3	(I) 3
	•	(I) $I$

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

TOTAL NO. OF PATIENTS	PRIMAXIN 21
Age Range (years)	21 - 78
Sex Male Female	13 8
EVALUATION	
EFFICACY	
No. of Cases Evaluable No. of Sites of Infection Evaluable	19 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/d	tay)
DURATION (days) - 5 - 14 days (13 15 - 21 days (3 34 - 37 days (3	patients)

## RESULTS

		PRIMAXIN		
		CLINICAL RESPO	INSE	
INFECTION	NO.	CURE	IMF	FAIL
SKIN & SKIN STRUCTURE	9	<del>2(22</del> %)	<del>6(6</del> 7%)	$\overline{1(11\%)}$
BONE/JOINT	l		1(100%)	
LOWER RESPIRATORY	2	1(50%)		1(50%)
UTI(Uncomplicated)	1		1(100%)	
INTRA-ABDOMINAL	6		5(8 <b>3%</b> )	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%)	

(COLUTTURED)				
		BACTERIOLOGIC		
ORGANISM	NO.	ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE	7	1 ( 7 70( )		0/2701
P. mirabilis	3	1(33%)		2( <b>67%</b> )
A. calcoaceticus P. aeruginosa	1	1(100%) 1(33%)		2(67%)
K, pneumoniae	ر ا	1())	1(100%)	2(67%)
Peptostreptococcus spp	3 1 1 3 1	1(100%)	1(100%)	
Bacteroides spp	3	3(100%)		
B. fragilis	1	1(100%)		
•				
BONE/JOINT				
S. faecalis	l i	1(100%)		. (
P. mirabilis				1(100%)
P. stuartii	1 1			1(100%)
P. arruginosa	Ţ			1(100%)
LOWER RESPIRATORY				
K. pneumoniae	1	1(100%)		
E. hafniae	Ī	_(,		1(100%)
P. aeruginosa	1			1(100%)
•				, ,
UTI (Uncomplicated)				
E. coli	1			1(100%)
TAITE A AD COMTMA				
INTRA-ABDOMINAL	1	1(100%)		
S. faecalis E. coli	1	1(10 <b>0%</b> ) 2(6 <b>7%</b> )		1(33%)
P. mirabilis	1	2(0/%)		1(100%)
K. pneumoniae	3 1 2	1(50%)		1(50%)
P. aeruginosa	1	1(100%)		1()0//
i acragriosa	_	I (ICOM)		

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

The state of the s	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

		DEFINITELY
	NO.	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	Ī	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

concentration assays).

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

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

Total No. of Patients	Primaxin 13	Clindamycin/Gentamicin
Age Range (yrs)	24 – 95	26 - 73
Mean Age	50.5	49.0
Sex Male Female	9 4	10 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
• •	<u>)</u>	2
Treatment course too short		
	~	1
Organism resistant to study drug Inadequate bacteriological cultures	1	1

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

DURATION OF

IMENIMENI (Days)			
5 - 14	8 patients	5 patients	5 patients

# RESULTS

		PR CLINICA	IMAXIN L RESPONSE		•	CLINDAMYC CLINICA	IN/GENTAMIC	IN
INFECTION SKIN & SKIN STRUCTURE (Wound infection, abscess)	<u>NO.</u> 2	<u>CURE</u> 2(100%)	IMP.	FAIL	<u>NO.</u>	CURE	IMP.	<u>FAI</u>
(Pheumonia, bronchopneumonia)	2	1(50%)	1(50%)		2		1(50%)	1,50

**-** 67 -

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ı	UUL	13	_ ' '	LIC	

(Continued)		DU.	TMANTN			C. TAIDREANOTAL	ACENTANTO TAL	
INFECTION	NO.		IMAXIN RESPONSE IMP.	, i	NO.	CLINICAL CURE	GENTAMICIN RESPONSE IMP. F	Δ
UTI (Complicated) (Pyelonephritis)	T	50,42	4.7.11	<u>(ŢĴ</u> Ū¯%)	_	<u> </u>		_
INTRA-ABDOMINAL (Peritonitis, abscess, cholangitis)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)	(
		_ "	IMAXIN DGIC RESPON	ISF		CLINDAMYCIN BACTERIOLOG		
ORGANISM	NO.	ERAD	NOT ERAE		NO.	ERAD	NOT ERA	<u>_</u>
SKIN & SKIN STRUCTURE S. viridans group	1	1(100%)						
Streptococcus spp	ī	1(100%)						
S. faecalis	1	1(100%)						
E. coli	1	1(100%)						
Peptococcus spp	1	1(100%)						
Bacteroides spp	5	2(100%)						
LOWER RESPIRATORY								
H. influenzae	1	. (1000()	1(100%)		-	171002		
E. coli	1	1(100%)			Ţ	1(100%)		
Enterobacter spp	-				1	1(100%)		ς
P. aeruginosa	••				1		1(100%	,
INTRA-ABDOMINAL S. aureus <sup>(S)</sup>					1	1(100%)	1	
Strep (Group A)	- 1	1(100%)			± -	1(100%)	,	
Strep (Group D	1	1(100%)			_			
enterococci)	1	1(100%)			_			
S. viridans group	1	1(100%)			_			
Beta-hemolytic Strep	1	T(T00%)			-			
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.	Ţ	1(100%)			-			
Peptostreptococcus spp	Ţ	1(100%)			2	2(100%	1	
B. fragilis	<u> </u>	4(100%)			<u>ک</u> ۱	$\frac{2(100\%)}{1(100\%)}$		
Bacteroides spp. Fusobacterium spp.	4 2	2(100%)			<b>-</b>	1(100%)	,	
, ,	4	2/100/6/			-			
UTI (Complicated)	ı		1/100%					
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:  $\pm$ Effectiv concomitant therapy: 14 No post-treatment culture: 20

No follow-up: 6

# DURATION OF TREATMENT

(Evaluable Cases)

Days 4-14	No. Patients
4-14	<i>3</i> 66
15-29	98
30-49	41
61	1

# RESUL IS

		CLIM	NICAL RESPONSE	1 •
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, abscess, cellulitis, carbuncle/furun decubitus and other skin ul		CURE 67(51.9%)	IMPROVE 56(43.4%)	FAIL 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%)		

	BACTERI	OLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
SKIN & SKIN STRUCTURE		
Corynebacterium spp.	4	4(100%)
S. aureus(S)	9	8(88.9%)
S. aureus <sup>(R)</sup>	43	<i>3</i> 6(83 <b>.</b> 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(1 <b>00%</b> )

(Continued)	No.	Eradicated
		10.041
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	<del>-</del> -	( ,
(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%)
Erkenelia 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%)

	BACTER:	IOLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
S. facecalis	2	2(100%)
Aceinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus		1(100%)
Enterobacter aerogenes	3	3(100%)
Enterobacter cloacae	6	6(10 <b>0%</b> )
Escherichia coli	2 2 1 2 3	1(50%)
Morganella morganii	2	2(10 <b>0%</b> )
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	1 3 1 2 3	1(50%)
Bacteroides fragilis	3	2(66.7%)
Fusobacterium spp.	1	1(100%)
LOWER RESPIRATORY		= ( 1 <b>2 2 2</b> )
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		0(50%)
(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	Т	1(100%)

,	BACTERIO	DLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
UPPER RESPIRATORY	-	
S. aureus(R)	1	<u>O</u>
Streptococcus spp.		1(100%)
Enterobacter aerogenes	]	1(100%)
Klebsiella pneumoniae	1 1 1 1 1	1(100%)
Peptostreptococcus spp.	1	1(100%)
	1	
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%)
·	3	3(100%)
Alpha-hemolytic Streptococci		
Group B Streptococci	13	13(100%)
Group D Streptococci		11/0: 40/
(Enterococci)	13	11(84.6%)
S. faecalis	3	3(100%)
Other Streptococcus species	6	6(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter diversus	2 1 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(100%)
Proteus mirabilis	<u> </u>	2(66.7%)
	1 3 1 2 1	0
Pseudomonas aeruginosa	1	
Bifidobacterium spp	2	2(100%)
Clostridium perfringens		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(10 <b>0%</b> )
Other Streptococcus species	8	8(100%)
Acinetobacter calcoaceticus	1	1(100%)
Citrobacter species	2	2(100%)
disipode of operator	٤.	2(100%)

(Continued)		
	BACTERI	OLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
Citrobacter freundii	1	I(100%)
Enterobacter aerogenes	2 <b>3</b>	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(100%)
Proteus mirabilis	3	2(66.7%)
Pseudomonas aeruginosa	2 3 5 1	4(80%)
Pseudomonas alcaligenes	ĺ	1(100%)
Bifidobacterium adolescentis	Ī	1(100%)
Clostridium spp	12	12(100%)
Propionibacterium acnes	3	3(100%)
Peptococcus spp	2	2(100%)
Peptostreptococcus spp	2 2	1(50%)
·	4	4(100%)
Bacteroides spp	19	18(94,7%)
Bacteroides fragilis	2	2(100%)
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 3 7 5	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	Ī	1(100%)
Bifidobacterium spp	ĺ	1(100%)
Peptococcus spp	ì	1(100%)
TOP COCOCOGO SPP	•	I (100%)

(OSI METHODA)	BACTERIO	JLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
BACTERIAL SEPTICEMIA		
S. aureus(S)	2	2(100%)
S. aureus <sup>(R)</sup>	9	8(88.9%)
S. epidermidis	1	1(100%)
S. pneumoniae	7	7(100%)
Group D Streptococci		
(enterococci)	2 1 9 1	2(100%)
S. faecalis	1	1(100%)
Other Streptococcus species	9	9(100%)
H. influenzae		1(100%)
Escherichia coli	17	17(100%)
Proteus mirabilis	1 3 1 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 1 1 1 1 3	4(100%)
Flavobacterium spp	Ţ	1(100%)
Salmonella (Group D)	Ţ	1(100%)
N. gonorrhoeae	+	1(100%)
Corynebacterium acnes	1	1(100%)
Clostridium bifermentans	Ţ	1(100%)
Bacteroides fragilis	3	2(66.7%)
BACTEREMIA		
S. aureus(S)	1	1(100%)
S. aureus(R)	1	2(100%)
S. epidermidis	2 1	1(100%)
S. pneumoniae	1	1(100%)
Group D Streptococci	τ.	1(100%)
(Enterococci)	1	1(100%)
H. influenzae		1(100%)
Escherichia coli	1 7	7(100%)
Enterobacter cloacae	3	3(100%)
Citrobacter diversus	ĺ	1(100%)
Providencia stuartii	1	1(100%)
Pseudomonas aeruginosa	4	4(100%)
Bacteroides bivius	ī	1(100%)
540 01101000 511100	-	1(100%)
ENDOCARDITIS		
S. aureus(S)	1	1(100%)
S. aureus(R)	5	5(100%)
Streptococcus spp	Ĩ	1(100%)
S. pneumoniae	$\bar{1}$	1(100%)
Streptococcus viridans group	$\overline{1}$	1(100%)
BRAIN ABSCESS		
S. aureus <sup>(R)</sup>	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%)

BIBLIANT BIBLI	22.2.2.0	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	LATED	RELATED
Nausea	$16(\overline{2.2\%})$	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%)	
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	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%) <u>Pseudomonas aeruginosa</u> isolates. Many of these were isolated from sputum or endotracheal tubes or from chronic wounds. One strain each of <u>Proteus mirabilis</u> and enterococcus also developed resistance to <u>Primaxin</u>.

#### 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

	<u></u>	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Nausea	$16(\overline{2.2\%})$	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%)	
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%)	2,0.4%)		
Chest pain	2(0.3%	1(0.1%)	1(0.1%)		
Dyspnea	1(0.1%)	1(01.%)			

SYSTEMIC SIDE EN	FECTS	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
Syncope	$\frac{NO.}{1(0.1\%)}$	NOT RELATED 1(0.1%)	RELATED	RELATED	RELATED
Cyanosis	1(0.1%)	•	1(0.1%)		
Polyarthropathy	1(0.1%)		1(0.1%)		
LOCAL SIDE EFFE					
Phlebitis/throm			2(0.2%)	12(1,7%)	2(0.3%)
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%)

<sup>\*</sup>Five other patients had abnormal intestinal mucosa on colonoscopy or sigmoidoscopy or had  $\underline{C}$ . 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) tenic/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 defamandole 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

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# 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 pormal. 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.

<u>Deaths</u>: 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

#### Abnormal Laboratory Tests

lest	
SGPT (ALT)	(I)25
Alkaline phosphatase	(I)23
Serum chloride	(I) 3
Urine protein	(I) $I$
WBCs in urine	(I) $I$
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 (COFD, 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.

#### Abnormal Laboratory Tests

Test	
SCPT (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

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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 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

## 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 RESPO	NSE	
INFECTION SKIN & SKIN STRUCTURE (cellulitis)	<u>NO.</u>	1(100%) CURE	IMPROVE	FAIL
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 RESPO ERADICATED	NSE NUT ERADICATED
SKIN & SKIN STRUCTURE Corynebacterium spp S. aureus <sup>(R)</sup> E. coli	1 1 1	1(100%) 1(100%) 1(100%)	
BONE/JOINT S. aureus(R) Streptococcus spp E. coli M. morganii P. mirabilis P. aeruginosa B. fragilis B. vulgatus	2 1 2 1 2 4 1 1	2(100%) 1(100%) 2(100%) 1(100%) 1(50%) 3(75%) 1(100%)	1(50%) 1(25%)
LOWER RESPIRATORY E. coli P. mirabilis P. aeruginosa S. marcescens	1 1 2 1	1(100%) 1(50%) 1(100%)	1(100%) 1*(50%)
UTI (Uncomplicated) E. coli	1	1(100%)	
UTI (Complicated) Strep. (Group B) Strep. (Group D	2	2(190%)	
enterococci) E. coli C. diversus	1. 4 1	1(100%) 2(50%)	2(50%) 1(100%)
Citrobacter spp	1	1(100%)	

<sup>\*</sup>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

TOTAL STOR STOR					
	<del></del>	PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
Fever	$\overline{1(5\%)}$	1(5%)	<del></del>		
Abdominal pain	1(5%)	1(5%)			
Diarrhea	1(5%)		1(5%)		

ORGANISM SKIN & SKIN STRUCTURE	NO.	BACTERIOLOGIC RESPON	NOT ERADICATED
Corynebacterium spp S. aureus <sup>(R)</sup> E. coli	1	1(100%) 1(100%) 1(100%)	
BONE/JOINT S. aureus <sup>(R)</sup>	2	2(100%)	
Streptococcus spp E. coli	1 2 1 2	1(100%) 2(100%)	
<ul><li>M. morganii</li><li>P. mirabilis</li><li>P. aeruginosa</li></ul>	1 2 4	1(100%) 1(50%) 3(75%)	1(50%) 1(25%)
B. fragilis B. vulgatus	1 1	1(100%) 1(100%)	
LOWER RESPIRATORY	,	. ( . 000)	
E. coli P. mirabilis	1 1 2	1(100%)	1(100%)
P. aeruginosa C. marcescens	2 1	1(50%) 1(100%)	1*(50%)
UTI (Uncomplicated) E. coli	1	1(100%)	
UTI (Complicated)	<b>-</b>	1(100%)	
Strep. (Group B) Strep. (Group D	2	2(100%)	
enterococci) E. coli	1 4	1(100%) 2(50%)	2(50%)
C. diversus Citrobacter spp	1	1(100%)	1(100%)

<sup>\*</sup>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

SISIEMIC SIDE ELI	-EU13				
	NO.	PROBABLY NGT KELATED	POSSIBLY RELATED	PROBABLY RELATED	DEFINITELY RELATED
Fever	$\overline{1(5\%)}$	1(5%)			
Abdominal pair	1(5%)	1(5%)			
Diarrhea	1(5%)		1 (5%)		

NDA 50-587

(Continued)

(COITETIQCA)		PROBABLY.	POSSIBLY	PROBABL Y	DEFINITELY
/ 000	NO.	NOT RELATED	RELATED	RELATED	RELATED
LOCAL Phlebitis	1(5%)		1(5%)		

Abnormal Laboratory Tests	
Hemoglobin	(D)1
Hematocrit	(D)1
WBC	I(D)
Eosinophils	(I)1
Platelets	(D)1
SGPT	I(I)
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 nean 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 iminonem 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  $\geq 16$  16 patients The results obtained in 13 patients considered eligible for efficacy evaluation were as follows:

INFECTION LOWER RESPIRATORY INTRA-ABDOMINAL	NO. 8 2 1	CLINICAL F CURE 1(12.5%)	IMPROVE 5(62.5%) 2(100%)	<u>FAIL</u> 2(25.0%)
BACTERIAL SEPTICEMIA SKIN & SKIN STRUCTURE	2		1(100%) 1(50%)	1 (50%)
ORGANISM LOWER RESPIRATORY	110.	BACTERIOLOGI ERADICATED		NOT ERADICATED
Acinetobacter calcoaceticus	3	2(66.7%)		1(33,3%)
P. aeruginosa	6			6(100%)
P. maltophilia	1 1			1(1.00%)
S. marcescens	i			1(100%)
INTRA-ABDOMINAL P. aeruginosa P. fluorescens	2	2(100%)		1(100%)
BACTERIAL SEPTICEMIA P. aeruginosa	1	1(100%)		
SKIN & SKIN STRUCTURE Strep (Group D enterococci) Enterobacter cloacae P. aexuginosa	2 1 2	1(50%)		1(50%) 1(100%) 2(100%)
SAFETY				
NO. OF PATIENTS: 40	SIDE EFFE	ECTS: 2(5%)		

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

SIDE EFFECTS					
<del></del>		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
LOCAL			4		
Erythema I.V.					
site	1(2.5%)	1(2.5%)			
Phlebitis/thro	mbo-				
phlebitis	1(2.5%)			1(2.5%)	

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

		CLINICAL	RESPONSE	
INFECTION	NO.	CURE	IMPROVE	FAIL
LOWER RESPIRATORY	8	$1(\overline{12.5}\%)$	5(62.5%)	
INTRA-ABDOMINAL	2	1(120)	2(100%)	2 (25 • 0/13)
BACTERIAL SEPTICEMIA	1.		1(100%)	
SKIN & SKIN STRUCTURE	2		1(50%)	1(50%)
SYTH & SYTH STROCTOUR	2		1 ( ) ( )	1()0%)
		BACTERIOLOG	NTO DESTIONS	_
ODCANICH	NO			-
ORGANISM	<u>NO.</u>	ERADICATE	<u>.u</u>	NOT ERADICATED
LOWER RESPIRATORY	7	0(44 70)		) ( 77 - 70)
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 S	SIDE EFF	ECTS: 2(5%)		
NO. OF PAILLING WITH COCAL S	DIOR CIT	LU13. 2(7%)		

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 TLATED	PROBABLY RELATED	DEFINITELY RELATED
LOCAL			**		
Erythema I.V.					
site	1(2.5%)	1(2.5%)			
Phlebitis/thromb	0-				
phlebitis	1(2.5%)			1(2.5%)	

CTOF			00
SIDE	F.F	トヒ	しっこ

SIDE EFFEC 3		PROBABLY	POSSIBLY	PROBABLY	DEFINITELY
	NO.	NOT RELATED	RELATED	RELATED	RELATED
SYSTEMIC			<del></del>	<del></del>	<del>10.10, 4.9, 4.11.</del>
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	l 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 Cotte de Nacre, Caen, France.
- M. Des Roseaux, Centre Hospitalier Universi aire, Cotte de Nacre, Caen, France.
- J. Modal, Hopital Claude Bernard, Paris, France.
- F. Vachon, Hopital Clauda 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 caphalothin 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 nationts provided a complete clinical history and underwent a ph, ical 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, Cotte 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 <b>-</b> 75
MEAN AGE (Years)	50.9	52.5
SEX		
Male	28	20
Female	19	18

# EVALUATION

-	Ξ	F	F		С	Д	c	`

معي منا منصر بالتنميم عيند	PRIMAXIN	CEPHALOTHIN
NO. OF CASES EVALUABLE	15	11
NO. OF SITES OF INFECTION EVALUABLE	16	11
NO. OF CASES UNEVALUABLE	32	2 <b>7</b>
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) (Evaluable Cases)	6-15	514

## RESULTS

		PRIMAXIN CLINICAL RESPONSE			CEPHALC TNICAL	THIN RESPONSE	
INFECTION SKIN & SKIN STRUCTURE (Abscess)	NO.	CURE IMP. 1(100%)	FAIL	<u>NO.</u>	ču.E	IMP.	<u>FA</u>
(Bronchitis, pneumonia, empyema)	7	5(71%)	2(2 <b>9%</b> )	5	4(80%)	1(20%)	
SEPTICEMIA	3	3(100%)		4	3(75%)	1(25%)	
<pre>UTI (Uncomp) (cystitis,    pyelonephritis)</pre>	4	4(100%)		1	1(100%)		
UTI (Complicated) (pyelonephritis)	1	1(100%)		1	1(100%)		

		PR DLAX	IN IC RESPONSE			CEPHAL BACTER IOLOG		
ORGANISM	NO.	ERAD	SUPP	NOT ERAD	<u>NO.</u>	ERAL	SUPP	NOT ERAL
SKIN & SKIN STRUCTURE								
S. aureus(S)*	1	1(100%)			~			
LOWER RESPIRATORY								
K. pnuemoniae	-				1	1(100%)		
P. multocída	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	3	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%)		
		, ,						
UTL (Complicated)								
K. pneumoniae	1	1(100%)			-			
E. coli	~				1	1(100%)		

#### \*(\$) = Sensitive

In the Primaxin treated group, I patient with an empyema developed a reinfection with a resistant P. aeruginosa strain. In the Cephalothin treated group, I 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		
SISTEMIC SIDE EFFECTS	1(2%)	1(3%)

#### LCCAL SIDE EFFECTS

		PRIMAXIN PROBABLY
Pain on infusion Phlebitis/thrombo-	$\frac{NO.}{1(2.12)}$	RELATED 1(2.1%)
phlebitis	1(2.1%)	1(2.1%)

		CEPHALOTH:	IN_
		PROBABLY	<del>_</del>
	NO.	RELATED	
Pain on infusion	$1(\overline{2.6\%})$	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%)
		CEPHALO THI	IN
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	I/I	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 <u>Primaxin</u>.

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, bilitubin, 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 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 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,

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

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,

Daikas, G., "King Paul" Hospital, University of Athens Medical

Glauser, M., Clinique Medicale Universitaire, Lausanne,

Hell, K., Chirurgische Abteiluy, Liestal, Switzerland Opperkuch, W., Ruhr-University of Bochum, Bochum, West Germany Ronald, A., Basic Sciences Center, St. Boniface General Hospital

Stamboulian, D., British Hospital of Buenos Aires, Buenos Aires,

Stille, W., Klinixum A. J. W. Goothe-Universitaet, Frankfurt,

Ten Napel, C., Hospital 'Ziekenzorg', Enschede, Holland Veriava, Y., Coronation Hosp.: al, Johannesburg, South Africa Wittmann, D., Allgemeines Krankenhaus Altona, Hamburg, West

Yourassowsky, E., Hospital Brugmann, Brussels, Belgium

N-50587-3

## Overall Summary of Studies Conducted Under Protocol 513

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

#### **EVALUATION**

#### EFF ICACY

	PR IMAXIN	CEFOTAXIME
NO. OF CASES EVALUABLE	69	69
NO. OF SITES OF INFECTION	0.0	84
EVALUABLE	88	•
NO. OF CASES UNEVALUABLE	54	42
REASONS CASES UNEVALUABLE		
	24	19
No pretreatment pathogen	1	0
Organism resistant to study drug	<u> </u>	1
Clinical diagnosis not clear	2	1.2
Inadequate bacteriologic cultures	8	1.3
Effective concomitant antibiotic	4	2
Treatment course too short	15	6
Treatment course too short	_	1
Infection not included in claims		
DOSE	PRIMAXIN 00 mg q 8 h	CEFOTAXIME 2 g q 8 h

### DURATION OF TREATMENT (Days)

•	5	patients patients patient
	65 patients 4 patients	4 patients 5

#### RESULTS

INFECTION SKIN & SKIN STRUCTURE (Wound infection, abs	cess,		IMAXIN L RESPONSE IMP. 2(.3%)	FAIL 1(62)	NO. 15	CEFOTA CLINICAL CURE 10(67%)	RESPONSE IMP. 3(20%)	FAIL 2(13%)
LOWER RESPIRATORY (Bronchitis, pneumoni bronchopneumonia, em	19 .a,	11(58%)	3(16%)	5( 26%)	24	18(75%)	3(12.5%)	3(12.5%)

Overall Summary of Studies Conducted Under Protocol 513

	PR IMAXIN	CEFOTAXIME
TOTAL NO. OF PATIENTS AGE RANGE (Years) MEAN AGE (Years)	123 16-80 52.6	111 18-81 54.9
SEX Male Female	78 45	o5 46
EVALUATION		

#### EFF ICACY

	PR IMAXIN	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	PR IMAX IN	CEFOTAX IME
	500 mg q 8 h	2 g q 8 h

#### DURATION OF TREATMENT (Days)

(Evaluable Cases)		
5-14	65 patients	63 patienus
15-17	4 patients	5 patients
33		l patient

#### RESULTS

			IMAXIN L RESPONSE			CEFOTA CLINICA	AXIME L RESPONSE	
INFECTION SKIN & SKIN STRUCTURE	16.	CURE 1,3(81%)	IMP. 2(13%)	FAIL 1(6%)	NO. 15	CURE 10(67%)	<u>BiP.</u> 3(20%)	FAIL 2(13%)
(Wound infection, absc cellulitis, erysipel	-		•	, .				
LOWER RESPIRATORY (Bronchitis, pneumonia bronchopneumonia, emplung abscess)		11(58%)	3(16%)	5(26%)	24	18(75%)	3(12.5%)	3(12.5%)

(Continued)			IMAXIN L RESPONSE			CLFOTA	AXIME RESPONSE	
INFECTION MEDIASTINITIS	$\frac{NO.}{1}$	CURE 1(100%)	IMP.	FAIL	$\frac{NO.}{1}$	CURE 1 ( 100%)	IMP.	FAIL
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, pyelonephr perinephric abscess		2(100%)			2	2(100%)		
INTRA-ABDOMINAL (Peritonitis, abscess cholangitis, cholec		6(40%)	5(33%)	4( 27%)	11	10(91%)	1(9%)	

		PR IMAX BACTER IOLOG		: <b>r</b> '		CEFOTA BACTER IOLOG		
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERAD
SKIN & SKIN STRUCTURE							- <u></u> -	
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 <b>%</b> )
K. pneumoniae	1.	1(100%)			1	1(100%)		
M. morganii	2	1(50%)		1(50 <b>%)</b>	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)

(Continued)		DD T. ( ) 1				CEROTA	VILLE	
		PRIMAX		τ.		CEFOTA BACTERIOLOG		-
	N/O	BACTERIOLOG		_	N/A		SUPP	<b>-</b> -
ORGANISM	NO.	ERAD	SUPP	NOT ERAD	<u>NO.</u>	ERAD	SOFF	NOT ERAL
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	_				ī	1(100%)		
F. coli	3	3(100%)			4	2(50%,		2(50%) <b>(</b>
H. influenzae	5	4(80%)		1(20%)	6	6(100%)		` '
H. parainfluenzae	1	1(100%)		2(0011)	1	1(100%)		
K. pneumoniae	1	1(100%)			ũ	2(100%)		
P. mirabilis	3	1(33%)		2(67%)	1	1(100%)		
	2	1(33%)		2(100%)	-	1(100%)		
P. aeruginosa	4			2(1004)				
MEDIASTINITIS								
S. aureus(R)	1	1(100%)						
S. marcescens	_				1			1(100%)
SEPTICEMIA								
S. aureus(S)	-				,	1/100%		
S. aureus <sup>(R)</sup>	ز	4(80%)		1(20%)	4	1(100%)		
S. pneumoniae	3	3(100%)			1	1(100%)		
E. cloacae	2	2(100%)			-	1/10083		
A. calcoaceticus	-				1	1(100%)		
C. diversus	_				1	1(100%)		2/128/
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. mirabílís	~				1	1(100%)		
P. vulgaris	~				2	2(100%)		•
S. marcescens	~				2	2(100%)		
Serratia spp.	1	1(100%)						
Meningococcus (Group 3)	) 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%)			_			
L. CIUBLAC	1	1(100%)						

•

(Continued)								
•		PRIMA				CEFOTA		
		BACTERIOLOG	IC RESPON				IC RESPONSE	
ORGANISM	NO.	ERAD	SUPP	NOT ERAD	<u>NO.</u>	ERAD	SUPP	NOT ERAD
LOWER RESPIRATORY		<del></del> -						
S. aureus <sup>(R)</sup>	-				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%) <b>(</b>
H. influenzae	5	4(80 <b>%</b> )		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 <b>%)</b>	1	1(100%)		
P. aeruginosa	2			2(100%)				
•								
MEDIASTINITIS								
S. aureus(K)	1	1(100%)						
S. marcescens	-				1			1(100%)
SEPTICEMIA								
S. aureus(S)	-							
S. aureus(R)	5	4(8 <b>0%</b> )		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%)		0.1.4.044.5
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	I	1(100%)						
UTI (Uncomp.)	•	1/10093			3	27.100%3		
E. ccli	1	1(100%)			2	2(100%)		
S. faecalis	1	1(100%)			~			
E. cloacae	1	1(100%)			~			

NDA 50~587

(Continued)								
		PR IMAX				CEFOTA		
	310	BACTER TO LOG			1/0		IC RESPONSE	-
ORGAN ISM	NO.	ERAD	SUPP	NOT ERAD	<u> 20.</u>	ERAD	SUPP	NOT ERAI
UTI (Complicated)								
S. aureus <sup>(R)</sup>	~				1	1(100%)		
E. coli	4	2(50 <b>%</b> )		2(50%)	3	3(100%)		
P. mirabilis	1	1(100%)			1	1(100%)		
P. vulgaris	1			l(100%)	-			
S. faecalis	1	1(100%)			-			
K. pneumoniae	1	1(100%)			-			
C. freundli	1			1(100%)				
C. diversus	-				1	1(100%)		
P. aeruginosa	3	2(67 <b>%</b> )		1(33%)	1			1(100%
INTRA-AB DOM INAL								
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%)		I(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. aeruginesa, 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,

,	m			<b>.</b> .
(	uon	т 1	nue	1

•		PR IMAX				ŒFOTA	XTME	
	]	BACTER LOLOG				BACTERIOLOG	IC RESPONSE	
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	<u>NO.</u>	ERAD	SUPP	NOT FRAI
UTI (Complicated)	<del></del> -							
S. aureus(R)	_				1	1,100%)		
E. coli	4	2(50%)		2(50%)	3	3(100%)		
P. mirabilis	1.	1(100%)		, ,	1	1(100%)		ــر
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-ANDOMINAL								
S. epidermidis	1	1(100%)			_			
S. mitis	_	•			1	1(100%)		
Strep (Group D)	2	2(100%)			_	, ,		
S. faecalis	7	5(717)		2(29%)	2	2(100%)		
E. cloacae	i	1(100%)			1	, ,		1(100%
E. 11	8	5(62.5%)		3(37.5%)	7	7(100%)		,
K. pheumoniae	3	2(67%)		1(33%)	1	1(100%)		
M. norganii	_				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  $\underline{E}$ ,  $\underline{coli}$  developed a reinfection with a different  $\underline{E}$ ,  $\underline{coli}$  strain.

Three patients in the defotaxime group, one with an infected ulcer due to  $\underline{M}$ . morganii, and two with complicated urinary tract infections due to  $\underline{E}$ . colirelapsed during the follow-up period.

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

SAFETY			PR IMAXIN	CEFOTAXIME	
TOTAL NO. OF PATIENTS NO. OF PATIENTS WITH NO. OF PATIENTS WITH	LOCAL SIDE B		123 8(6.5%)	111 3(3%)	
EFFECTS			13(10.5%)	9(8%)	
LOCAL SIDE EFFECTS					
		PROBABLY	PR IMAXIN		
T.C A sector	NO.	NOT	POSSIBLY	PROBABLY	DEF IN ITE LY
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-	- · · · · · · · · · · · · · · · · · · ·	_( - ( )		_ ( - v - v - v	
phlebitis	6(4.8%)			3(2.4%)	3(2,4%)
			CEFOTAXIME		
Phlebitis/thrombo-	3/3 <b>7%</b> \		1/0 0%)	1(0,0%)	1(0 0%)
phlebitis	3(2.7%)		1(0.9%)	1(0.9%)	1(0.9%)
SYSTEMIC SIDE LFFECTS	-		PRIMAXIN		
		PROBABLY	DAGG TREE		N 1979 TA ( TOUT
Navaaa	$\frac{NO.}{2(1.6\%)}$	NOT	POSSIBLY	PROBABLY 1(0.8%)	DEF IN ITE LY 1(0.8%)
Nausea Vomiting	2(1.0%)			1(0.0%)	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(0,00)	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		
Vomiting	1(0.9%)			1(0.9%)	
Diarrhea	3(2.7%)		2(1.8%)		1(0.9%)
Mucous in feces	1(0.9%)		1(0.9%)		
(C. difticile posit	ive)				
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 defotaxine 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 defotaxine for six days for complicated dystitis with bacteremia and died of septic shock.

#### Abnormal Laboratory Tests

TEST		PR IN	<b>MAXIN</b>	CEF	TAXIME
Hemoglobin		(D)	2	(D)	2
Hematocrit		(D)	1	(D)	ì
RB C			_	(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
Creatining			1	(I)	1
SGOT (AST)		(1)	6	(I)	4
SGPT (ALT)		(I)	6	(I)	5
Bilirubin		(I)	2	(I)	1
Alk. phosphatase		(I)		(I)	6
Serum potassium		` ,	_	(D)	1
	test		4	` '	-
Urine protein		(I)	2	(I)	I,
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 in a tions 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 Primakin 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  $\Gamma$ . 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 cafotaxime 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 the study drug was kept. Tolerance was evaluated on the basis of pain, erythema, induration of the vein, and ulceration of the

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 Serum concentrations of gentamicin were determined at least twice weekly for adjustment in gentamicin were determined at least twice Blood cultures and cultures of other suspected sites were obtained 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,
Guerra, J., Instituto de Enfermedades Tropicales Alexander Von

# Overall Summary of Studies Conducted Under Protocol 5004

	1000col 5004				
TOTAL NO. OF PATIENTS AGE RANCE (Years) MEAN AGE (Years) SEX Male	PR IMAXIN 102 15-79 48.9	GENTAMICIN/CLINDAMYCIN 112 16-84 50.4			
Female	64				
	38	57			
		55			

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#### EFF ICACY

	PR IMAXIN	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 pretrearment pathogen	19	24
Treatmen, course too short	10	4
Organism resistant to study drug	1	1
Inadequate bacteriologic cultures	2	3

DOSE	PRIMAXIN 500 mg q 6 h	GENTAMICIN 1.5 mg/kg q 8 h	CLINDAMYCIN 600 mg q 6 h
DURATION OF TRE	ATMENT (days)	PRIMAXIN	GENTAMICIN/CLINDAMYCIN
4-14 15-20		65 patients 5 patients	77 patients 3 patients

#### RESULTS

			MAXIN RESPONSE		GE!	NTAMICIN/CL	INDAMYCIN RESPONSE	
INFECTION  SKIN & SKIN STRUCTURE  (Wound infection, above cellulitis, carbuncle furuncle, ulcers)		QURE 9(64.3%)	IMP. 5(37.7%)	FAIL	NO. 17	CURE 11(64.7%)	IMP.	FAIL 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%)			1.1	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, cholecys	20 stitis)	16(80%)	2(10%)	2(10%)	24	14(58.3%)	8(33.3%)	2(8,3%)

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#### EFF ICACY

	PR IMAXIN	GENTAMICIN/CLINDAMICIN
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

DOSE

PRIMAXIN
500 mg q 6 h

1.5 mg/kg q 8 h

DURATION OF TREATHENT (days)

(Evaluable Cases)

GENTAMICIN
1.5 mg/kg q 8 h

CLINDAMYCIN
600 mg q 6 h

CENTAMICIN/CLINDAMYCIN

4-14 65 patients 77 patients 15-20 5 patients patients

#### RESULTS

		PR IMAXIN			GENTAMICIN/CLINDAMYCIN				
		CLINICAT	RESPONSE			CL IN ICAL	RESPONSE		
INFECTION	$\frac{NO.}{14}$	CURE	IMP.	FAIL	NO.	CURE	IMP,	FAIL	
SKIN & SKIN STRUCTURE		$9(\overline{64.3}x)$	5(37.7%)		17	11(64.7%)	4(23.5%)	2(11.8%)	
(Wound infection, absorbed cellulitis, carbuncle furuncle, ulcers)									
LOWER RESPIRATORY	12	11(91.7%)	1(8.3%)		21	16(76.2%)	4(19.0%)	1(4.8%)	
(Pneumonia, empyema, lung abscess)		, ,	• • •			,	, ,		
<u>SEPTICEMIA</u>	10	10(100%)			11	8(72.7%)	1(9.1%)	2(18.2%)	
UTI (Uncomplicated)	3	2(66.7%)	1(33.3%)		3	2(66.7%)	1(33.3%)		
(Cystitis, pyelo- nephritis)									
UTf (Complicated)	8	5(62.5%)	3(37.5%)		2	2(100 <b>%</b> )			
(Cystitis,		, ,	,						
pyelonephritis)									
INTRA-ABDOMINAL	20	16(80%)	2(10%)	2(10%)	24	14(58.3%)	8(33.3%)	2(8.3%)	
(Peritonitis, abscess, cholangitis, cholecys	stitis)								

- 105 -

1(100%)

NDA 50-587

(Continued)

**ENTERITIS** 

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

1 1(100%)

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

(Continued)		PR IMAX	TN:			GENTAMICIN:	CLINDAMYCIN	
		BACTER TO LOG		F.			JIC RESPONSE	
OD CANTEM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPP	NOT ERA.
OR GAN ISM	1	$1\overline{(100}$ %)		1101 11111				
Klebsiella spp.	ì	1(100%)			_			
B. catarrhalis	-	1(100%)			I	1(100%)		
S. marcescens	1	1(100%)			1	1(100%)		
M. meningitidis	_	1(100%)			î 1	1(100%)		
B. fragilis	_				1	1(100%)		
Fusobacterium	_				*	1(100%)		
SE PT I CEMIA								
S. aureus(S)	1	1(100%)			1	1(100%)		
S. aureus(R)	$\frac{1}{2}$	2(100%)			_	, ,		
S. epidermidis	_	<b>-</b> (,			1	1(100%)		
Alpha-hem-strep	1	1(100%)			1	1(100%)		
S. pneumoniae	1	1(100%)			1	1(100%)		
S. bovis	ī	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	ì	1(100%)			1	1(100%)		
B. fragilis	Ī	1(100%)			_			
B. melaninogenicus	1	1(100%)			_			
B. corrodens	1.	1(100%)			-			
UTI (Uncomp.)					_	3446 <b>34</b> 4		
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 <b>%</b> )		
P. mirabilis	1	2(00.7%)		1(100%)		2(100%)		
P. stuartii	1			1(100%)				
Pseudomonas spp	2	2(100%)		1(100%)	_			
<del>-</del> -	1	1(100%)			_			
P. aeruginosa	1	1(100%)						
INTRA-AB DOM INAL								
S. aureus(S)	_				1	1(100%)		
S. aureus(R)	2	1(50%)		1(50%)	2	2(100%)		
S. epidermidis	-	1(30%)		2(20%)	<del>-</del> 4	2(50%)		2(50%)
Streptococcus spp	_				1	1(100%)		-( J. J. J. J.
Alpha-hem-Strep	1	1(100%)			_	1(100%)		
Beta-hem-Strep	1	1(100%)			!		1(100%)	
S. faecalis	-	1(100%)			4	3(75%)	2(100%)	1(25%)
A. calcoaceticus	1	1(100%)			_	2(124)		-(
K. pneumonia:	2	2(100%)			2	1(50%)		1(50%)
K. Pitenmonita:	2	2(100%)			_	1,00%		-( ) ( 4 )

(Continued)		PR IMAX	IN			GENTAMICIN,	CLINDAMYCI	N
		BACTER IOLOG		E		BACTER IOLOG		
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	NO.	ERAD	SUPF	NOT ERA
Klebsiella spp.	1	1(100%)				<del></del>		
B. catarrhalis	Ī	1(100%)			-			
	~	1(1004)			ı	1(100%)		
S. marcescens	1	1(100%)			î	1(100%)		
<ul><li>M. meningitidis</li><li>B. fragilis</li></ul>	-	1(100%)			1	1(100%)		
Fusobacterium					1	1(100%)		
rusobacterium					-	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	ì	1(100%)			1	1(100%)		
S. bovis	ī	1(106%)			_	- ( - : - ;		
E. coli	4	4(100%)			6	4(66.7%)		2(33.3%
Klebsiella spp	_	.(255,4)			ī	1(100%)		•
P. mirabilis	~				1	i(100%)		
Salmonella (Group B)	1	1(100%)			-	_(		
Bacteroides spp	ì	1(100%)			1	1(100%)		
B. fragilis	ì	1(100%)			-	_(400.0)		
B. melaninogenicus	ì	1(100%)			_			
B. corrodens	1	1(100%)			_,			
b. corroadis	•	1(100%)						
UTI_(Uncomp.)								
E. coli	3	2(66.7%)		1(33.3%)	3	2(66.7%)		1(33,3%
2. 0011	·	•(00,000)		-((-,-,	_	( • • • • • • • • • • • • • • • • • • •		
UTI (Complicated)								
E. coli	3	2(66.7%)		1(33.3%)	2	2(100%)		
P. mirabilis	1	2(*******)		1(100%)	_	(- ',		
P. stuartii	ì			1(100%)	_			
Pseudomonas spp	2	2(100%)		_(_,,,,,	_			
P. aeruginosa	1	1(100%)			_			
INTRA-AB DOM IN AL	•	1(100,0)						
HITING ADDOTTERNAL								
S. aureus(S)					1	1(100%)		
S. aureus(R)	2	1(50%)		1(50%)	2	2(100%)		
S. epidermidis	-	1(30%)		1(30%)	4	2(50%)		2(50%)
Streptococcus spp					1	1(100%)		( )/
Alpha-hem-Strep	1	1(100%)			_	1(1004)		
Beta-hem-Strep	I	1(100%)			1		1(100%)	
S. faecalis	_	1(100%)			4	3(75%)	-(0/2)	1(25%)
A. calcoaceticus	1	1(100%)			_	5(.54)		-(/
K. pneumoniae	2	2(100%)			2	1(50%)		1(50%)
K. PHEUMONIAE	2	2(100%)			<del>-</del>	1 200)		-( ) 40 /

(Continued)								
		PR IMAX				GENTAMICIN,		
			GIC RESPONSE			BACTER TOLOG		
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	NO.	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. mírabilis	-				1			1(100%)
P. rettgeri	-				ì	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%)
R. bivius	1	1(100%)				<b>,</b> ,		,
B. melaninogenicus	_				1	1(100%)		
B. ruminicola	_				1	1(100%)		
						, ,		
GYNE COLOGIC								
S. aureus(R)	_				1			1(100%)
S. epidermidis	1	1(100%)			_			
Strep (non-hem)	ī	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	Î	1(100%)			_			
K. pneumoniae	1	1(100%)			_			
P. mirabilis	î	1(100%)			_			
P. aeruginosa		1(100%)			1	1(100%)		
N. gonorrhoeae	_				î.	1(100%)		
E. Lentum	_				1	1(100%)		
e. Tenedm					-	1(100%)		

(Continued)								
•		PR IMAX	IN			GENTAMICIN/		
		BACTER TO LOG	IC RESPON	SE		BACTERIOLOC	IC RESPO	NSE
OR GAN ISM	NO.	ERAD	SUPP	NOT ERAD	NO.	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 / JO INT								
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		
	PR IMAXIN	CLINDAMYCIN/GENTAMICIN
TOTAL NO. OF PATIENTS	102	112
NO. OF PATIENTS WITH LOCAL SIDE		
EFFECTS	6(5.9%)	5( 4 <b>.5%)</b>
NO. OF PATIENTS WITH SYSTEMIC		
SIDE EFFECTS	17(16.7%)	25(22.3 <b>%</b> )

LOCAL SIDE EFFECTS			PR IMAXIN		
	NO.	PROBABLY NOT	POSSIBLY	PROBABLY	DEF IN ITELY
Phlebitis/thrombo- phlebitis	6(5.9%)	1(1.0%)		3(3.0%)	2(1.9%)
		G	ENTAMICIN/CLIND	AMY C IN	
Infused vein pain	2(1.8%)			2(1.8%)	
Vein induration Phlebitis/thrombo-	1(0.9%)			1(0.9%)	
phlebitis	2(1.8%)			1(0.9%)	1(0.9%)

#### SYSTEMIC SIDE EFFECTS

SISTEMIC SIDE EFFECT.	2_		PRIMAXIN		
		PROBABLY			
	110.	NOT	POSS IBLY	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%)		
Hemoptys1s	1(1.0%)	1(1%)			
Anxiety	1(1.0%)	1(1%)			
		GE	NTAMICIN/CLINDA	MYCIN	
		GE	NTAMICIN/CLINDA	MYCIN	
Nausea	1(0.9%)	GE 1(0.9%)	NTAMICIN/CLINDA	MYCIN	
Nausea Vomiting	1(0,9%) 1(0,9%)		NTAMICIN/CLINDA	MYCIN	
	•	1(0.9%)	NTAMICIN/CLINDA	2(1.8%)	1(0.9%)
Vomiting	1(0,9%)	1(0.9%) 1(0.9%)			1(0.9%)
Vomiting Diarrhea	1(0,9%) 10(8,9%) 2(1,8%)	1(0.9%) 1(0.9%) 6(5.3%)			1(0.9%)
Vomiting Diarrhea Hiccups	1(0,9%) 10(8,9%) 2(1,8%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%)			1(0.9%)
Vomiting Diarrhea Hiccups Increased salivation	1(0,9%) 10(8,9%) 2(1,8%) 1(0,9%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%)	1(0.9%)		1(0.9%)
Vomiting Diarrhea Hiccups Increased salivation Fever	1(0,9%) 10(8,9%) 2(1,8%) 1(0,9%) 2(1,8%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%)	1(0.9%)		1(0.9%) 2(1.8%)
Vomiting Diarrhea Hiccups Increased salivation Fever Chills	1(0,9%) 10(8,9%) 2(1,8%) 1(0,9%) 2(1,8%) 1(0,9%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%)	1(0.9%) 2(1.8%)	2(1.8%)	
Vomiting Diarrhea Hiccups Increased salivation Fever Chills Rash	1(0,9%) 10(8,9%) 2(1,8%) 1(0,9%) 2(1,8%) 1(0,9%) 8(7,1%) 1(0,9%) 2(1,8%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%) 1(0.9%)	1(0.9%) 2(1.8%)	2(1.8%) 3(2.6%)	
Vomiting Diarrhea Hiccups Increased salivation Fever Chills Rash Urticaria	1(0,9%) 10(8.9%) 2(1.8%) 1(0.9%) 2(1.8%) 1(0.9%) 8(7.1%) 1(0.9%) 2(1.8%) 1(0.9%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%) 1(0.9%) 1(0.9%) 1(0.9%) 2(1.8%)	1(0.9%) 2(1.8%)	2(1.8%)	
Vomiting Diarrhea Hiccups Increased salivation Fever Chills Rash Urticaria Headache	1(0,9%) 10(8,9%) 2(1,8%) 1(0,9%) 2(1,8%) 1(0,9%) 8(7,1%) 1(0,9%) 2(1,8%) 1(0,9%) 1(0,9%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%) 1(0.9%) 1(0.9%)	1(0.9%) 2(1.8%)	2(1.8%) 3(2.6%) 1(0.9%)	
Vomiting Diarrhea Hiccups Increased salivation Fever Chills Rash Urticaria Headache Dizziness	1(0,9%) 10(8.9%) 2(1.8%) 1(0.9%) 2(1.8%) 1(0.9%) 8(7.1%) 1(0.9%) 2(1.8%) 1(0.9%)	1(0.9%) 1(0.9%) 6(5.3%) 2(1.8%) 1(0.9%) 1(0.9%) 1(0.9%) 1(0.9%) 2(1.8%)	1(0.9%) 2(1.8%)	2(1.8%) 3(2.6%)	

\*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) I
Platelet count	_	(I) 2
Platelet estimate	(I) 4	(D) 1
Positive Coombs' Test	2	2
BUN	(I) l	(I) 2
Blood urea	(I) 1	(I) 2
Creatinine	(I) 4	(I) 22
Serum uric acid	-	(I) 6
SGOT (AS AI)	(I) 9	(I) 10
SGPT (ALAT)	(I) 12	(I) 11
Bilirubin	(I) l	(I) 1
Alk. phosphatase	(I) 7	(I) 6
Serum potassium	(I) l	(I) 2
	(D) 1	(D) 1
Serum chloride	(D) 1	(D) 4
Urine protein	(1) 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  $1.5~\rm grams$  (500 mg q 8 h) or  $2.0~\rm grams$  (500 mg q 6 h), depending on the severity of the infection. Each dose was given by intravenous infusion over a  $15-\rm minute$  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. 500

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 EVALU	ABLE: 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	IM PRO VE	FAIL_
SKIN & SKIN STRUCTURE	44	34 (77.3%)	8 (18.2%)	2 (4.5%)
(Wound infection,				

abscess, cellulitis, carbuncle/furuncle, decubitus & other skin ulcers

NDA 50-587	- 113			
(Continued)				
BONE / JOINT	1	1 (100%)		
(Pyugenic 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 F	DEC DONCE	
	<del></del>	CLIVICAL F	RESTORSE	
UTI (Uncomplicated)	NO.	CURE	IMPROVE	FAIL
(Cystitis,	5	5 (100%)		
pyelonephritis)				
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 RESI	PONSE
SKIN & SKIN STRUCTURE	NO.		ERADICATED	
Gemella	1		1 (100%)	
S. aureus <sup>S</sup>	5		5 (100%)	
S. aureus <sup>R</sup>	9		8 (89.9%)	
S. epidermidis	4		3 (75%)	
Streptococcus spp.	2		2 (100%)	
Streptococcus (Group A)	3		3 (100%)	
Streptococcus (Group C)	1 6		1 (100%) 4 (66.7%)	
Streptococcus (Group D) Enterococci)	C		7 (00.7%)	
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	i	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%)
_	1	1 (100%)
Pseudomonas aeruginosa	1	1 (100%)
Clostridium perfringens	3	3 (100%)
Pertococcus spp.	2	2 (100%)
Peptostreptococcus spp.	3	3 (100%)
Bacteroides fragilis	1	1 (100%)
Fusobacterium spp.		1 (100%)
Acidaminococcus fermentans	1	1 (100%)
ORGANISM BONE/JOINT	NO.	BACTERIOLOGIC RESPONSE ERADICATED
S. aureus <sup>R</sup>	1	1 (100%)
INTRA-ABDOMINAL		
S. aureus <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	3 3	3 (100%)
S. epidermidis	4	4 (100%)
Streptococcus spp.	1	1 (100%)
Streptococcus (Group D)	3	3 (100%)
Enterococci)		,
Streptococcus faecalis	1	1 (100%)
Streptococcus viridans	5	5 (100%)
Non-hemolytic	2	2 (100%)
streptococci		,
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	ī	1 (100%)
Clostridium spp.	1	1 (100%)
Clostridium perfringens	<u>1</u>	1 (100%)
Propionibacterium spp.	1	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	8	5 (83.3%)
Bacteroides fragilis	1	1 (100%)
<b>*</b> ***		

(Continued)	NO.	<u>ERADICATED</u>
Acinetobacter spp.	1	0
Enterobacter spp.	4	3 (75%)
	i	0
Enterobacter aerogenes	19	
Escherichia coli		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 <sup>R</sup>	1	1 (100%)
INTRA-ABDOMINAL		
S. aureus <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	3	3 (100%)
S. epidermidis	4	4 (100%)
Streptococcus spp.	1.	1 (100%)
Streptococcus (Group D)	3	3 (100%)
Enterococci)	•	(200%)
Streptococcus faecalis	1	1 (100%)
Streptococcus viridans	5	5 (100%)
Non-hemolytic	2	2 (100%)
streptococci	<b>2-</b>	2 (130%)
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 (36.7%)
Proteus mirabilis	2	2 (100%)
	3	2 (66,7%)
Proteus vulgaris		•
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.	i	1 (100%)
Peptostreptococcus spp.	1	1 (100%)
Bacteroides spp.	6	5 (83.3%)
Bacteroides fragilis	1	1 (100%)

LOWER RESPIRATORY	NO.	ERADICATED
S. aureus <sup>S</sup>	4	4 (100%)
S. aureus <sup>R</sup>	2	2 (100%)
S. epidermidis	1	0
Streptococcus spp.	1	1 (100%)
S. pneumoniae	2	2 (100%)
Streptonoccus (Group D)	3	2 (66.7%)
Encerococci)		
Escherichia coli	3	2 (66.7%)
Haemophilus influenzae	4	3 (75%)
Klebsiella pheumoniae	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  $\underline{P}$ .  $\underline{aeruginosa}$  persisted in the sputum were considered clinically cured by the investigator. Both these patients were in the same intensive care unit where  $\underline{P}$ .  $\underline{aeurginosa}$  was frequently isolated.

ORGANISM		BACTERIOLOGIC RESPONSE
GYNECOLOGIC	NO.	ERAD I CATED
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 <sup>R</sup>	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.	ERAD LCATED
S. aureus <sup>R</sup> S. epidermidis Streptococcus (Group D Enterococci)	5 4 5	5 (100%) 4 (100%) 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 <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	2	2 (100%)
S. epidermidis	2	2 (100%)
Streptococcus pneumoniae	1	1 (100%)
Streptococcus (Group D	1.	1 (100%)
Enterococci)		
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 <sup>R</sup> S. epidermidis Streptococcus (Group D	5 4 5	5 (100%) 4 (100%) 5 (100%)
Enterococci) Streptococcus faecalis Escherichia coli Proteus mirabilis	1 13 4 1	0 - 6 (46.2%) 1 (25%) 1 (100%)
Enterobacter spp. Citrobacter freundii Klebsiella pneumoniae Pseudomonas aeruginosa	1 1 3	0 - 0 - 2 (66.7%)
BACTERIAL SEPTICEMIA		
S. aureus <sup>S</sup> S. aureus <sup>R</sup> S. epidermidis Streptococcus pneumoniae Streptococcus (Group D	3 2 2 1 1	3 (100%) 2 (100%) 2 (100%) 1 (100%) 1 (100%)
Enterococci) Streptococcus faecalis Acinetobacter spp. Enterobacter aerogenes Escherichia coli Klebsiella neumoniae Salmonella (Group A) Bacteroides spp.	1 1 1 6 1 1	1 (100%) 1 (100%) 1 (100%) 6 (100%) 1 (100%) 1 (100%) 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 SI	E EFF	ECTS	 27	(11.5%)

Probably Not Related	Possible Related	Probably Related	Definitely Related
4.7%)	2 (0.8%)	6 (2.6%)	•
		, ,	
-	1 (0.4%)		3 (1.3%)
-		1 (0.4%)	
0.4%)	1 (0.4%)		
1.3%)		3 (1.3%)	
0.4%)		1 (0.4%)	
0.4%)		1 (0.4%)	
0.4%)			1 (0.4%)
1.3%)		1 (0.4%)	2 (0.8%)
0.4%)		1 (0.4%)	
0.4%)	1 (0.4%)		
3 8%) 4 (1 7%)	3 (1 3%)	1 (0.4%)	1 (0.4%)
		1 (0, 1,0)	1 (0:1,0)
• • •	• •		
2.1%)	4 (1.7%)	1 (0.4%)	
	4.7%) 4.3%) 2.6%) 0.4%) 1.3%) 0.4%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 1.	4.7%) 4.3%) 2.6%) 2.6%) 1.0.4%) 0.4%) 1.3%) 0.4%) 0.4%) 0.4%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 1.3%) 0.4%) 0.4%) 1.3%) 0.4%	4.7%)       2 (0.8%)       6 (2.6%)         4.3%)       2 (0.8%)       5 (2.1%)         2.6%)       1 (0.4%)       2 (0.8%)         0.4%)       1 (0.4%)         0.4%)       3 (1.3%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       1 (0.4%)         0.4%)       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		
WB C	(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 PAI	TIENTS
TOTAL NO. OF PATIENTS	1,656	
AGE RANGE (years)	12 - 101	
SEX		
Male Female	994 662	
EVALUATION		
EFF ICACY		
TOTAL NO. OF PATIENTS	1,656	
NO. OF PATIENTS EVALUABLE	1,116	
NO. OF SITES OF INFECTION EVA	LUABLE 1,253	
RESULTS		

#### 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%)	

INTRA-ABDOMINAL	NO.	CURE	IMPRO VE	FAIL
(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%)
ENDOCARLITIS	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  (Abscess, peritonitis, cholecystitis, cholangitis, liver abscess, perirectal abscess)	NO. 156	CURE 112 (71.8%)	IMPROVE 32 (20.5%)	FAIL 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 _		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	NO.	ERADICATED
S. aureus <sup>S*</sup>	7	7 (100%)
S. aureus <sup>R**</sup>	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	2	2 (100%)
not Group A		
S. bovis	1	1 (100%)
Other streptococcus species	9	9 (100%)
Group D streptococcus	7	4 (57%)
(enterococcus)		
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

All these factors contributed to the low eradication rate of  $\underline{P}$ . 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. marcescers	6	4 (67%)	
Alcaligens spp.	1	1 (100%)	

<sup>\*\*\* =</sup> 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.

(Continued)		
ORGANISM		BACTERIOLOGIC RESPONSE
LOWER RESPIRATORY	NO.	ERADICATED
	,	4
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%)
		, ,
		BACTERIOLOGIC RESPONSE
ORGANISM	NO.	ERADICATED
URINARY TRACT		
(UNCOMPLICATED)		
S. aureus <sup>S</sup>	1	1 (100%)
Group D Streptococcus	1	1 (100%)
(enterococci)		
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%)
r. aeruginosa	1	1 (100%)
URINARY TRACT		
COMPLICATED)		
<del></del>		
S. aureus <sup>R</sup>	6	5 (83%)
S. epidermidis	4	4 (100%)
Group B Streptococcus	2	2 (100%)
Group D Streptococcus	10	9 (90%)
(enterococci)	10	5 (30%)
S. faecalis	2	1 (50%)
		• • • • • • • • • • • • • • • • • • • •
E. coli	43	26 (60%)
P. mirabilis	12	6 (50%)
P. vulgaris	1	0
P. rettgeri	3 3	2 (67%)
M. morganii		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)		
Durant dament a series	1	0
Providencia spp.	1 2	0
Citrobacter diversus	2	0
Citrobacter freundii	1	1 (100%)
Citrobacter spp.	43	, ,
P. aeruginosa	2	36 (84%) 2 (100%)
Pseudomonas spp.	2	1 (50%)
S. marcescens	1	1 (100%)
Serratia spp.		1 (100%)
Bifidobacterium spp.	1	1 (100%)
Peptococcus spp.	1	1 (100%)
INTRA-ABDOMINAL	_	
S. aureus <sup>S</sup>	3	3 (100%)
S. aureus <sup>R</sup>	6	5 (83%)
S. epidermidis	6	6 (100%)
Streptococcus (Group A)	1	1 (100%)
S. viridans group	15	14 (93%)
Alpha-hemolytic	1	1 (100%)
streptococus	•	2 (200%)
Beta-hemolytic	2	2 (100%)
streptococcus	_	
Non-hemolytic	2	2 (100%)
streptococcus	<del></del>	~ (====,
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	13	11 (85%)
(enterococcus)	-	•
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 alongenes	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 freundíi	3	2 (67%)	
Citrobacter spp.	3	3 (100%)	
Acinetobacter	2	2 (100%)	
calcoaceticus		<b>,</b> , ,	
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%)	
Propionibecterium spp.	I	1 (100%)	
C. perfri gens	4	4 (100%)	
Clostridium spp.	22	22 (100%)	
Bifidobacterium	1	1 (100%)	
adolescentis	1	1 (100%)	
Bifidobacterium spp.	1	1 (100%)	
	1 6	6 (100%)	
Peptococcus spp.	9	8 (89%)	
Peptostreptococcus spp.		•	
Bacteroides spp.	21	20 (95%)	
B. fragilis	35	34 (97%)	
B. melaninogenicus	I.	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%)	
Salmoneila type B	1	0	

M. hominis

Ureaplasma urealyticum

		BACTERIOLOGIC RESPONSE		
ORGAN ISM				
GYNE COLOGIC	NO.	ERADICATED		
<b>.</b> *	2	2 /100%)		
S. aureus S* S. aureus R*	3	3 (100%)		
D. acreso	8	7 (88%)		
S. epidermidis	17	17 (100%)		
Alpha-nemolytic	3	3 (100%)		
streptococus	2	2 (100 <b>%</b> )		
S. viridans group	2	2 (100%)		
Non-hemolytic	3	3 (100%)		
streptococcus	20	20 / 20%		
Group B streptococcus	20	20 (100%)		
Other streptococcus spp.	7	7 (100%)		
Group D streptococcus	14	12 (86%)		
(enterococcus)		20 (01%)		
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	1	1 (100%)		
calcoaceticus				
Pseudomonas aeruginosa	1	0		
N. gonorrhoeae	3	3 (100%)		
Propionibacterium	1	1 (100%)		
granulosum				
Propionibacterium spp.	1	1 (100%)		
Clostridium perfringens	1	1 (100%)		
Bifidobacterium spp.	3	3 (100%)		
Gaffkya anaerobia	1	1 (100%)		
Peprococcus 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%)		
V handed	•	1 (100%)		

L

1 (100%) 2 (100%)

BACTERIOLOGIC	RESPONSE
---------------	----------

		PROTEKTOROGIC MEDICINOL
ORGAN ISM		
GYNT COLOGIC	NO.	ERAD I CATED
<b>*</b>	•	2 (100%)
S. aureus <sup>S*</sup> S. aureus <sup>R*</sup>	3	3 (100%)
b. dareas	8	7 (88%)
S. epidermidis	17	17 (100%)
Alpha-hemolytic	3	3 (100%)
streptococus		
S. viridans group	2	2 (100%)
Non-hemolytic	3	3 (100%)
streptococcus		
Group B streptococcus	20	20 (100%)
Other streptococcus spp.	7	7 (100%)
Group D streptococcus	1.4	12 (86%)
(enterococcus)		
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.	i	1 (100%)
Enterobacter aerogenes	2	2 (100%)
Enterobacter cloacae	1	1 (100%)
Enterobacter agglomerans	1	1 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter diversus Citrobacter freundii		1 (100%)
	1	1 (100%)
Acinetobacter calcoaceticus	1	1 (100%)
	,	0
Pseudomonas aeruginosa	1	0
N. gonorrhoeae	3	3 (100%)
Propionibacterium	1	1 (100%)
granulosum	_	. (100%)
Propionibacterium spp.	i	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%)
Veillonelia parvula	2	2 (100%)
Gardnerella vaginalis	7	7 (100%)
M. hominis		1 (100%)
Ureaplasma urealyticum	2	2 (100%)
•		

Flavobacterium spp.

	BACTERIOLOGIC RESPONSE	
ORGANISM		
BACTERIAL SEPTICEMIA	NO.	ERADICATED
S. aureusS	7	7 (100%)
	1	, ,
Micrococcus S.aureus <sup>R</sup>	21	1 (100%) 19 (90%)
	6	• •
S. epidermidis		6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic	1	1 (100%)
streptococcus	1	1 (100%)
Beta-hemolycic	1	1 (100%)
streptococcus	1	1 (100%)
Group A streptococcus	1,	1 (100%)
Streptococcus sanguis	I.	1 (100%)
Streptococcus bovis	1	1 (100%)
Other streptococcus spp.	10	10 (100%)
Group D streptococcus	4	4 (100%)
(enterocuccus)	2	3 (100W)
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. pneumoníae	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	1	1 (100%)
calcoaceticus		
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	l	1 (100%)
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides corrodens	1	1 (100%)
Bacteroides	1	1 (100%)
melaninogenicus		
Bacteroides spp.	4	4 (100%)
Fusobacterium spp.	2	2 (100%)
Flavohactorium can	1	1 (100%)

1 (100%)

		BACTERIOLOGIC RESPONSE
ORGANISM		
BACTERIAL SEPTICEMIA	NO.	ERADICATED
£		T
S. aureus <sup>S</sup>	7	7 (100%)
Micrococcus	1	1 (100%)
S.aureus <sup>R</sup>	21	19 (90%)
S. epidermidis	6	6 (100%)
S. pneumoniae	18	18 (100%)
Alpha-hemolytic	1	1 (100%)
streptococcus	_	
Beta-hemolytic	1	1 (100%)
streptococcus		
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	4	4 (100%)
(enterococcus)		
S. faecalis	3	3 (100%)
Bacillus subtilis	1 2	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	ī	1 (100%)
Acinetobacter	ī	1 (100%)
calcoaceticus	••	2 (2001)
Acinetobacter spp.	2	2 (100%)
Yersinia enterocolitica	ĩ	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 (100%)
	i	0
Clostridium spp.		1 (100%)
Corynebacterium acnes	1	· · · · · · · · · · · · · · · · · · ·
Peptostreptococcus spp.	2	2 (100%)
Bacteroides fragilis	6	5 (83%)
Bacteroides corrodens	1	1 (100%)
Bacteroides	1	1 (100%)
melaninogenicus	,	/ /100%)
Bacteroides spp.	4	4 (100%)
Fusobacterium spp.	2	2 (100%)
Flavobacterium spp.	1	1 (100%)

BACTE	RIC	OLOGIC	RES	PONSE

	<del></del>	DITOTORIO TO REDITORIO
ORGANISM	22.0	ED AD I CAMER
BACTEREMIA	NO.	ERADICATED
S S	1	1 (100%)
S. aureus <sup>S</sup>	1	1 (100%)
S. aureus <sup>R</sup>	2	2 (100%)
S. epidermidis	1	1 (100%)
S. pneumoniae	1	1 (100%)
Group D streptococcus	1	1 (100%)
(enterococcus)		
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	1	1 (100%)
S. aureus <sup>S</sup>	1	1 (100%)
S. aureus <sup>R</sup>	6	6 (100%)
S. pneumoniae	1	1 (100%)
3. sanguis	1	1 (100%)
Streptococcus spp.	1	1 (100%)
S. viridans group	1	1 (100%)
BONE / JO INT		
S. aureusS	8	8 (100%)
S. aureus <sup>R</sup>	23	22 (96%)
S. epidermidis	5	5 (100%)
S. pyogenes	1	1 (100%)
Beta-hemolytic	2	2 (100%)
streptococcus	<i>-</i>	2 (100%)
Streptococcus spp.	12	12 (100%)
Group D Streptococcus	5	5 (100%)
(enterococci)	•	5 (100%)
S. faecalis	5	5 (100%)
E. coli	5	4 (80%)
r. mirabilis		5 (63%)
P. vulgaris	8 2	1 (50%)
•	3	3 (100%)
M. morganii	1	0
Proteus spp.		0
Providencia stuartii	1 3	
Enterobacter aerogenes		3 (100%)
Enterobacter cloacae	6	6 (100%)
Citrobacter diversus	]	1 (100%)
Acinetobacter	1	1 (100%)
calcoace ticus	28	22 (79%)
P. aeruginosa	20	22 (13%)

		BACTERIOLOGIC RESPONSE
ORGANISM		
BONE/JOINT	NO.	ERAD I CATED
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	l	1 (100%)
S. aureus <sup>S</sup>	25	21 (84%)
S. aureus <sup>R</sup>	116	98 (84%)
S. epidermidis	23	18 (78%)
Alpha-hemolytic	11	11 (100%)
streptococcus		(,
S. viridars	3	3 (100%)
Beta-hemolytic	24	22 (92%)
streptococcus		
Group A streptococcus	28	26 (93%)
Group B streptococcus	13	11 (85%)
Group C streptococcus	1	1 (100%)
S. intermedius	ī	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%)
		1 (100%)
Enterobacter agglomerans	1	·
Enterobacter spp.	5	4 (80%)
Citrobacter freundii	4	4 (100%)
Citrobacter diversus	2	2 (100%)
Citrobacter spp.	2	2 (100%)
Acinetobacter	6	6 (100%)
calcoaceticus		

	BACTERIOLOGIC RESPONSE			
ORGANISM SKIN & SKIN STRUCTURE	NO.	ERADICATED		
SKIN & SKIN SIRUCIURE	110 .	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	i	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%)		
	2	2 (100%)		
OTITIS				
S. pneumoniae	1	1 (100%)		
UPPER RESPIRATORY				
S. aureus <sup>R</sup>	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 <sup>R</sup>	1	1 (100%)		

BRAIN ABSCESS	NO.	ERADICATED
S. aureus <sup>R</sup> SAFETY	1	1 (100%)
NO. OF CASES EVALUABLE		1,696
NO. OF PATIENTS WITH LOCA	L SIDE EFFECTS	79 (4.7%)
NO. OF PATIENTS WITH SYST	EMIC 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/	56 (3.3%)	3 (0.2%)	24 (1.4%)	22 (1.3%)	7 (0.4%)
thrombophlebitis					
SYSTEMIC SIDE EFFECTS					
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%)	,	<b>,</b>	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%)		<b>\</b>	
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%)	(1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 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	1 (0 05%)	1 (0.05%)			
syndrome	(	, , ,			

# SYSTEMIC SIDE

EFFECTS		Probably	Possibly	Probably	Definitely
	NO.	Not			·
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 )	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%)	1 (0.03%)	0 (0.5%)	2 (0.1%)	1 (0.05%)
Erythema multiforme	1 (0.05%)			2 (0.1%)	1 (0.05%)
Polyarthropathy	1 (0.05%)		1 (0.05%)		1 (0.00%)
Thoracic spine pain	1 (0.05%)		1 (0.03%)		1 (0.05%)
Pharyngeal pain	1 (0.05%)			1 (0.05%)	1 (0.0.0)
Increased salivation	1 (0.05%)			1 (0.05%)	
	1 (0.05%)			1 (0.00%)	1 (0.05%)
Glossitis	3 (0.2%)			3 (0.2%)	1 (0.00%)
Brown tongue			1 (0.05%)	•	
Hea:tburn	2 (0.1%)	1 (0 05%)	1 (0.03%)	1 (0.05%)	
Hiccups	1 (0.05%)	1 (0.05%)	17. (0. 9%)	16 (() 0%)	5 (0 3%)
Nausea	38 (2.2%)	3 (0.2%)	14 (0.8%)	16 (0.9%)	5 (0.3%)
Vemiting	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%)	
Pseudomembrancus 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 (%)
Parameter I PRCs	1 (0.1%)
Decreased RBCs	
Decreased hemoglobin	<b>\</b> - /
Decreased hematocrit	14 (0.8%)
Decreased WBC	22 (1.3%) 10 (0.6%)
Decreased neutrophils	· · · · /
Increased lymphocytes	2 (0.1%)
Increased monocytes	13 (0.8%) 69 (4.1%)
Increased eosinophils	` ' '
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).

#### Abnormal Laboratory Tests

	NO ABNOR	MAL (%)
1 226	1	/ O 1 7/ )
Decreased RBCs	1	(0.1%)
Decreased hemoglobin	17	<b>\</b> = • - · · ·
Decreased hematocrit	14	` '
Decreased WBC	22	, , , , , ,
Decreased neutrophils	10	,
Increased lymphocytes	2	(0.1%)
Increased monocytes	13	
Increased eosinophils	69	(4.1%)
Increased basophils	3	(0.2%)
Increased platelets	27	
Decreased platelets	12	
Prothrombin time (abnormal)	13	
Increased BUN	10	
Increased blood urea	4	
Increased creatinine	13	· · · · · · · ·
Increased bilirubin	13	•
Increased AST (SGOT)		(4.5%)
Increased ALT (SGPT)	83	• •
Increased alkaline phosphatase	61	/
Increased LDH	6	(0,4%)
Increased blood glucose	2	(0.1%)
Increased potassium	1	, ,
Decreased potassium	1	• •
Increased chloride	4	• • •
Decreased chloride	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

			DRUG RELATION	SHIP	
		Probably	Possibly	Probably	Definitely
	NO.	Not			
LOCAL SIDE EFFECTS					
Infusion site ulcer	0.07%)			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/	53 (3.9%)	12 (0.9%)	13 (1.0%)	21 (1.5%)	7 (0.5%)
thrombophlebitis	, ,	, ,	, .	•	·
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%))	t
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 (6,15%)	
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
Urtícaria	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

			DRUG RELATIONSHIP			
		<del></del>	Probably	Possibly	Probably	Definitely
SYSTEMIC SIDE EFFECTS	NO.	NO.	Not			
Pharyngeal discomfort	1	(0.07%)		1 (0.07%)		
Dry mouth		(0.15%)		2 (0.15%)		
Glossitis		(0.15%)		, ,	2 (0.15%)	
Heartburn		(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		(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		(0.4%)	2 (0.15%)	1 (0.07%)	2 (0.15%)	•
Pseudomembranous colitis	2	(0.15%)	•	,	1 (0.07%)	1 (0.07%)
Oral candidiasis		(0.3%)			4 (0,3%)	•
Taste perversion		(0.36)	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		(0.15%)	1 (0.07%)	1 (0.07%)		
Abnormal urine cclor		(0.22%)	1 (0.07%)	1 (0.07%)	1 (0.07%)	

Adverse Experiences in 133 Patients (usually one dose)

		DRUG RELATIONSHIP				
SYSTEMIC SIDE EFFECTS	_	Probably	Possibly	Probably	Definitely	
	NO.	Not				
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 losufficiency 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 veniting 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 2.9% 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.	Prob.					
	<u>Hot</u>	Not	Poss.	<u>Prob.</u>	Def.	Total	_ 5_
Hemoglobin decrease	2	4	1	1	0	8	.58
Hematocrit decrease	1	5	2	0	0	8	.58
MBC decrease	3	2	6	3	1	15	1.1
MBC increase	4(1)	4	1	0	0	9(1)	.66
Neutrophils decrease	C	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	7	4	27	13	2	47	3.4
Atypicai Lyc	0	1	0	0	0	7.	.07
Platelets decrease	4(1)	6(2)	6(1)	2(1)	0	· <del>1</del> 8(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	O	13(1)	.95
RBC Morph. Abnormal	1	1	0	0	0	2	. 15
BUN increase	7(2)	8(3)	2(1)	0	٥	17(6)	1.2
Creatinine increase	7(2)	12(2)	7(2)	1.	0	27(6)	2.0
Bilirubia 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)	12	9	0	<b>65(1)</b>	4.7
GGT	0	0	0	1	0	1	.07
Bl. Glucose	1(1)	1	Ö	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 MBCs	5	2	4	0	0	11	.80
Urine RBCs	5	4	r)	0	0	9	. <b>6</b> 6
Urine Epithelial Cells	2	٥	0	0	0	2	. 15
Urine Casts	0	0	1	0	0	1	.07
MBC 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/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 straptococci (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.
- . 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).

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# I. MICROSIDLOGY

II. GIGCHEMICAL, METABOLIC & PHARMACOLOGIC STUDIES

Animals: rabbit, rhesus monkey, rat

Reason for Creating Imigenem from Thienamycin: The Niz i gasup of thieramycin is highly ionizable in aqueous solin; therefore, its relatively high a kaline pH is high enough to induce the hydrolysis of the pola-i-ctam ring leading to the inactivation of the antibiotic.

Solution: By conating a formaridine derivative of the many in which the langer aroup, the ionization of the alkaline mainly or this new in as waped out. Note that this aikyl end of the drug shows a new pharmachoginally active moiety, an aminine; however, since this aminine is attached to is attached to is attached to is aitrogen along to the aikyl chain of one very right ring, we should call have derivative at alkalated aminine. The well known offerable and the aminine quantities group at drugs (particularly die) is not evident and the results of pharmachological studies. There is no reason to be concerned.

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search for the individual in a bountifully clammed, organized and executor study, the subject teams by searing the combest compound possession the pocksion promo al surecture (configuration) as interconyclin or imipenendisting the recen bis of 952-1. Into estimply, the inhibitor does not contain a begains semining, but a popular (carbokamide) in which the nearest 2 carbon acous (to the peptide cond) if the andre asid are a hymnogenated. That is the the enzymb which is implified by the discussed chanical motery is called "denydropeptodase.". (misequently, the imbilition is named a "ible-t iminities. So we conclude, by tending the enzyme with a talso (open) gab dropoutic, (without a bota-lactor ring actached), shouth only the recenters of the subusar epithelium (broth border) nzyme (DNP-1). specific for the ver right-hand ring (which posses) the dependential aciety) are Blocked by two inhibitor (cilastatin); paradoxically, another activity of this complex and highly unusual mambalian marks boush border untype, that pora lacianase function is inh. to: " cosulted a worlden nown enzymologist about these interestions spignation modes at vita of the enzymological decides. was transit is face reating and "I would rive to wrive this problem." In the are counciling appearing too be an entree. That there are to the academic than properly all them one of the will not be the condition and are view to that the formula by hippen or to modical cost to, herides its a sollect antibution or four at it is a now the disall refers ones around by the genlicant subject. It Stanific to be come to be no recommendation of the state to be or various collular room out, with more an earn comment.

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remail pathology. The coadministration of unlastatin had no effect on the excretion pattern of  ${\rm RA}_{\rm m}$ 

Radioactivity in the Feces: Megligible

Man: Uninary recovery of intact imipenem was 20%. The coadministration of cilastatin raises the amount of intact imipenem to 70%. The corresponding renal clearance estimates of impenem were 74% 182 mi/min. 95% of the RA in human urine was associated with intact imipenem & matabolite I.

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

Rat, Rabbit & Monkey: The chromatogram exhibited 2 peaks. One (major) corresponded to the impenem & 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 (140 & 358) 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 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: rhosus mankey, rat, rabbit, dog a man

Administration: Radiolabeled cilastatin Na alone or in combination with an equal dose of non-adioactive imigenem was administenced IV at doses of 5, 10 or 30 mpk of either drug in caidals. Humans were given 250 mg of imigenem. If C-cilastatin Na alone or in cambination with 250 or 1000 mg of imigenem.

Renal Excretion: In morkey, rabbit 3 man, this was the sole route of climination of cilastatic Ni doug-related naterials. (The NA found in the feces was negligible.) In one rat 8 dog, though renal excretion was over 50%, fecal excretion was also substantial (approx. ADC). In the rat, biliary excretion was significant, and enterohopatic circulation was evident.

Imponen does not alter the excretion of intact dilastatin Na. Approx. amounts of intact dilastatin Na excreted in the unine were 15% for the rabbit, 45% for the monkey & 37% for man, whether or not impenem was doadministered. For a given species, repal clearance of intact dilastatin Na are similar

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between treatments; the values for the rabbit, mankey & min 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 impenem. Plasma RA levels decreased rapidly in all species; greater than a 100-fold reduction occurred within 6 lms, with or without the coadministration of impenem. The metabolism of cilastatin Na in primates appears to be mainly acetylation to the N-acetyl conjugate. In the rat, lower uninary recoveries of  $^{55}\rm -RA$  vs.  $^{14}\rm C-RA$  suggest cleavage of the cysteinyl moiety of cilastatin Na

There was no accumulation of radiolabeled material by rac tissues. Liver, kidney & small intestine gave the highest tissue-classe ratios. Although the levels were high in the early time periods, the tissue conclus 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 mats as measured by pH, additity, volume or add bepsin output.

Imipenem did not alter the transit time of chargoal test meal in mice at Hoses up to 20 mpk SC & 100 mpk IV.

# Cardiovascular System

Blood pressure, heart rate & autonomic activity in anesthetized dogs were not altered by independ at 4 mpk 17. The autonomic resonnse of BP to high IV doses of imipenem were twastred in the anesthetized dog. At doses up to 100 mpk, it did not affect autonomic activity.

Tested at 20 mpk  $1^{\circ}$  in 5 spontaneously hypertensive rats, it did not significantly lower DF. It did, however, cause a slight, transient presson 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 rosp, rate, systolic BP & HP.

## Central Nervous System

In a standard pharmacometric screen for CNS effects in the mouse, imipenengave 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. FEG arousal was increased 45 min. after admin. of 200 mpk.

The effects of high doses of imipenem on locomotor activity and normal brdv 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 probabilism of charcoal test meal in mice was not affected at doses up to  $100~\mathrm{mpk}$  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 after 3P or 12 and it neither blocked by enhanced any of a variety of autonomic stimuli.

the autonomic responses of BP to high IV the a were measured in the anesthetized dug. Gi)astatin did not affect BP, HR, resp. rate or ECG.

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## Central Nervous System

Cilastatin Na was tested at doses of 6, 20 & 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.

### IHIPENEM/CILASTATIN

#### G.I. System

IV doses up to 100 mpk each of imipener & 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 impened at doses up to 100 mpk.

# Cardiovascular System

The autonomic responses of BP to high duses of the combination were measured in the anesthetized dog. At doses of 25%5 or 300%00 mpk, there was no signification of the carotid sinus reflex which may be a lated so a decrease in mean 8%.

When studied for effect on BP BR resp. rate & ECC in anesthetized dogs, the combination at 100.100 mpk IV (hightly decreased mean BP; lower doses (25:25 mpk) had no effect on BP or other parameters.

### Central Nervous System

In nice, the combination in doses up to 100:100 had no effect on gross behavior or pupil size and possessed no anticonvulsant activity.

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The effect of the combination was studied in rats in locomotor activity and normal body temp. Boses of  $100.100~\rm mg\,k$  had no affect on the neuromiscular 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 FOXICITY

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 everyiew of the toxicity, the results of all toxicity studies will be summarized here, following that of the applicant.

#### A. Studies with Impenen

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 ED50 values for imipenem in both species ranges approx. 1500 to greater than 2000 mpk with no sexor species-related differences apparent.

Rats administered iminenem 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 iminenem to this same species at a lovel of 120 mak May for 6 mos, produced no evidence of renal damage. Thus, a mathem him threshold exists for industion of nephrotoxicity by unit auticious or this species.

## B. Studies with Cilastatin

The low order of toxicity of cilastatin Na was demonstrated initially in acute toxicity tests. Oral LDgg values in mice 4 rats are greater than 10 gm/kg. IV LDg0 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 sits of SC injection, indicating slight local irritation produces by this route of admin. This route was necessitated by the high viscosity of the dosing so: '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 leute toxicity of imipener/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 LD50 values ranged from apprex. 900-1200 mpk/day in mice & rats.

SO 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 mmk/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 lever dose levels—ho other evidence of adverse effect was observed with this combination of drugs in this species.

## D. Staties in Inter. Amkeys

The toxicity of imigener/culastatingle was evaluated in nechatal & infant rhasus mankeys at gosego levels up to 188:180 mok/day. In the former bridy, dray, idean, was begun within 3 days of birth and continued for 10-12 wks. The latter study began within 5-8 was of age and continued for 16 wks. He evidence of induced toxicity was observed in either study.

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#### V. REPRODUCTION STUDIES

# IMTPENEM - 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 mats received up to 900 mpk/day during the period of organogenesis. The mat, being the least sensitive abidal to the toxicity of the drug, showed an unusually high level of tolerance, even in these studies.
- B. Rabbits: Docage Invels up to 60 mol/day during organogenesis did cause embryo- & fetotoxicity at maternotoxic dose levels, but no evidence of fetal malformation. The level telemated by the dams & embryos/feti was 30 mok/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.

## 8. Effect on Fetal Development in Rats & Mice

I.P.: The applicant's remarks: "Excessive toxicity observed in maphits at row dosage levels in range finding studies practiced the use of this species for evaluation." (Though the letails of the range-finding study are submitted, the study will not be reviewed until the problem is resolved.)

Reviewer's Comments: This indusual charge of texticity in the same species [40:70] mpk/day = nephrotexicity) vs. other raphit studies whose the "no deparatoxicity dose effect revel" was 120:320 mpk/day (single dose, 180:180 mpk/day for binos.) is presently discussed with the reviewing group and Dr. Blois of MSD. Though this appears to be a cosmetic problem, it is not. If the e is so much difference in nephrotexicity 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 prognant 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 F1 pups at 80:80 mpk/day. Although no consistent similar response was observed at higher cose 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 Ha
  - 1. V-79 mammalian cell; forward (mtation: without metabolic activation.

Results: No evidence of mutation.

2. Hopatocyte unscheduled DNA synthesis; without metabolic activation.

Poscits: No evidence of mutagenesis; no clastegenic potential.

conclusions: "The results of in vitro & in vivo assays with imidenem and cilascatin Na alone and in combination have revealed no potential for introduction with genetic material."

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#### 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 mephrotoxic 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 & lord 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 citemae of the rough endoplasmic reticulum, and loss of mibosomes; mitochondrial injury was not apparent until 8 hrs after treatment.

lo 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 neghrotoxicaty stalles in addits evaluated mephrotoxicity, votantial of repeated admin of imponential statio Na.

In a range-finding study in rabbits prior to a produce coratology study, moreality & most tubular degeneration were observed at relatively low done lovels (Ar-Ar, rok/day). The norphologic appearance of these changes was different from that observed in rabbits receiving impeneu alone. In a witton, no evidence of renal damage was observed in rabbits given the dombitation at much higher dose levels (up to 360:360 mpk). The additional witiple dose negree toxicity studies described in this volume

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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 imiponem-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 & cephsionides.

Studies were performed in rabbits to evaluate the nephrototic potential of the principal metabolites of impenes. Metabolites were administered by at doses shown to echieve sig. intracellular conclus in the kidner context. No evidence of renal damage was neserved.

Further studies were performed to explore the relationship between nephrotoxicity & alterations in tissue glutachione 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 impenem 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 concins 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 homolytic activity of imponem & cilastatin alone and in combination was evaluated in vitro. No evidence of hemolytic activity was observed. Concins of impenem flone at 10 mg/ml & higher produced a positive direct Coordic test; no similar results as observed at lower concins.

Ocular & dermal irritation studies were done in rabbits with imperom of cilastatin Ma. Very dight dermal irritation was observed with either agent after pracing 501 mg of the test agent in direct contact with abraded skin for 24 nrs: no irritation was observed in insact skin.

Ocular irritancy of the bolk compound was evaluated by placing 100 mm of the dry powder into the confectival bacs of robbits. The eye was closed for 50 sees, then degree on imitancy assessed. Moderate (reitation with cilastacin & slight irritation with emipenem were observed.

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#### CORMENTS & 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 vil. summarize the results and my request for repetition of toxicity studies in pregnant subbits. (This is in the framework of the teratogenicity studies which will include an extra group of nonpregnant frabbits otherwise receiving the same treatment as the pregnant sabbits.)

Reason for the Study: In the above pregnancy range-finding study, the applicant found & reported moderate-severe departopathology in the rabbits treated at 40:40 mpk/day parentically. The elaboration of the applicant on the etiology of the lesions is quite tranquilizing, but unacceptable. This elaboration indicates that the naphropathology of the treated pregnant rabbits is the result of drug-induced delydration & 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. Plois & 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 tipk/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 coxicologist 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 or octential endotoxic shock in among, and in particular pregnant women, needs no explanation. However, the point I would like to make here is that endotoxic sheer treated properly well on time is not always fatal. In spite of this, endotoxic spock resulting from an intrauterine accident in pregnant women is also always fatal. If the patient recovers from the acute inisode, the estimated the appropriate agencies might be very great, i.e., the Pouter thirds of the appropriate of the adversarial and another mecrosis. In its matter than be superimposed with a very well known complicating syndrome leading to a severe importance with a very well known complicating syndrome leading to a severe importance gathy, consequently making the fatal outcome more contain.

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The increasing of the above phenomenon in rabbass is probably the cest 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 TV/SC renatology Study in the Bat, "Slight decreases in fetal weight were observed for rats at 320:320 apk/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 Equal pure 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 "Expessive hephrotoxicity in rabbits at law dasage 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 night 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 indepent of the reviewing Medical Officer.
- 6. Drug Interaction: My consern is the potential interaction of theornylline with primaring with particular attention to the convulsigenic effects of primarin itself. As a understand it, the applicant is pinning special human studies for this. It leave the inclusion of this potential brownstick also to the stell.
- ্ৰ (my Mse of tar Tema Marily afficomaths") Asis versis interpretic in animal ৰিশ্বিতিয়া নি নি ভিত্তি ( lvc ) িন্ত টাইফালে । এক চাম with unimary

monost-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 "polyarthraldia". Or. Albrecht should be consulted about this.

Lorant Buko, D.V.M., M.Sc.

cc: Orig. NDA HFN-815 7: 9/16/85 HFN-815/MO CSO HFN-340 HFN-815/LBuko/smc/8/27/85 R/d init.by:JMDavitt 0045p