PRODUCT MONOGRAPH

PRIMAXIN®

(imipenem and cilastatin sodium for injection, USP)

I.V. Infusion

ANTIBIOTIC

MERCK FROSST CANADA LTD.
Kirkland, Quebec, Canada

Control: 133602 Date of Revision: February 19, 2010

NAME OF DRUG

PRIMAXIN®

(imipenem and cilastatin sodium for injection, USP)

I.V. Infusion

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

Imipenem exerts a bactericidal action by inhibiting cell wall synthesis in aerobic and anaerobic gram-positive and gram-negative bacteria.

PRIMAXIN® (imipenem and cilastatin sodium) consists of two components: (1) imipenem, a derivative of thienamycin, a carbapenem antibiotic; and (2) cilastatin sodium, a specific inhibitor of dehydropeptidase-I a renal enzyme which metabolizes and inactivates imipenem. Cilastatin blocks the metabolism of imipenem in the kidney, so that concomitant administration of imipenem and cilastatin allows antibacterial levels of imipenem to be attained in the urine.

Inhibition of cell-wall synthesis is achieved in gram-negative bacteria by the binding of imipenem to penicillin binding proteins (PBPs). In the case of *Escherichia coli* and selected strains of *Pseudomonas aeruginosa*, imipenem has been shown to have highest affinity for PBP-2, PBP-1a and PBP-1b, with lower activity against PBP-3. The preferential binding of imipenem on PBP-2 and PBP-1b leads to direct conversion of the individual cell to a spheroplast resulting in rapid lysis and cell death without filament formation. When imipenem is removed prior to complete killing of gram-negative species, the remaining viable cells show a measurable lag, termed a "post-antibiotic effect" (PAE), prior to resumption of new growth.

INDICATIONS AND CLINICAL USE

PRIMAXIN® (imipenem and cilastatin sodium) may be indicated in the treatment of serious infections when caused by sensitive strains of bacteria. Where considered necessary, therapy may be initiated on the basis of clinical judgment before results of sensitivity testings are available. Continuation of therapy should be reevaluated on the basis of bacteriological findings and of the patient's clinical condition.

Imipenem is active *in vitro* against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria, including most strains which are beta-lactamase producing. Patients have responded while under treatment with PRIMAXIN® for single or mixed infections of the following body systems, when they were associated with a number of pathogenic species and strains of the genera listed:

1. Lower Respiratory Tract Infections
2. Urinary Tract Infections
3. Intra-Abdominal Infections
4. Gynecological Infections
5. Septicemia
6. Endocarditis caused by *Staphylococcus aureus*
7. Bone and Joint Infections
8. Skin Structure Infections

PRIMAXIN® is not indicated for the treatment of meningitis.

Gram-positive Aerobes

Listeria monocytogenes
Nocardia asteroides
Staphylococcus (excluding many strains which are methicillin resistant)
Streptococcus

[Enterococcus faecium (formerly Streptococcus faecium) is not susceptible to PRIMAXIN®.]

Gram-negative Aerobes

Acinetobacter
Citrobacter
Enterobacter
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella
Morganella morganii
Neisseria
Proteus (indole positive and indole negative strains)
Providencia
Pseudomonas aeruginosa
Serratia marcescens

Gram-positive Anaerobes

Clostridium (excluding *C. difficile*)
Peptococcus
Peptostreptococcus

Gram-negative Anaerobes

Bacteroides fragilis
Bacteroides (non fragilis)

CONTRAINDICATIONS

PRIMAXIN® (imipenem and cilastatin sodium) is contraindicated in patients who have shown hypersensitivity to either component of this product.

WARNINGS

PRIMAXIN® (imipenem and cilastatin sodium) SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO STRUCTURALLY-RELATED DRUGS. IF AN ALLERGIC REACTION TO PRIMAXIN® OCCURS, DISCONTINUE THE

DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including PRIMAXIN®. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile. Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile.* In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile.* Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases. (see ADVERSE REACTIONS).

PRECAUTIONS

General

Prolonged use of PRIMAXIN® (imipenem and cilastatin sodium) may result in overgrowth of resistant organisms. Repeated evaluation of the patient's condition

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

Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction in serum valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction. In some cases of co-administration of imipenem with valproic acid, breakthrough seizures have occurred. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. The concomitant use of imipenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of PRIMAXIN® is necessary, supplemental anti-convulsant therapy should be considered (see Drug-Drug Interactions).

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN® especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or who have compromised renal function. However, there were rare reports in which there was no recognized or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged especially in patients with known factors that predispose to seizures (see DOSAGE AND ADMINISTRATION).

Anticonvulsant therapy should be continued in patients with a known seizure disorder. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of PRIMAXIN® should be decreased or discontinued (see Drug-Drug Interactions).

Use in Patients with Impaired Renal Function

Dosage in patients with impaired renal function is based on the severity of infection but the maximum daily dose varies with the degree of renal functional impairment (see DOSAGE AND ADMINISTRATION - Dosage in Patients with Renal Insufficiency).

Use in Pregnancy

The use of PRIMAXIN® in pregnant women has not been studied, therefore, PRIMAXIN® should be used during pregnancy only if clearly needed. Use of this drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards.

Reproduction studies with bolus I.V. doses suggest an apparent intolerance to PRIMAXIN® (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN® was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice (see REPRODUCTION STUDIES under TOXICOLOGY).

Nursing Mothers

Imipenem has been detected in human milk. If the use of PRIMAXIN® is deemed essential, the patient should stop nursing.

Pediatric Use

Efficacy and tolerability in infants under the age of 3 months have not yet been established; therefore, PRIMAXIN® is not recommended in the pediatric age group below the age of 3 months.

Drug Interactions

Drug-Drug Interactions

Generalized seizures have been reported in patients who received ganciclovir and PRIMAXIN®. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.

Case reports in the literature have shown that co-administration of carbapenems, including imipenem, to patients receiving valproic acid or divalproex sodium results in a reduction of serum valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction. In some cases of co-administration of imipenem with valproic acid, breakthrough seizures have occurred. The mechanism of this interaction is unknown (See PRECAUTIONS - General).

Concomitant administration of PRIMAXIN® and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life. It is not recommended that probenecid be given with PRIMAXIN®.

PRIMAXIN® should not be mixed with or physically added to other antibiotics. PRIMAXIN® has been administered concomitantly with some antibiotics, such as aminoglycosides.

There is no evidence to suggest that association of PRIMAXIN® with any other beta-lactam antibiotics has any therapeutic advantage.

ADVERSE REACTIONS

PRIMAXIN® (imipenem and cilastatin sodium) is generally well tolerated. The following adverse reactions were reported on 1,723 patients treated in clinical trials. Many of these patients were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN®.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with PRIMAXIN® were:

	Incidence (%)
Phlebitis/thrombophlebitis	1.7
Infused vein pain	0.6
Vein induration	0.2
Infused vein infection	0.1

Systemic Adverse Reactions

Adverse clinical reactions that were reported as possibly, probably or definitely related to PRIMAXIN® were:

	Incidence (%)
Gastrointestinal	
nausea	2.0
diarrhea	1.7
vomiting	1.6
tongue papillar hypertrophy	0.2
pseudomembranous colitis (see WARNINGS)	0.1
hemorrhagic colitis	<0.1
gastroenteritis	<0.1
abdominal pain	<0.1
glossitis	<0.1
heartburn	<0.1
pharyngeal pain	<0.1
increased salivation	<0.1

	Incidence (%)
CNS	
fever	0.4
dizziness	0.3
seizures (see PRECAUTIONS)	0.2
somnolence	0.2
confusion	0.2
myoclonus	0.1
vertigo	0.1
headache	0.1
encephalopathy	<0.1
paresthesia	<0.1
Special Senses	
transient hearing loss in patients with impaired hearing	<0.1
tinnitus	<0.1
Respiratory	
dyspnea	0.1
hyperventilation	<0.1
thoracic spine pain	<0.1
Cardiovascular	
hypotension	0.4
palpitations	0.1
tachycardia	<0.1
Renal	
oliguria/anuria	<0.1
polyuria	<0.1
Skin	
rash	0.9
pruritus	0.3
urticaria	0.2
skin texture changes	0.1
candidiasis	0.1
erythema multiforme	<0.1
facial edema	<0.1

	Incidence (%)
flushing	<0.1
cyanosis	<0.1
hyperhidrosis	<0.1
pruritus vulvae	<0.1
Body as a whole	
polyarthralgia	<0.1
asthenia/weakness	<0.1

Adverse Laboratory Changes

Adverse laboratory changes, without regard to drug relationship, that were reported during clinical trials were:

Hepatic: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs' test, decreased WBC and neutrophils, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils.

Electrolytes: Decreased serum sodium, increased potassium, increased chloride.

Renal: Increased BUN, creatinine.

Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

Post-Market Adverse Drug Reactions

The following reactions have been reported since the drug was marketed, but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians and pharmacists:

- Acute renal failure. The role of PRIMAXIN® in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.
- Anaphylactic reactions
- Bone marrow depression
- Exfoliative dermatitis
- Hallucinations
- Hearing loss
- Hemolytic anemia
- Hepatic failure
- Hepatitis
- Fulminant hepatitis
- Pancytopenia
- Psychic disturbances
- Staining of teeth
- Stevens-Johnson syndrome
- Taste perversion
- Toxic epidermal necrolysis
- Urine discoloration.

OVERDOSAGE

There are no data available on overdosage. PRIMAXIN® (imipenem and cilastatin sodium) is cleared by hemodialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

The dosage recommendations for PRIMAXIN® (imipenem and cilastatin sodium) represent the quantity of imipenem to be administered by I.V. infusion only. An equivalent amount of cilastatin is also present in the solution.

The dosage of PRIMAXIN® should be determined by the severity of the infection, renal function, body weight, the antibiotic susceptibility of the causative organism(s) and the condition of the patient. Doses cited are based on body weight of 70 kilos.

The median duration of treatment with PRIMAXIN® in clinical trials for infections of the various body systems ranged from 6 to 10 days except for endocarditis and bone and joint infections for which the median duration of treatment was 4 weeks.

Dosage in Adults

The recommended daily dose is 1 to 2 g administered in equally divided doses every 6 to 8 hours (see Table 1).

TABLE 1
ADULT DOSAGE OF PRIMAXIN®

	I.V. Administration		
Severity of infection	**Dose (mg of imipenem)**	**Dosage Interval**	**Daily Dose**
Mild	250 mg	6 h	1.0 g
Moderate	500 mg	8 h	1.5 g
Severe (fully susceptible)	500 mg	6 h	2.0 g
Severe* infections due to less susceptible organisms or life threatening conditions	1000 mg 1000 mg	8 h 6 h	3.0 g 4.0 g

* Primarily some strains of *P. aeruginosa*.

The maximum daily dose should not exceed 4 g or 50 mg/kg, whichever is less.

Dosage in Elderly Patients

The recommended dosage of PRIMAXIN® in elderly patients with normal renal function is the same as given for adults above. Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Dosage in Patients with Renal Insufficiency

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 (≤ 0.08 mL/s/1.73 m^2) should not receive PRIMAXIN® unless hemodialysis is instituted within 48 hours. Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive PRIMAXIN® after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN® is recommended only when the benefit outweighs the potential risk of seizures (see PRECAUTIONS). Currently, there are inadequate data to recommend the use of PRIMAXIN® in patients undergoing peritoneal dialysis.

TABLE 2
MAXIMUM DOSAGE OF PRIMAXIN® IN RELATION TO RENAL FUNCTION

RENAL FUNCTION	CREATININE CLEARANCE mL/min/1.73 m^2 (mL/s/1.73 m^2)	MAXIMUM TOTAL DAILY DOSAGE for infections due to fully susceptible organisms	MAXIMUM TOTAL DAILY DOSAGE for infections due to less susceptible organisms**
Mild impairment	31 - 70 (0.52 - 1.17)	1.5 g (0.5 g q8h)	2.0 g (0.5 g q6h)
Moderate impairment	21 - 30 (0.35 - 0.50)	1.0 g (0.5 g q12h)	1.5 g (0.5 g q8h)
Severe impairment*	0 - 20 (0 - 0.33)	0.5 g (0.25 g q12h)	1.0 g (0.5 g q12h)

* Patients with creatinine clearance of 6 to 20 mL/min/1.73 m^2 (0.1 - 0.3 mL/s/1.73 m^2) should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

** Primarily some strains of *P. aeruginosa.*

A further proportionate reduction in dose administered must be made for patients with a body weight <70kg.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance (mL/min). The serum creatinine should represent a steady state of renal function.

Males: $\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/100 mL)}}$

Females: 0.85 x above value.

When using the International System of units (SI), the estimated creatinine clearance (mL/s) in males can be calculated as follows:

$$\frac{\text{(lean body weight, kg) x (140 - age, years) x 1.4736}}{\text{(72) x (serum creatinine concentration, µmol/L)}}$$

and in females, the estimated creatinine clearance (mL/s) is:

$$\frac{\text{(lean body weight, kg) x (140 - age, years) x 1.2526}}{\text{(72) x (serum creatinine concentration, µmol/L)}}$$

PRIMAXIN® is cleared by hemodialysis. After each dialysis session the dosage schedule should be restarted.

Dosage in Infants and Children

The recommended total daily dosage of PRIMAXIN® in children and infants 3 months of age and older is 60 to 100 mg/kg of body weight divided into 4 equal doses given at six hour intervals. The higher dosages should be used for infants and young children. The total daily dosage should not exceed 2 grams. Clinical data are insufficient to recommend an optimum dose for infants and children with impaired renal function.

PRIMAXIN® is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

PRIMAXIN® may be used in children with sepsis as long as they are not suspected of having meningitis.

Administration

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

Each reconstituted 250 mg or 500 mg dose should be given by intravenous infusion over twenty to thirty minutes. Each 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed (for reconstitution, see RECONSTITUTION under PHARMACEUTICAL INFORMATION).

PHARMACEUTICAL INFORMATION

CHEMISTRY

Proper name: imipenem and cilastatin sodium for injection

Chemical names:

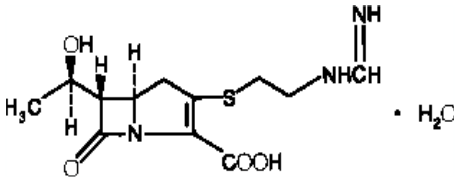
Imipenem

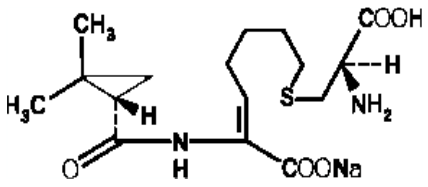
(5*R*,6*S*)-3-[[2-(formimidoylamino)ethyl] thio]-6-[(*R*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate.

Cilastatin sodium

Sodium (*Z*)-7-[[(*R*)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopropane-carboxamido]-2-heptenoate.

Structural Formulae:





Molecular Formulae:

$C_{12}H_{17}N_3O_4S \cdot H_2O$

$C_{16}H_{25}N_2O_5S\ Na$

Molecular Weights:

317.37

380.43

Descriptions:

Imipenem is an off-white, nonhygroscopic crystalline compound. It is sparingly soluble in water, and slightly soluble in methanol.

Cilastatin is an off-white to yellowish-white, hygroscopic, amorphous compound. It is very soluble in water and in methanol.

Composition:

Imipenem and cilastatin sodium are present in PRIMAXIN® in a 1:1 ratio by weight with sodium bicarbonate as a buffer.

Reconstitution

PRIMAXIN® is supplied in vials of either 250 mg or 500 mg imipenem equivalent and cilastatin equivalent when reconstituted.

Vials - PRIMAXIN®

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

A suggested procedure is to transfer approximately 10 mL from the 100 mL of the appropriate infusion solution to the vial (see list of diluents under **COMPATIBILITY AND STABILITY**). Shake well. Return the resulting 10 mL of suspension to the remaining 90 mL of the infusion solution.

Repeat, using 10 mL of the diluted suspension, to ensure complete transfer of the contents of the vial to the infusion solution.

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

COMPATIBILITY AND STABILITY

List of diluents

- 0.9% Sodium Chloride Injection
- 5% or 10% Dextrose Injection
- 5% Dextrose Injection with 0.02% sodium bicarbonate solution
- 5% Dextrose with 0.9% Sodium Chloride Injection
- 5% Dextrose with 0.225% or 0.45% saline solution
- 5% Dextrose with 0.15% potassium chloride solution
- Mannitol 5% and 10%

Reconstituted solutions

Solutions of PRIMAXIN® range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

PRIMAXIN®, as supplied in vials and reconstituted as above maintains satisfactory potency for **four hours at room temperature and for 24 hours under refrigeration (4°C)**.

AVAILABILITY OF DOSAGE FORMS

PRIMAXIN® (imipenem and cilastatin sodium) is supplied as a sterile powder mixture in vials containing imipenem anhydrous and cilastatin sodium with sodium bicarbonate as a buffer as follows:

250 mg imipenem equivalent and 250 mg cilastatin equivalent in vials.

500 mg imipenem equivalent and 500 mg cilastatin equivalent in vials.

STORAGE

The dry powder should be stored at 15°C-30°C.

MICROBIOLOGY

Mechanism of action

PRIMAXIN® (imipenem and cilastatin sodium) consists of two components: imipenem and cilastatin sodium in a 1:1 ratio by weight.

Imipenem is a B-lactam carbapenem antibacterial which is also referred to as N-formimidoyl-thienamycin. It is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium *Streptomyces cattleya*.

Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity.

Mechanism of resistance

Bacterial resistance to imipenem which has been observed clinically may be due to the following:

- Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins)
- Imipenem may be actively removed from the cell with an efflux pump.
- Reduced affinity of PBPs to imipenem
- Imipenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of some carbapenem hydrolysing beta-lactamases known as carbapenemases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target-based cross-resistance between imipenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes.

Interaction with Other Antimicrobials

Antagonism by imipenem of the activity of other beta-lactam antibiotics has been observed, *in vitro*, when tested against species of *Enterobacteriaceae* and *Pseudomonas aeruginosa* that contain Type-I chromosomal encoded cephalosporinase. The antagonism results from the reversible induction of the cephalosporinase by subinhibitory levels of imipenem. The organisms with induced levels of cephalosporinase, however, remain susceptible to imipenem.

Synergistic interaction with other antibiotics such as amino-glycosides has been observed in gram-negative species including *P. aeruginosa* and gram-positive species such as *E. faecalis and Nocardia asteroides*.

Spectrum of activity

The *in vitro* activity of imipenem against clinical isolates of various gram-positive and gram-negative aerobic and anaerobic species is shown in Table 3. Published studies were compiled to show the mean MIC_{50}s, MIC_{90}s and upper range as well as the distribution of these statistics among the many studies. The distribution is calculated as a frequency weighted cumulative distribution showing the minimum percent of isolates susceptible at the indicated concentrations.

Imipenem has antimicrobial activity against a range of clinically significant gram-positive and gram-negative aerobic and anaerobic pathogens (Table 3).

TABLE 3
THE *IN VITRO* ACTIVITY OF IMIPENEM AGAINST CLINICAL ISOLATES OF VARIOUS GRAM-POSITIVE AND GRAM-NEGATIVE AEROBIC AND ANAEROBIC SPECIES *

Organism	No. Strains	No. Studies	Range MICs	Geom Mean MIC_{50} (mg/L)	Geom Mean MIC_{90} (mg/L)	Distribution of Susceptibility, Minimum % Inhibited at Indicated Concentrations (mg/L) (+)								
						0.06	0.13	0.25	0.5	1	2	4	8	16
Gram Negative Aerobes														
Achromobacter xylosoxidans	64	3	1 - 8	2.67	4.79						21	63	100	
Acinetobacter calc. anitratus	183	8	0.007 - 12.5	0.21	0.39	4	6	55	90	96	97	97	97	100
Acinetobacter calc. alcaligenes	12	1	0.25 - 0.5	0.50	0.50				100					
Acinetobacter calc. haemolyticus	15	1	0.25 - 1	0.50	1.00				50	100				
Acinetobacter calcoaceticus	209	6	0.03 - 8	0.25	0.51			48	90	96	99	99	100	
Acinetobacter lwoffii	88	5	0.018 - 1	0.08	0.23	18	38	82	93	100				
Acinetobacter spp.	139	6	0.01 - >50	0.12	0.34		45	87	87	99	99	99	99	99
Aeromonas hydrophila	50	2	<0.05 - 4	0.21	0.79	5	10	55	55	91	91	100		
Alcaligenes faecalis	30	3	0.125 - 2	0.31	0.71			33	83	92	100			
Alcaligenes spp.	33	1	0.125 - 2	1.00	2.00					50	100			
Bordetella bronchicanis	18	2	0.125 - 32	2.24	4.00				14	14	14	93	93	93
Citrobacter diversus	173	8	0.1 - 2	0.35	0.64		7	37	74	79	100			
Citrobacter freundil	181	5	0.06 - 4	0.30	0.67		21	38	60	78	98	100		
Enterobacter aerogenes	136	1	0.05 - 8	0.29	0.93	6	19	32	56	69	91	98	100	
Enterobacter agglomerans	75	6	<0.13 - 4	0.46	0.92			5	54	90	90	100		
Enterobacter cloacae	306	2	0.03 - 12.5	0.21	1.07		34	36	47	80	98	99	99	100
Enterobacter spp.	824	6	0.03 - 8	0.34	1.18			32	47	77	90	99	100	
Escherichia coli	958	13	<0.06 - 25	0.11	0.24	19	54	75	92	97	98	98	99	99
Flavobacterium llb	33	18	0.15 - 128	2.97	28.07							50	50	50
Flavobacterium meningosepticum	14	3	16 - 64	21.53	43.07									29
Haemophilus influenzae	341	2	0.01 - 32	0.97	1.88	2	4	7	27	45	77	80	94	99
Hafnia alvei	14	11	0.1 - 1	0.18	0.46		18	50	90	100				
Klebsiella oxytoca	31	2	0.1 - 0.5	0.19	0.37	7	23	70	100					
Klebsiella pneumoniae	499	2	0.01 - 4	0.16	0.38	4	31	69	89	93	98	100		
Klebsiella spp.	376	11	<0.06 - 4	0.20	0.33		22	71	89	97	97	100		
Moraxella spp.	28	9	0.125 - 16	0.06	0.25	50	50	90	90	90	190	90	90	100
Morganella morganii	426	1 16	0.05 - 16	1.58	2.94				9	20	57	90	99	100

(+) Cumulative susceptibility distributions were tabulated by assigning for each study 50% of the number tested to the MIC_{50}, 40% to the MIC_{90} and 10% to the upper range cited and then taking the sum within each concentration range. Susceptibility was determined by both broth and agar dilution methods using an inoculum of 10^5 colony forming units (CFU) per mL.

* Bacterial samples were obtained prior to 1987 from international as well as North American sources which include pivotal clinical trials. Locally variable resistances have since been reported for organisms such as, among others, Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter, Staphylococcus.

TABLE 3 (continued)
THE *IN VITRO* ACTIVITY OF IMIPENEM AGAINST CLINICAL ISOLATES OF VARIOUS GRAM-POSITIVE AND GRAM-NEGATIVE AEROBIC AND ANAEROBIC SPECIES

Organism	No. Strains	No. Studies	Range MICs	Geom Mean MIC_{50} (mg/L)	Geom Mean MIC_{90} (mg/L)	Distribution of Susceptibility, Minimum % Inhibited at Indicated Concentrations (mg/L) (+)								
						0.06	0.13	0.25	0.5	1	2	4	8	16
Gram Negative Aerobes (cont'd)														
Neisseria gonorrhoeae	379	8	<0.004 - 1.28	0.09	0.28	18	41	75	83	97	100			
Neisseria gonorrhoeae (lact+)	23	1	<0.008 - 2	0.06	0.25	50	50	90	90	90	100			
Neisseria meningitidis	275	5	0.005 - >0.25	0.05	0.10	40	77	96	96	96	96	96	96	96
Pasteurella multocida	10	1	<0.06 - 2	0.50	1.00				50	90	100			
Plesiomonas shigelloides	15	1	<0.13 - 0.25	0.06	0.25		50	100						
Proteus mirabilis	581	15	0.03 - 32	1.12	2.90			10	13	29	62	89	99	99
Proteus vulgaris	158	8	0.05 - 8	0.92	2.96			12	17	29	64	90	100	
Proteus spp.	65	3	0.5 - 4	1.86	3.72					12	41	82	100	
Proteus/Providencia spp.	315	2	0.12 - 8	2.00	4.00						50	90	100	
Providencia rettgeri	88	5	0.05 - 8	0.64	1.47				37	70	86	93	100	
Providencia stuartii	131	7	<0.06 - 8	1.04	2.18			1	19	38	75	97	100	
Providencia spp.	87	5	0.12 - 8	1.19	1.80					41	93	96	100	
Pseudomonas acidovorans [a]	39	3	0.075 - 2	0.41	0.89				44	81	100			
Pseudomonas aeruginosa	1917	32	0.05 - 250	1.42	3.25					27	64	85	93	99
Pseudomonas cepacia [b]	77	6	0.018 - >50	13.84	26.46							10	30	68
Pseudomonas fluorescens	20	2	<0.13 - 16	2.00	11.31						50	50	75	100
Pseudomonas maltophilia [c]	191	10	0.08 - >128	117.00	133.00									0
Pseudomonas pseudomallei	4	1	0.5 - 64	2.00	64.00						50	50	50	50
Pseudomonas putida	47	5	0.15 - 2	0.92	1.39				6	57	100			
Pseudomonas putrefaciens [d]	20	2	0.5 - 5	1.41	4.73						50	63	100	
Pseudomonas stutzeri	53	3	0.15 - 2	0.61	0.88			5	45	66	100			
Pseudomonas alc.-P. Pseudoalcaligenes	16	2	<0.13 - 2	0.15	0.77		34	34	62	84	100			
Pseudomonas picketii [VA-1] [e]	11	1	0.5 - 4	2.00	2.00						90	100		
Pseudomonas spp.	11	1	<0.39 - <0.39	<0.39	<0.39				100					
Rhodococcus spp.	50	3	0.06 - 2	0.13	0.28		55	85	85	85	100			
Salmonella spp.	10	1	<0.13 - 0.5	0.50	0.50				100					
Salmonella/Citrobacter spp.	880	23	0.016 - 25	0.60	1.37		1	15	31	74	83	96	99	99
Serratia marcescens	33	2	0.1 - 1	0.17	0.27		33	67	97	100				
Shigella	13	1	<0.12 - 0.25	0.25	0.25			100						
Yersinia like	198	4	0.06 - 1	0.24	0.48	2	4	52	97	100				
Yersinia enterocolitica	15	1	<0.12 - 0.25	0.06	0.25	50	50	100						
Yersinia pseudotuberculosis														

(+) Cumulative susceptibility distributions were tabulated by assigning for each study 50% of the number tested to the MIC_{50}, 40% to the MIC_{90} and 10% to the upper range cited and then taking the sum within each concentration range. Susceptibility was determined by both broth and agar dilution methods using an inoculum of 10^5 colony forming units (CFU) per mL.

[a] *Pseudomonas acidovorans* is now called *Delftia acidovorans*
[b] *Pseudomonas cepacia* is now called *Burkholderia cepacia*
[c] *Pseudomonas maltophilia* is now called *Stenotrophomonas maltophilia*
[d] *Pseudomonas putrefaciens* is now called *Shewanella putrefaciens*
[e] *Pseudomonas picketii* is now called *Ralstonia pickettii*

TABLE 3 (continued)
THE *IN VITRO* ACTIVITY OF IMIPENEM AGAINST CLINICAL ISOLATES OF VARIOUS GRAM-POSITIVE AND GRAM-NEGATIVE AEROBIC AND ANAEROBIC SPECIES

Organism	No. Strains	No. Studies	Range MICs	Geom Mean MIC_{50} (mg/L)	Geom Mean MIC_{90} (mg/L)	Distribution of Susceptibility, Minimum % Inhibited at Indicated Concentrations (mg/L) (+)								
						0.06	0.13	0.25	0.5	1	2	4	8	16
Gram Positive Aerobes														
Listeria monocytogenes	43	4	<0.025 - 0.25	0.09	0.12	16	53	100						
Nocardia asteroides	74	4	<0.06 - 128	0.84	2.05			7	7	39	77	95	98	98
Staphylococcus aureus	855	20	0.008 - 8	0.03	0.07	73	80	87	93	99	99	99	100	
Staphylococcus aureus [Pen sen]	42	4	0.016 - 0.12	0.03	0.05	97	100							
Staphylococcus aureus [Pen res]	79	5	0.03 - 0.2	0.03	0.08	74	84	100						
Staphylococcus aureus [Meth res]	140	8	0.01 - 100	0.59	7.84	9	19	23	31	35	57	61	74	81
Staphylococcus epidermidis	509	16	0.008 - >64.0	0.08	1.59	29	36	49	56	61	81	88	89	90
Staphylococcus epidermidis [Pen res]	10	1	0.03 - 0.06	0.01	0.05	100								
Streptococcus (Beta Grp. B)	265	8	0.005 - 0.6	0.02	0.03	97	100							
Streptococcus (Grp. C)	8	1	<0.015	<0.015	<0.015	100								
Streptococcus (Grp. G)	10	1	<0.015	<0.015	<0.015	100								
Streptococcus agalactiae	115	5	0.012 - 0.1	0.02	0.04	93	100							
Streptococcus bovis	20	1	<0.015 - 0.1	0.02	0.10	50	100							
Streptococcus faecalis [f]	778	22	0.016 - 128	0.94	1.69				16	52	87	91	97	98
Streptococcus faecium [g]	22	2	2 - 64	23.35	46.70									23
Streptococcus pneumoniae [Pen res]	30	2	0.01 - 1	0.40	1.00			17	50	100				
Streptococcus pneumoniae	283	14	0.003 - 1.25	0.01	0.03	86	90	95	97	98	100			
Streptococcus pyogenes	304	10	0.0025 - 0.1	0.01	0.02	95	100							
Streptococcus spp.	194	5	0.002 - 2	0.02	0.03	81	87	87	94	94	100			
Viridans strep.	60	4	<0.001 - 4	0.01	0.05	71	78	96	96	96	96	100		
Viridans strep. [Pen res]	16	1	0.06 - 2	0.50	2.00				50	50	100			

(+) Cumulative susceptibility distributions were tabulated by assigning for each study 50% of the number tested to the MIC_{50}, 40% to the MIC_{90} and 10% to the upper range cited and then taking the sum within each concentration range. Susceptibility was determined by both broth and agar dilution methods using an inoculum of 10^5 colony forming units (CFU) per mL.

[f] *Streptococcus faecalis* is now called *Enterococus faecalis*
[g] *Streptococcus faecium* is now called *Enterococus faecium*

TABLE 3 (continued)
THE *IN VITRO* ACTIVITY OF IMIPENEM AGAINST CLINICAL ISOLATES OF VARIOUS GRAM-POSITIVE AND GRAM-NEGATIVE AEROBIC AND ANAEROBIC SPECIES

Organism	No. Strains	No. Studies	Range MICs	Geom Mean MIC_{50} (mg/L)	Geom Mean MIC_{90} (mg/L)	Distribution of Susceptibility, Minimum % Inhibited at Indicated Concentrations (mg/L) (+)								
						0.06	0.13	0.25	0.5	1	2	4	8	16
Gram Negative Anaerobes														
Bacteroides fragilis	745	14	<0.004 - 8	0.08	0.31	29	43	75	90	98	99	100		
Bacteroides distasonis	39	3	0.008 - 1	0.13	0.26	23	42	73	97	100				
Bacteroides fragilis spp.	74	3	0.03 - 2	0.05	0.33	42	42	66	92	96	100			
Bacteroides melanin. intermedius	47	3	<0.004 - 0.25	0.02	0.07	85	98	100						
Bacteroides ovatus	11	1	0.063 - 0.25	0.06	0.25	50	50	100						
Bacteroides thetaiotaomicron	109	5	0.008 - 2	0.15	0.41	11	32	61	95	97	100			
Bacteroides uniformis	10	1	0.016 - 0.25	0.13	0.25		50	100						
Bacteroides vulgatus	25	2	0.016 - 0.5	0.06	0.29	50	70	70	100					
Bacteroides spp.	279	7	<0.004 - 8	0.09	0.57	41	42	44	73	91	99	99	100	
Campylobacter fetus jejuni	88	2	0.01 - 0.125	0.05	0.07	76	100							
Eikenella corrodens	56	2	0.1 - 0.25	0.15	0.22		25	100						
Fusobacterium nucleatum	108	5	<0.004 - >256	0.04	1.21	50	50	56	89	93	93	93	93	93
Veillonella parvula	56	4	0.015 - 4	0.13	0.50	32	33	49	75	77	95	100		
Gram Positive Anaerobes														
Actinomyces spp.	8	2	<0.03 - 0.125	0.036	0.089	69	100							
Clostridium bifermentans	21	1	0.031 - 1	0.250	1.000			50	50	100				
Clostridium botulinum	16	1	<0.016 - 0.25	0.063	0.125	50	90	100						
Clostridium difficile	88	4	0.5 - 16	3.201	4.760						44	57	82	100
Clostridium perfringens	61	5	0.008 - 4	0.170	1.055	37	47	47	47	67	67	100		
Clostridium spp.	184	9	<0.004 - >16	0.115	0.590	34	45	57	78	89	90	90	97	99
Eubacterium spp.	4	1	0.06 - 0.5	0.125	0.500		50	50	100					
Gardnerella vaginalis	25	1	0.12 - 0.5	0.250	0.250			90	100					
Peptococcus asaccharolyticus	31	1	<0.008 - <0.01	0.004	0.008	100								
Peptococcus magnus	26	2	<0.008 - 0.063	0.025	0.050	100								
Peptococcus prevotii	25	1	<0.008 - 0.03	0.004	0.015	100								
Peptococcus/Peptostreptococcus spp.	230	5	<0.004 - 2	0.030	0.093	66	89	90	95	97	100			
Propionibacterium acnes	112	3	0.004 - 0.06	0.009	0.016	100								

(+) Cumulative susceptibility distributions were tabulated by assigning for each study 50% of the number tested to the MIC_{50}, 40% to the MIC_{90} and 10% to the upper range cited and then taking the sum within each concentration range. Susceptibility was determined by both broth and agar dilution methods using an inoculum of 10^5 colony forming units (CFU) per mL.

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia,* formerly *Pseudomonas maltophilia*), *Burkholderia cepacia* (formerly *Pseudomonas cepacia)*, Methicillin-resistant *S. aureus* and *S. epidermidis*, *Enterococcus faecium* (formerly *Streptococcus faecium*), *Flavobacterium* spp., *Corynebacterium* (J.K.), *Fusobacterium varium*, and species of *Mycobacterium* and *Chlamydia are* species generally reported insensitive to imipenem.

Susceptibility Testing

Bacterial susceptibility to imipenem is conducted via standardized methods. Dilution and diffusion techniques are used for aerobes and dilution techniques only for anaerobes.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of imipenem powder. The MIC values should be interpreted according to criteria and methods provided in Table 4

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg imipenem to test the susceptibility of microorganisms to imipenem. The disk diffusion interpretive criteria and methods are provided in Table 4.

TABLE 4

CLSI INTERPRETIVE BACTERIALSUSCEPTIBILITY CRITERIA FOR IMIPENEM [a]

	Dilution Test (MICs in mcg/mL)			Disk Diffusion Test (zone diameters in mm)		
Pathogen [a]	S	I	R	S	I	R
Aerobes (with exceptions below).	≤4	8	≥16	≥16	14-15	≤13
Streptococcus pneumoniae	≤0.12	0.25-0.5	≥1	—	—	—
Streptococcus spp. other than S. pneumoniae [b]	—	—	—	—	—	—
Haemophilus spp [c]	≤4	—	—	≥16	—	—
Anaerobes	≤4	8	≥16	—	—	—

[a] reference is made to those pathogens listed in INDICATIONS section of product monograph; broth and agar dilution methods apply to aerobes other than Hemophilus spp and Streptococcus pneumoniae for which only broth dilution applies; the numbers presented for anaerobes reference agar dilution; a hyphen indicates Not Applicable; for further details and applicable laboratory methods see CLSI (Clinical and Laboratory Standards Institute) documents: M7-A7: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically (Jan 2006);–M11- A7: Methods for antimicrobial susceptibility testing for anaerobic bacteria (Jan 2007); M100-S20: Performance standards for antimicrobial susceptibility testing (Jan 2010)

[b] there are no CLSI interpretive criteria for MIC testing of beta hemolytic Streptococcus spp or viridans group Streptococci against imipenem (ref CLSI ref M100-S20, table 2 H1 and table 2 H2);

[c] absence of data on resistant strains precludes defining any other category than 'susceptible' (see CLSI document M100–S20,table 2E)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard

imipenem powder as used in the dilution test and 10 mcg imipenem impregnated discs as used in the diffusion test should provide the following range of values noted in Table 5.

TABLE 5

ACCEPTABLE QUALITY CONTROL ORGANISMS and TEST RANGES for IMINIPENEM

QC Strain	ATCC® [a]	Dilution Test (MICs in mcg/mL)	Disk Diffusion Test (zone diameters in mm)
Enterococcus faecalis [b]	29212	0.5-2	Not Applicable
Staphylococcus aureus [b]	29213	0.015-0.06	Not Applicable
Streptococcus pneumoniae [c]	49619	0.03-0.12	Not Applicable
Escherichia coli [b]	25922	0.06-0.25	26-32
Haemophilus influenzae [c]	49766	0.25-1	Not Applicable
Haemophilus influenzae [c]	49247	Not Applicable	21-29
Pseudomonas aeruginosa [b]	27853	1-4	20-28
Bacteroides fragilis [d]	25285	0.03-0.125	Not Applicable
Bacteroides thetaiotaomicron [d]	29741	0.125-0.5	Not Applicable
Eubacterium lentum [d]	43055	0.125-0.5	Not Applicable

[a] ATCC® is the registered trademark of the American Type Culture Collection.
[b] reference CLSI document M100-S20 (broth dilution table 4 ; disk diffusion table 3)
[c] reference CLSI document M100-S20 (broth dilution table 4A ; disk diffusion table 3A)
[d] reference CLSI document M11-A7 (agar dilution table 5)

PHARMACOLOGY

Animal pharmacology

Central Nervous System

Imipenem

In female mice (5 per dose level) imipenem at doses of 6, 30 and 150 mg/kg, I.P. showed no effect on behavior or in various pharmacological tests of central nervous system activity.

In male rats (11 per dose level) imipenem at doses up to 100 mg/kg, I.V. showed no effect on spontaneous locomotor activity and had no effect on the neuromuscular junction.

No behavioral or overt signs of central nervous system activity were observed when imipenem was given to squirrel monkeys at cumulative oral doses of 1, 3 and 9 mg/kg given at 90 minute intervals (0, 90 and 180 minutes) in an avoidance response test.

The effects of imipenem on the electrocardiogram (ECG), spontaneous electroencephalogram (EEG) and the EEG arousal response in rabbits immobilized by gallamine were studied. ECG and EEG were recorded for 60 minutes following drug administration. A single dose of 50 mg/kg, I.V. of imipenem (5 animals) had no effect on either the ECG or EEG. A single I.V. dose of 200 mg/kg, (6 animals) increased the threshold voltage for EEG arousal response significantly (22.9 ± 9.5%) only at 45 minutes.

Cilastatin Sodium

Cilastatin sodium was studied in mice in the same pharmacological tests of CNS activity as used for imipenem at doses of 6, 30 and 150 mg/kg, I.P. With the exception of a possible antagonism of neurotensin hypothermia in 2 out of 5 mice given 30 mg/kg, I.P., no effects were observed.

In rats at doses up to 100 mg/kg, I.V. cilastatin sodium showed no effect on spontaneous locomotor activity and had no effect on the neuromuscular junction.

In squirrel monkeys trained on a continuous avoidance schedule, avoidance response was unaltered by cilastatin sodium at cumulative oral doses of 5, 10 and 20 mg/kg administered at 90 minute intervals (0, 90 and 180 minutes).

Imipenem/Cilastatin Sodium

Imipenem/cilastatin sodium at doses of 25/25 and 100/100 mg/kg, I.V. induced no significant effect on central or autonomic nervous system activities in conscious mice.

The anticonvulsant activity of imipenem/cilastatin sodium was evaluated in mice on convulsions induced by electroshock, strychnine or pentylenetetrazol. At doses up to 100/100 mg/kg, I.V. no anticonvulsant effect was observed.

Imipenem/cilastatin sodium at doses up to 100/100 mg/kg, I.V. had no effect on spontaneous locomotor activity in rats. Imipenem/cilastatin sodium at doses up to 100/100 mg/kg, I.V. had no effect on the neuromuscular junction in rats (as measured by the contractile response of the gastrocnemius muscle to electrical stimulation of the peroneal nerve).

Imipenem alone, cilastatin sodium alone and the combination (1:1 ratio) were administered intravenously to male rabbits at dosage levels of 50, 100 and 200 mg/kg to study the effect on the spontaneous electroencephalogram (EEG). Cefazolin was administered as a comparative agent at doses of 200, 400 or 1000 mg/kg. At 200 mg/kg imipenem alone caused seizure discharge in 1 of 11 rabbits 27 minutes after drug administration. This seizure discharge did not continue, but appeared again at 45 and 61 minutes. No effect on the spontaneous EEG activity was observed in the remaining 10 animals receiving 200 mg/kg of imipenem. Cilastatin had no effect on the EEG. Among rabbits receiving imipenem/cilastatin sodium at 200/200 mg/kg (the highest dose given), seizure discharge was observed in 2 of 11 rabbits from 15 minutes to 58 minutes

after drug administration. Seizure discharge was observed with cefazolin at a dosage level of 400 mg/kg in 2 of 5 rabbits from 13 to 60 minutes after injection. Electrical disturbance of EEG activity was observed in all rabbits receiving cefazolin at 1000 mg/kg.

When tested in rat hippocampal slices *in vitro*, the GABA receptor blocking activity of imipenem was comparable to that seen with cefazolin. The GABA receptor blocking activity of imipenem/cilastatin sodium was somewhat less than that of imipenem alone. Cilastatin sodium alone had some antagonistic effect although it was significantly less than that observed with imipenem and other reference beta-lactam antibiotics.

In vivo studies in rats have shown that imipenem is convulsive after direct application of the drug into the cisterna magna. Coadministration of cilastatin sodium and imipenem in this model showed no differences in the convulsant potential compared to imipenem alone. Although direct introduction of imipenem into the rat brain is capable of producing convulsant activity, no evidence of such activity was observed in rats receiving imipenem alone at dosage levels up to 180 mg/kg/day S.C., once daily, for 6 months or with imipenem/cilastatin sodium at dosage levels up to 320/320 mg/kg/day S.C., once daily, for 6 months. In addition, no evidence of convulsant activity was observed in rhesus monkeys receiving imipenem alone, at doses up to 180 mg/kg/day I.V., once daily, for 5 weeks or imipenem/cilastatin sodium at dosage levels up to 180/180 mg/kg/day S.C., once daily, for 6 months.

Imipenem, cilastatin sodium, and the 1:1 combination were evaluated in male rabbits at dosage levels of 50 and 100 mg/kg, I.V. for their effect on the EEG arousal response. At a dosage level of 200 mg/kg, imipenem alone increased the threshold voltage by approximately 23% at 45 minutes after drug administration. Cilastatin sodium at 50 mg/kg produced a slight but statistically significant decrease in the threshold voltage for EEG arousal response. A similar slight decrease in threshold voltage was noted for the combination at a dose of

200/200 mg/kg. The reference compound for this study (diazepam, 5 mg/kg) increased the threshold voltage by 87% at 15 minutes and by 70% at 60 minutes.

Cardiovascular and Respiratory System

Imipenem

Imipenem did not significantly lower blood pressure at 20 mg/kg, I.P. in spontaneously hypertensive rats, although a slight transient increase (11%) in mean arterial blood pressure was observed two hours after treatment.

In groups of 3 dogs anesthetized with sodium pentobarbital, imipenem given intravenously at doses of 25 mg/kg and 100 mg/kg had no effect on heart rate, arterial blood pressure, respiratory rate or ECG. In one dog (dosed at 100 mg/kg) heart rate increased by about 25 beats/min (21%) and systolic blood pressure increased about 16 mmHg (12%). In respiratory studies in dogs anesthetized with thiopental, imipenem at doses of 2.5 and 10 mg/kg, I.V. had no effect on the respiratory parameters measured (total lung resistance, dynamic lung compliance, tidal volume and respiratory rate).

Cilastatin Sodium

No appreciable change in basal blood pressure or heart rate was observed in spontaneously hypertensive rats or dogs dosed with cilastatin sodium at 10 mg/kg, I.V.

Cilastatin sodium at doses up to 100 mg/kg, I.V. did not change blood pressure, heart rate, respiratory rate and ECG in dogs anesthetized with sodium pentobarbital.

Imipenem/cilastatin sodium

At doses of 25/25 and 100/100 mg/kg, I.V. imipenem/cilastatin sodium significantly ($p < 0.05$) inhibited the carotid sinus reflexes (24.5% and 36% respectively) in dogs anesthetized with sodium pentobarbital.

In other studies in dogs anesthetized with sodium pentobarbital, a dose of imipenem/cilastatin sodium 100/100 mg/kg, I.V. decreased mean blood pressure (7 to 13 mmHg) within 4 to 15 minutes after the start of drug infusion, without any significant change in heart rate and respiration rate. This may have been related to the inhibition of the carotid sinus reflexes observed in the previous study. A dose of 25/25 mg/kg, I.V. did not affect these parameters.

Other Systems

Imipenem

In mice (male, 8 per dosage level), imipenem administered subcutaneously at doses of 2.5 to 20 mg/kg or intravenously at doses of 25 and 100 mg/kg had no effect on the intestinal propulsion rate.

No diuretic activity was observed in rats given imipenem at doses up to 10 mg/kg, I.P. or in dogs given 5 mg/kg, I.V.

In seven female dogs, gastric secretion evoked by gastrin tetrapeptide resulted in total acid output at the 0- to 30-minute collection which was significantly reduced (59%, $p < 0.05$) following an oral dose of imipenem of 20 mg/kg. This was related to a reduction in output volume. The integrated 0- to 90-minute total acid output and output volume did not differ significantly ($p > 0.05$) from those in a placebo trial in the same animals. Acid concentration was not affected by imipenem. Basal gastric secretion in dogs was not affected following oral doses of 10 or 20 mg/kg of imipenem.

Cilastatin Sodium

In pylorus-ligated rats, cilastatin sodium (25 and 100 mg/kg, I.V.) showed no effect on basal gastric output, acid output, pH and pepsin output.

Cilastatin sodium (25 and 100 mg/kg, I.V.) showed no effect on intestinal propulsion in male mice.

Cilastatin sodium (10 mg/kg, I.V.) did not substantially change urinary Na^+, K^+ or Ca^{++} excretion in beagle dogs.

In female dogs, cilastatin sodium (10 mg/kg, I.V.) did not significantly alter the response to gastrin tetrapeptide. Basal gastric output was reduced but not to a statistically significant degree.

Imipenem/cilastatin sodium

Imipenem/cilastatin sodium at doses of 25/25 and 100/100 mg/kg, I.V. had no effect on basal gastric secretion in pylorus-ligated rats. In mice, imipenem/cilastatin sodium (25/25 and 100/100 mg/kg, I.V.) had no effect on intestinal propulsion.

Metabolism and excretion

During the laboratory evaluation of imipenem as a single entity, low urinary recovery of the antibiotic was found in the mouse (26%), rabbit (51%), dog (8%), Rhesus monkey (41%) and the chimpanzee (13%), and this was subsequently confirmed in man. Metabolism was shown to occur primarily in the kidney, affecting the secreted and filtered fraction of the antibiotic after its clearance from the blood.

The major pathway of metabolism of imipenem is by hydrolysis of the beta-lactam ring by the enzyme known as dehydropeptidase-I localized on the luminal (brush-border) surface of the proximal renal tubular epithelium. This enzyme has access to the antibiotic both in the glomerular filtrate and during the transcellular secretory process.

This low urinary tract bioavailability of imipenem is avoided by coadministration of cilastatin sodium, a potent inhibitor of dehydropeptidase-I.

The inhibition of dehydropeptidase-I by cilastatin sodium is competitive and freely reversible. Cilastatin sodium has been shown not to inhibit the activity of four other zinc metalloenzyme peptidases, including angiotensin converting enzyme.

Cilastatin sodium is devoid of antimicrobial activity *per se*, and has no effect on the antimicrobial activity of imipenem.

HUMAN PHARMACOLOGY

Pharmacokinetics

PRIMAXIN® (imipenem and cilastatin sodium) was administered via intravenous infusion over 20 minutes at a single dose of 250/250 mg to 4 male subjects (mean age: 31.5 ± 0.6 years), at a single dose of 500/500 mg to 20 male subjects (mean age: 26.8 ± 4.1 years), and at a single dose of 1000/1000 mg to 8 male subjects (mean age: 24.8 ± 3.7 years). Peak plasma levels of imipenem and of cilastatin were measured at the end of a 20 minute infusion, and are presented in Table 6. Plasma levels of imipenem antimicrobial activity are proportional to the dose and decline to below 1 µg/mL or less in 4 to 6 hours.

TABLE 6
RANGE OF PEAK PLASMA LEVELS OF IMIPENEM AND CILASTATIN FOLLOWING A 20 MINUTE I.V. INFUSION OF PRIMAXIN®

	250/250 mg	500/500 mg	1000/1000 mg
Imipenem (µg/mL)	12 - 20	21 - 58	41 – 83
Cilastatin (µg/mL)	21 - 26	21 - 55	56 - 88

PRIMAXIN® was administered via the intravenous route, over a 30 minute period, every 6 hours, for a period of 10 days, at a dose of 1000/1000 mg, to a group of six male volunteers (mean age 28.2 ± 5.0).

Mean plasma and urine concentrations for imipenem are given in Figure 1 and Table 7 respectively.

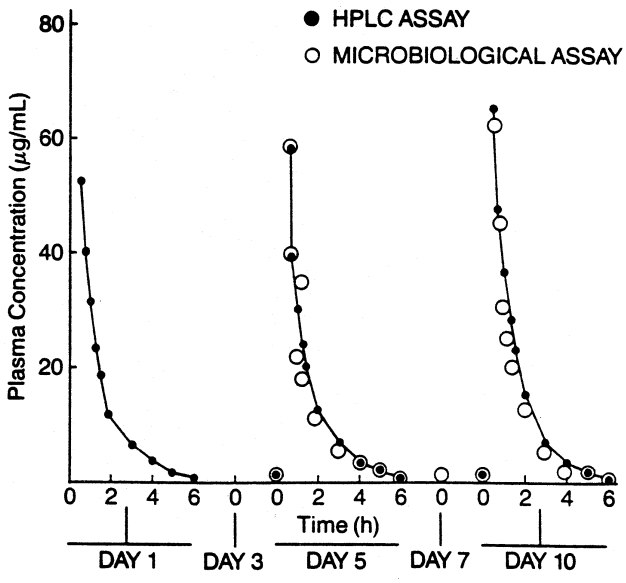


FIGURE 1
MEAN IMIPENEM PLASMA CONCENTRATION PROFILES WHEN PRIMAXIN® IS ADMINISTERED AT A DOSE OF1000/1000 mg, BY I.V. INFUSION, OVER 30 min (every 6 h) (n = 6)

TABLE 7
MEAN IMIPENEM URINE CONCENTRATIONS (µg/mL ± S.D.) WHEN PRIMAXIN® IS ADMINISTERED AT A DOSE OF 1000/1000 mg BY I.V. INFUSION, OVER 30 min (every 6 h)

	0 - 2 h	2 - 4 h	4 - 6 h
Day 1	886.6 (±511.3)	562.8 (±269.3)	175.8 (±167.9)
Day 5	1026.1 (±503.9)	1185.8 (±932.4)	156.1 (± 93.77)
Day 10	1389.5 (±616.4)	891.5 (±430.6)	159.9 (± 49.1)

The pharmacokinetic parameters for imipenem and cilastatin, when PRIMAXIN® was administered at a dose of 1000/1000 mg, are summarized in Table 8.

TABLE 8
PHARMACOKINETIC PARAMETERS OF IMIPENEM AND CILASTATIN WHEN PRIMAXIN® IS ADMINISTERED AT A DOSE OF 1000/1000 MG BY I.V. INFUSION OVER 30 MIN (N = 6)

Time (days)	Volume of Distribution (L)	Area under the Plasma Concentration Time Curve Between 0 and 6 h (µg.h/mL)	Plasma Half-Lives (min)*	Dose Recovered in urine through 6 h (mg)	Cumulative Renal Clearance (mL/min)	Plasma Clearance (mL/min)
IMIPENEM						
Day 1	13.6 (±3.7)	73.3 (±10.4)	59.6	540.2 (±54.1)	126.5 (±29.9)	227.7 (±30.9)
Day 5	11.4 (±3.8)	74.5 (±10.9)	61.3	651.8 (±148.1)	139.9 (±27.4)	227.8 (±36.1)
Day 10	10.9 (±1.6)	79.7 (±7.1)	59.4	626.5 (±77.2)	131.3 (±21.0)	210.4 (±18.3)
CILASTATIN						
Day 1	10.3 (±3.9)	82.1 (±19.3)	57.5	698.6 (±33.9)	142.7 (±33.6)	208.9 (±43.0)
Day 5	9.5 (±1.4)	73.0 (±16.1)	50.7	ND	ND	236.5 (±44.9)
Day 10	9.7 (±2.1)	77.4 (±15.1)	50.8	ND	ND	221.6 (±38.6)

*Harmonic means

Excretion and metabolism

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase-I and therefore achieves relatively low levels in urine.

Cilastatin sodium is a specific inhibitor of this enzyme and it prevents renal metabolism of imipenem. When imipenem and cilastatin sodium are given concomitantly, approximately 70% of the administered imipenem and cilastatin sodium are recovered unchanged in the urine within 10 hours of administration, after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 µg/mL can be maintained for up to 8 hours with PRIMAXIN®, at the 500 mg dose.

The remainder of the administered dose of imipenem is recovered in the urine as antibacterially inactive metabolites and fecal elimination of imipenem is essentially nil.

Approximately 10% of the cilastatin sodium administered is found as the N-acetyl metabolite, which has inhibitory activity against dehydropeptidase comparable to that of the parent drug. Activity of dehydropeptidase-I in the kidney returns to normal levels within approximately 8-12 hours after the elimination of cilastatin from the bloodstream.

No accumulation of imipenem and cilastatin in plasma is observed with regimens of PRIMAXIN® administered at therapeutic doses, in patients with normal renal function.

Serum Protein Binding

At serum concentration of 25 mg/L, the human serum protein binding of imipenem is 20%. Cilastatin sodium binding to protein was found to be approximately 35% in the human serum.

Tissue Concentrations

Concurrent imipenem concentrations in serum, tissues and body fluids are given in Table 9.

TABLE 9
IMIPENEM CONCENTRATIONS IN HUMAN TISSUES AFTER ADMINISTRATION BY I.V. INFUSION

Tissue/Fluid	Dose of Imipenem (mg)	Sampling time (min after dose)	No. of Specimens	Concentration: Tissue/Fluid (mg/L or mg/kg)	Concentration: Serum (mg/L)
				MEAN MAX (RANGE)	
Bile[1]	500	20	9	12.5 (5.25 - 20.3)	-
		180		>1 (0.46 - 2.73)	-
	1000	20	8	25.0 (10.7 - 51.28)	-
		180		(1.45 - 4.12)	-
				MEAN ± S.D.	MEAN ± S.D.(n=4)
Cerebrospinal[2]	1000	60	4	2.0 (±1.3)	22.3 (±14.6)
		90		1.5 (±0.1)	8.0 (± 1.6)
		120		2.7 (±2.3)	13.9 (±14.4)
				MEAN(RANGE)	MEAN PEAK±S.D.**
Saliva[3]	1000	15 - 60	10	0.38 (0.3 - 0.6)	34.9 (±4.0)
Sputum[3]	1000	15 - 120	7	4.4 (2.1 - 10.4)	(n=32)
Bone[3]	1000	30 - 120	10	2.6 (0.4 - 5.4)	
Wound Drainage[3]	1000	15 - 120	9	7.2 (1.7 - 22.6)	
Gastric Fluid[3]	1000	15 - 90	6	0.9 (0.4 - 1.7)	
				MEAN ± S.E.	MEAN ± S.E.
Heart Valves[4]	1000	0 - 60	3	3.3 (±0.7)	47.2 (±4.7)
Fat[4]	1000	0 - 60	10	0.8 (±0.3)	(n=16)
Muscle[4]	1000	0 - 60	10	2.5 (±0.7)	
Myometrium[4]	500	60 - 120	5	2.5 (±0.3)	14.6 (±1.6)
Endometrium[4]	500	60 - 120	5	1.6 (±0.3)	(n=5)
Salpinges[4]	500	60 - 120	2	1.4 (±0.1)	

** 15 min post infusion

(1) Mayer M, Tophoff C, Opperkuch W. Bile levels of imipenem following different dose regimens. Int J Clin Pharmacol Res 1985; V(5):325-9.

(2) Modal J, Vittecoq D, Decazes JM, Meulemans A. Penetration of imipenem and cilastatin into cerebrospinal fluid of patients with bacterial meningitis. J Antimicrob Chemother 1985;16: 751-5.

(3) MacGregor RR, Gibson GA, Bland JA. Imipenem pharmacokinetics and body fluid concentrations in patients receiving high-dose treatment of serious infections. Antimicrob Agents Chemother 1986;29(2):188-92.

(4) Kümmel A, Schlosser V, Petersen E, Daschner FD. Pharmacokinetics of imipenem-cilastatin in serum and tissue. Eur J Clin Microbiol 1985;4(6):609-10.

Factors influencing pharmacokinetics

Age

Children

The pharmacokinetic results from two pediatric single dose studies are summarized in Table 10.

TABLE 10

MEAN VALUES OF PHARMACOKINETIC PARAMETERS OF IMIPENEM/CILASTATIN IN CHILDREN AFTER A SINGLE DOSE OF PRIMAXIN® (10/10 or 25/25 mg/kg) ADMINISTERED I.V. OVER 10-20 min

AGE RANGE (years)	No. PATIENTS	[AUC*] (µg.h/mL/mg)	PLASMA CLEARANCE (mL/min/kg)	VOLUME OF DISTRIBUTION (L/kg)	T½+ (min)	URINE RECOVERY (% OF DOSE)
2-12	20†	0.20 / 0.29 (n=9)/(n=3)	5.33 / 4.20 (n=9)/(n=3)	0.25 / 0.17 (n=9)/(n=3)	55.8 / 36.5 (n=20)/(n=10)	61.0 / 79.0 (n=7)/(n=5)
2- 9	9	0.18 / 0.20	5.40 / 4.90	0.22 / 0.15	53.7 / 37.9	41.0 / 66.0

* AUC expressed per milligram of drug administered.
+ Harmonic means.
† Number of patients from which pharmacokinetic parameters were calculated are given in between parentheses.

The pharmacokinetic results from two pediatric studies in which PRIMAXIN® was administered in multiple doses are summarized in Table 11. PRIMAXIN® was administered at a dose of 25/25 mg/kg/q6 h for patients aged 3 months to <3 years and at a dose of 15/15 mg/kg/q6 h for patients aged 3 to 12 years.

TABLE 11
MEAN VALUES OF PHARMACOKINETIC PARAMETERS OF IMIPENEM/CILASTATIN IN CHILDREN AFTER MULTIPLE DOSES

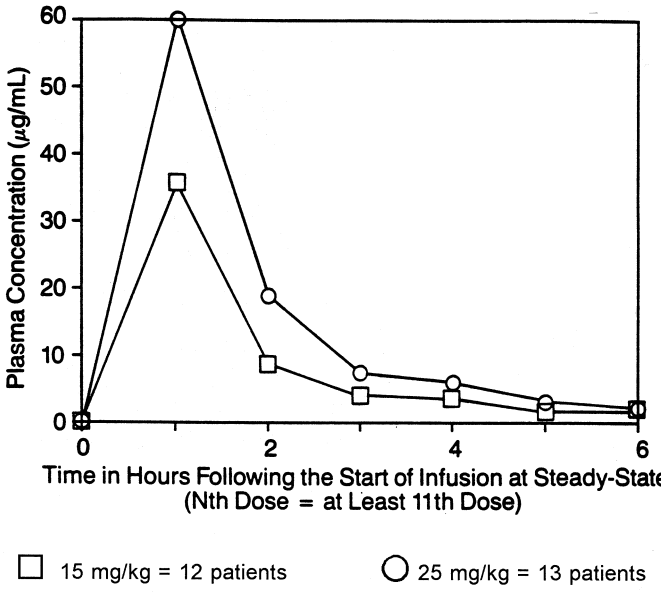
TOTAL No. PTS	AGE RANGE (yrs)	TOTAL AUC[xx] (µg.h/mL/mg)**	PLASMA CLEARANCE (mL/min/kg)**	VOLUME OF DISTRIBUTION (L/kg)**	RENAL CLEARANCE (mL/min)	T ½[+] (min)	DOSING INTERVAL UINARY RECOVERY (% OF DOSE)
106[†]	1 ≤ 3	0.18/[x] (n=1)/-	6.9/[x] (n=1)/-	0.23/[x] (n=1)/-	59/[x] (n=1)/-	67.9/[x] (n=1)/-	63.5/78.6 (n=1)/(n=1)
	3 ≤ 6	0.08/[x] (n=1)/-	12.7/[x] (n=1)/-	0.55/[x] (n=1)/-	85/[x] (n=1)/-	60.0/[x] (n=2)/-	39.4/61.7 (n=1)/(n=1)
	6 ≤ 9	0.10/[x] (n=1)/-	6.4/[x] (n=1)/-	0.33/[x] (n=1)/-	100/[x] (n=1)/-	54.7/[x] (n=1)/-	57.0/71.3 (n=1)/(n=1)
	9 ≤ 12	0.07/[x] (n=3)/-	6.0/[x] (n=3)/-	0.24/[x] (n=3)/-	118 to 161/[x] (n=3)/-	52.3/[x] (n=3)/-	53.0/65.6 (n=4)/(n=4)
178[†]	≤ 1	0.42/0.34 (n=10)/(n=3)	5.1/5.3 (n=10)/(n=3)	0.30/0.19 (n=10)/(n=3)	20 to 47/ 37 to 64 (n=6)/(n=3)	58.0/59.0 (n=10)/(n=3)	≥ 44/ ≥ 67[xxx] (n=6)/(n=5)
	1 ≤ 3	0.40/0.41 (n=10)/(n=3)	3.8/4.0 (n=6)/(n=3)	0.14/0.11 (n=6)/(n=3)	32 to 51/ 54 to 57 (n=5)/(n=2)	52.0/41.0 (n=6)/(n=3)	≥ 77/ ≥ 73[xxx] (n=5)/(n=4)
	3 ≤ 6	0.19/0.24 (n=7)/(n=2)	5.2/5.4 (n=7)/(n=2)	0.22/0.13 (n=7)/(n=1)	48 to 99/44 (n=6)/(n=1)	48.0/23.0 (n=7)/(n=2)	≥ 73/ ≥ 51[xxx] (n=6)/(n=5)
	6 ≤ 9	0.14/[x] (n=7)/-	4.7/[x] (n=7)/-	0.21/[x] (n=7)/-	53 to 116/[x] (n=4)/-	55.0/[x] (n=7)/-	≥ 63/ ≥ 89[xxx] (n=4)/(n=2)
	9 ≥ 12	0.17/0.22 (n=4)/(n=2)	4.4/4.4 (n=4)/(n=2)	0.22/0.13 (n=4)/(n=2)	28 to 124/ 37 to 87 (n=2)/(n=2)	73.0/39.0 (n=4)/(n=2)	≥ 75/ ≥ 64[xxx] (n=2)/(n=2)

** Geometric means
[+] Harmonic means
[†] Number of patients evaluated pharmacokinetically is indicated in parentheses
[x] Insufficient data
[xx] Dosing interval AUC (0-6h) expressed per mg of drug administered
[xxx] Means not provided

Representative plasma concentration profiles of imipenem and cilastatin at doses of 15/15 and 25/25 mg/kg are shown in Figure 2. In these studies, plasma concentrations of cilastatin were below detectable limits three hours postdosing. Steady state conditions for imipenem and cilastatin prevailed before the end of the fourth dose on Day 1.

Because of the short half-lives of imipenem and cilastatin, no accumulation was observed when PRIMAXIN® was given every 6 hours. As in the single dose pediatric studies, the disposition of imipenem and cilastatin resembled that of adults, except for a greater rate of cilastatin elimination.

Imipenem Plasma Concentration



Cilastatin Plasma Concentration

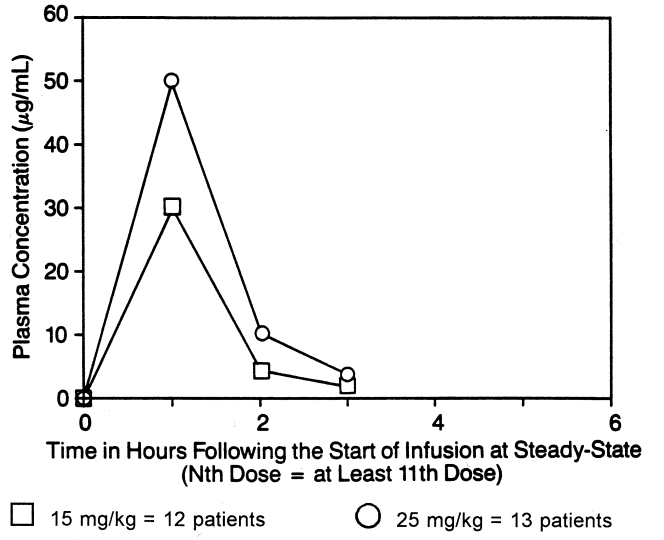


FIGURE 2
Representative Mean Steady-State Plasma Concentrations of Imipenem and Cilastatin in Pediatric Patients Receiving Imipenem/Cilastatin Sodium Every Six Hours

Elderly

In 4 female and 2 male healthy volunteers, 65 to 75 years old (mean age 68.8) with normal renal function for their age, i.e., creatinine clearance 84.3 (±13.0) mL/min/1.73 m^2 (1.41(±0.2) mL/s/1.73 m^2), PRIMAXIN® was administered by intravenous infusion at a dose of 500/500 mg in 100 mL saline over a period of 20 minutes.

The pharmacokinetic parameters for imipenem and cilastatin are summarized in Table 12.

TABLE 12
PHARMACOKINETIC PARAMETERS FOR
IMIPENEM AND CILASTATIN IN THE ELDERLY
(SINGLE DOSE OF 500/500 mg BY I.V. INFUSION OVER 20 min)

	IMIPENEM		CILASTATIN	
PARAMETER	**MEAN (±S.D.)**	**RANGE**	**MEAN**	**RANGE**
Total urinary recovery (% dose)	58 ± 7	49 - 66	69 ± 11	49 - 80
Renal clearance (mL/min)	79 ± 11	67 - 95	98 ± 26	64 - 133
Plasma clearance (mL/min)	132 ± 10	122 - 147	142 ± 22	117 - 171
Total AUC (µg . h/mL)	64 ± 5	57 - 68	60 ± 9.1	49 - 71
Plasma half-life (min)	90[+]	84 - 102	66[+]	54 - 96

[+] Harmonic means

No dosage adjustment is necessary for elderly patients whose degree of renal function is normal for their age.

Impaired Renal Function

PRIMAXIN® was administered to six healthy male volunteers and 25 patients with different degrees of renal impairment at a dose of 250/250 mg, in single I.V. infusions over 5 minutes.

The pharmacokinetic parameters for imipenem and cilastatin are summarized in Table 13 and the plasma concentration profiles are shown in Figures 3 and 4 respectively.

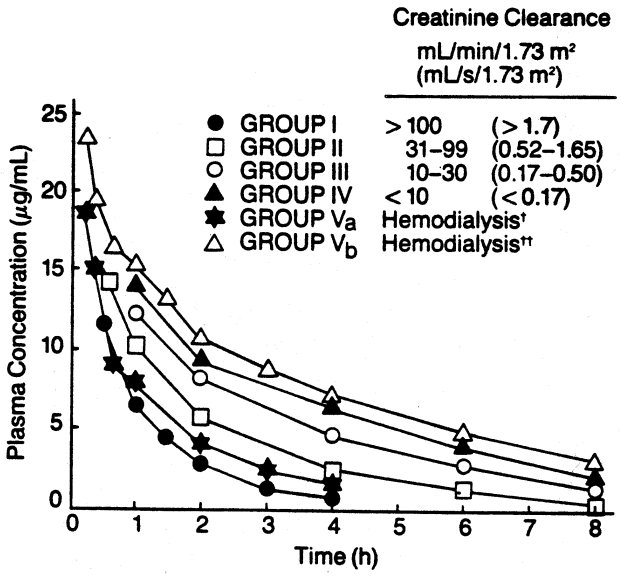
TABLE 13

PHARMACOKINETIC PARAMETERS FOR IMIPENEM AND CILASTATIN IN PATIENTS WITH RENAL FAILURE

(SINGLE DOSE OF 250/250 mg BY I.V. INFUSION OVER 5 min)

GROUP No.	No. PTS	MEAN AGE (yrs)	CREATININE CLEARANCE mL/min/1.73 m^2 (mL/s/1.73 m^2)	% DOSE URINARY RECOVERY	RENAL CLEARANCE (mL/min	PLASMA CLEARANCE (mL/min)	[AUC]^{x} µg.h/mL	T1/2^{xx} (min)
			IMIPENEM					
I	6	22.8	>100 (>1.7)	46.2	101.9	219.5	19.8	56
II	6	41.8	31-99 (0.52-1.65)	51.0^{y}	77.7^{y}	157.2	30.3	92
III	9	50.8	10-30 (0.17-0.50)	26.1^{zz}	24.2^{zz}	86.2	51.6	139
IV	2	32&67	<10 (<0.17)	11.3	8.5	69.3	60.6	160
V_a	4	42.3	Hemodialysis†			184.0	23.1	74
V_b	4	61.5	Hemodialysis††	3.4	1.8	59.1	73.1	181
			CILASTATIN					
I	6	22.8	>100 (>1.7)	59.4	100.7	168.5	25.4	54
II	6	41.8	31-99 (0.52-1.65)	71.2^{y}	71.3^{y}	99.9	45.7	84
III	9	50.8	10-30 (0.17-0.50)	61.9^{z}	23.9^{zz}	38.4	135.3	198
IV	2	32&67	<10 (<0.17)	39.4	6.5	16.2	261.4	462
V_a	4	42.3	Hemodialysis†			74.9	56.7	132
V_b	4	61.5	Hemodialysis††	17.9	2.0	11.4	416.8	696

† Received dose during hemodialysis
†† Measurements done between dialysis sessions
^{x} AUC normalised to a 250 mg dose
^{xx} Harmonic means
^{y} n = 5
^{z} n = 6
^{zz} n = 8



† Received dose during hemodialysis
†† Measurements done between dialysis sessions

FIGURE 3

MEAN IMIPENEM PLASMA CONCENTRATIONS FOLLOWING A SINGLE-DOSE OF PRIMAXIN® (250/250 mg I.V., OVER 5 min) TO SUBJECTS WITH VARYING DEGREES OF RENAL INSUFFICIENCY

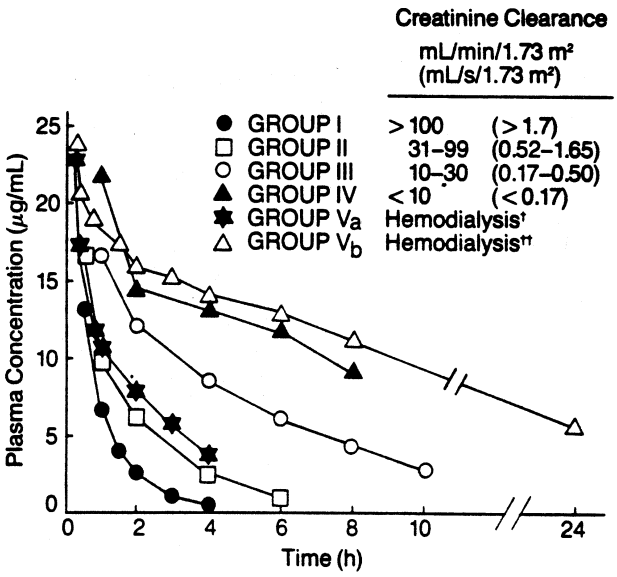


FIGURE 4

MEAN CILASTATIN PLASMA CONCENTRATIONS FOLLOWING A SINGLE-DOSE OF PRIMAXIN® (250/250 mg I.V., OVER 5 min) TO SUBJECTS WITH VARYING DEGREES OF RENAL INSUFFICIENCY

PRIMAXIN® was administered to 15 hospitalized patients (age range: 39-72 years) with proven or suspected urinary infection, at a dose of 500/500 mg by I.V. infusion over 20 minutes, repeated every 6 hours, for 3 to 10 days.

The pharmacokinetic parameters for imipenem and cilastatin are summarized in Table 15.

Repeated administration did not alter the disposition of either imipenem or cilastatin from that observed after a single dose and steady state prevailed by the end of first day dosing.

TABLE 14

PHARMACOKINETIC PARAMETERS FOR IMIPENEM AND CILASTATIN WHEN PRIMAXIN® WAS ADMINISTERED AT 500/500 mg BY I.V. INFUSION OVER 20 min - EVERY 6 h

GROUP	DOSE	URINARY RECOVERY 0 - 6 h (mg)	PLASMA CLEARANCE RENAL CLEARANCE (mL/min)	PLASMA CLEARANCE (mL/min)	[AUC] 0 - 6 h (µg.h/mL)	T1/2[x] (min)
IMIPENEM						
I[a]	1st	250.1 (± 45.5) n = 9	105.1 (±39.0) n = 9	201.2 (±63.8) n = 9	42.9(±10.7) n = 9	80 n = 9
	N[th]	287.0 (±100.7) n = 8	128.3 (±69.1) n = 8	222.5 (±46.8) n = 8	39.1 (± 8.9) n = 8	72 n = 9
II[b]	1st	183.5 (± 39.8) n = 4	69.3 (±14.0) n = 4	167.0 (±50.9) n = 5	50.7(±16.8) n = 5	98 n = 5
	N[th]	231.5 (± 40.3) n = 4	87.8 (±26.2) n = 4	175.7 (±49.5) n = 5	51.0(±15.9) n = 5	100 n = 5
CILASTATIN						
I[a]	1st	342.1 (± 70.6) n = 3	122.5 (±22.7) n = 3	214.7 (±59.3) n = 9	40.9(±11.8) n = 9	57 n = 9
	N[th]	258.7 (± 73.6) n = 3	100.8 (±26.2) n = 3	222.6 (±60.2) n = 8	39.9(±10.9) n = 8	55 n = 9
II[b]	1st	204.6 n = 1	50.3 n = 1	148.6 (±60.4) n = 6	59.6(±23.9) n = 6	92 n = 6
	N[th]	224.9 (± 59.6) n = 2	71.8 (±26.6) n = 2	158.8 (±60.8) n = 6	60.7(±27.1) n = 6	86 n = 6

[a] Group I = glomerular filtration rate ≥ 100 mL/min/1.73 m^2 (1.667 mL/s/1.73 m^2) and N ≥ 16 doses.

[b] Group II = glomerular filtration rate ≤ 100 mL/min/1.73 m^2 (1.667 mL/s/1.73 m^2) but ≥ 50 mL/min/1.73 m^2 (0.834 mL/s/1.73 m^2) and N ≥ 15 doses.

[x] Harmonic means.

Six hospitalized patients (4 females, 2 males, mean age 52.3) with a glomerular filtration rate of less than 15 mL/min/1.73 m^2 (0.25 mL/s/1.73 m^2) but not requiring hemodialysis, were administered PRIMAXIN® at a dose of 500/500 mg by I.V. infusion over 20 minutes, every 12 hours for nine doses.

The pharmacokinetic parameter estimates are summarized in Table 15.

TABLE 15

PHARMACOKINETIC PARAMETER ESTIMATES IN PATIENTS WITH SEVERELY IMPAIRED RENAL FUNCTION

	DOSE No.	IMIPENEM MEAN	CILASTATIN MEAN
Urinary recovery	1	15.2	38.0
(% administered dose)	9	13.8	46.7[x]
		(1.2)	(6.5)
Renal clearance	1	7.8	10.4
(mL/min)	9	7.1[x]	9.1
		(0.6)	(1.6)
Plasma clearance	1	51	21
(mL/min)	9	54[xxx]	19
		(1.2)	(1.9)
12-hour AUC	1	158	313
(µg hr/mL)	9	159	431[xxx]
		(4.3)	(33)
Plasma half-life[a]	1	2.9	5.7
(h)	9	2.6[xx]	5.5

[x] Different from Dose 1, .05 < p. .10
[xx] Different from Dose 1, .01 < p. .05
[xxx] Different from Dose 1, p. .01
[a] Inverse (harmonic) transformed data
Numbers in parentheses are within patient standard deviations.

Probenecid

In twelve male volunteers (mean age 29.5, range 23-37) PRIMAXIN® was administered at a dose of 500/500 mg with and without probenecid (1 g orally at ten hours and one hour prior to treatment). The urinary recovery of imipenem and cilastatin and their pharmacokinetic data are given in Table 16.

TABLE 16
EFFECT OF PROBENECID ON THE PHARMACOKINETICS AND URINARY RECOVERY OF IMIPENEM AND CILASTATIN WHEN IMIPENEM/CILASTATIN SODIUM (500/500 mg) WAS ADMINISTERED

	IMIPENEM/ CILASTATIN SODIUM	IMIPENEM/CILASTATIN SODIUM PLUS PROBENECID
Imipenem		
Plasma clearance (mL/min)	185 (± 32)[x]	159 (± 24)
AUC (µg.h/mL)	46 (± 7)	53 (± 8)
Plasma half-life (min)[xx]	58	66
Urinary recovery (% dose)	66 (± 3)	55 (± 6)
Renal clearance (mL/min)	125 (± 20)	88 (± 17)
Cilastatin		
Plasma clearance (mL/min)	218 (± 39)	89 (± 10)
AUC (µg.h/mL)	39 (± 7)	95 (± 11)
Plasma half-life (min)[xx]	48	102
Urinary recovery (% dose)	75 (± 6)	75 (± 8)
Renal clearance (mL/min)	173 (± 31)	70 (± 9)

[x] Mean (±S.D.)

[xx] Harmonic means

TOXICOLOGY

Acute Toxicity

	LD_{50}	
	RAT	**MOUSE**
Imipenem I.V.	>2000 mg/kg	≅1500 mg/kg
Cilastatin Sodium I.V.	≅5000 mg/kg	≅8709 mg/kg
PRIMAXIN® I.V.	≅1000 mg/kg	≅1100 mg/kg

Subacute and Chronic Toxicity

Imipenem

The principal studies used to evaluate the subacute and chronic toxicity of the product are shown in Table 17.

Animal studies showed that the toxicity produced by imipenem as a single entity, was limited to the kidney. Nephrotoxicity (characterized by proximal tubular necrosis) was observed in rabbits and monkeys receiving high doses of imipenem (150 mg/kg, I.V. and 180 mg/kg, I.V. respectively); the rabbit is more sensitive to the nephrotoxic effect of imipenem than is the monkey. No adverse effects were observed after 6 months of administration of imipenem in rats (25 males and 25 females per dosage level), at dosage levels up to 180 mg/kg/day, or in monkeys (5 males and 5 females per dosage level) at dosage levels up to 120 mg/kg/day.

TABLE 17

PRINCIPAL SUBACUTE AND CHRONIC TOXICITY STUDIES WITH PRIMAXIN®[1]

Duration	Species, Number/Sex/ Group	Dosage Levels (mg/kg/day)	No Adverse Effect Level (mg/kg/day)	Principal Effects Observed
Studies with Imipenem Alone				
5-Week, I.V.	Rat, 15	20, 60, 180	180	No adverse effects observed.
5-Week, I.V.	Monkey, 3M, 3F	20, 60, 180	60	1/6 dead with renal tubular necrosis at 180; an additional death from unknown cause at 180 presumed related to injection of highly concentrated drug solution necessitated by dosage level.
6-Month, I.V. (w/3-mo interim necropsy)	Rat, 25 (10 for interim necropsy)	20, 60, 180	180	Increased rate of weight gain in males at 60 and 180; no adverse effects seen.
6-Month, I.V. S.C. (w/3-mo interim necropsy)	Monkey, 5 (2 for interim necropsy)	30, 60 I.V. 120 S.C.	120	No adverse systemic effects seen.
Studies with Cilastatin Alone				
5-Week, I.V.	Rat, 15	20, 100, 500	500	No adverse effects seen.
5-Week, S.C	Rat, 15	500, 1250, 3125	500	Renal tubular vacuolation seen at 1250 and 3125.
5-Week, I.V.	Monkey, 3	20, 100, 500	500	No drug-induced adverse effects.
14-Week, I.V.	Rat, 15	20, 100, 500	500	No changes related to treatment.

[1] Although many studies in addition to those listed here were conducted, this list presents the principal studies which formed the basis of the safety evaluation of this drug.

TABLE 17
PRINCIPAL SUBACUTE AND CHRONIC TOXICITY STUDIES WITH PRIMAXIN® (continued)

Duration	Species, Number/Sex/ Group	Dosage Levels (mg/kg/day)	No Adverse Effect Level (mg/kg/day)	Principal Effects Observed
Studies with Imipenem and Cilastatin Sodium in Combination (PRIMAXIN®)				
5-Week, I.V., S.C.	Rat, 15	20/20, 80/80 I.V. 320/320 S.C.	320/320	No drug-induced adverse effects.
5-Week, I.V., S.C.	Monkey, 3	20/20, 60/60 I.V. 180/180 S.C.	180/180	No changes related to treatment.
14-Week, I.V., S.C.	Rat, 15	20/20, 80/80, 320/320	320/320	No changes related to treatment.
14-Week, S.C.	Infant Monkey, 3	20/20, 60/60 180/180	180/180	No adverse drug-induced changes.
10-Week, S.C.	Newborn Monkey, 5M, 3F	180/180	180/180	No drug-induced adverse effects.
6-Month, I.V., S.C.	Rat, 30	20/20, 80/80 I.V. 320/320 S.C.	320/320	No adverse effects observed.
6-Month, I.V., S.C.	Monkey, 4	20/20, 60/60 I.V. 180/180 S.C.	180/180	No adverse effects observed.

Cilastatin Sodium

No adverse effects were noted after intravenous administration of cilastatin sodium to rats (15 males and 15 females per dosage level) at doses up to 500 mg/kg for 14 weeks and monkeys (3 males and 3 females per dosage level) at doses up to 500 mg/kg for five weeks. In rats (15 males and 15 females per dosage level) given cilastatin sodium at dosages of 1250 or 3125 mg/kg/day, subcutaneously, very slight to slight proximal renal tubular degeneration was observed. After 5 weeks on these doses, no tubular necrosis was found, and there were no changes in any other tissues. Renal function remained normal.

Imipenem/Cilastatin Sodium

Co-administration of cilastatin sodium with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys, even when the dose of imipenem was 360 mg/kg or 180 mg/kg/day, respectively. These dosage levels are nephrotoxic when administered without cilastatin. This protective effect was seen in the monkey through 6 months of co-administration.

A series of studies performed in rabbits demonstrated that cilastatin sodium prevents the nephrotoxicity of imipenem in animals by preventing its entry into the tubular cells; this action is apparently distinct from the inhibition by administration of dehydropeptidase-I.

Reproduction studies

The principal studies performed to evaluate the effect of imipenem or cilastatin sodium alone or in combination on reproductive parameters or fetal development are shown in Table 18.

Fertility

The effect of imipenem/cilastatin sodium on fertility was assessed in male and female rats administered doses up to 320/320 mg/kg/day. Drug was administered to males for 12 weeks prior to mating and throughout the mating

period. Females received drug beginning 15 days prior to mating, during mating and through Day 19 of gestation.

The only effect of imipenem/cilastatin sodium in these studies was a very slight but statistically significant embryotoxicity and/or fetotoxicity. This was expressed as an increase in the resorption rate among animals receiving 80/80 and 320/320 mg/kg/day as well as a decrease in the number of live fetuses per pregnant female at 20/20 and 80/80 mg/kg/day. No decrease in the number of live fetuses per pregnant female was observed at the highest dosage level and the number of live pups per pregnant female on Day 1 postpartum in all dosage groups were comparable to the control group. The incidence of incompletely ossified sternebra was slightly increased in the 320/320 mg/kg/day group compared to the controls. Although these effects are subtle in nature and small in magnitude, they suggest a slight embryotoxic effect of imipenem/cilastatin sodium at high dosage levels in the rat.

TABLE 18

PRINCIPAL REPRODUCTIVE TOXICITY STUDIES WITH PRIMAXIN®[1]

Type of Study	Species, Number/Sex/Group	Dosage Levels (mg/kg/day)	Principal Effects Observed
Studies with Imipenem Alone			
Teratology, I.V.	Rat, 23	100, 300, 900	No evidence of fetal malformations; no effect postnatal growth and Behavior
Teratology, I.V.	Rabbit, 20	10, 30, 60	No teratogenic effect.
Studies with Cilastatin Sodium Alone			
Teratology, I.V./S.C.	Rat, 25	40, 200, 1000	No teratogenic effect.
Teratology, I.V./S.C.	Rabbit, 10	30, 100, 300	No teratogenic effect.
Studies with Imipenem and Cilastatin Sodium in Combination (PRIMAXIN®)			
Fertility, I.V./S.C.. (w/o post-weanling exam)	Rat: 15 male, 30 female	20/20, 80/80, 320/320	No evidence of adverse effect on fertility (slight decrease in live fetal weight at 320/320).
Teratology, I.V.	Mouse, 25	20/20, 80/80, 320/320	No teratogenic effect
Teratology, I.V./S.C. (with post-natal exam)	Rat, 35	20/20, 80/80, 320/320	No teratogenic effect, no adverse effect postnatal growth or behavior.
Late Gestation and Lactation I.V./S.C	Rat, 20	20/20, 80/80, 320/320	No adverse effects observed.
Teratology, I.V./S.C.	Cynomolgus Monkey, 11 (I.V.), 14 (S.C.)	I.V.: 40/40 S.C.: 160/160	Emesis, body weight loss, deaths, abortions at both dose levels; histologic examination of tissues showed no cause of death. No evidence of teratogenicity
Teratology by Infusion 45 (total)	Cynomolgus Monkey	100/100 (Days 21-30; 31-40; 41-50).	Drugs infused daily at 3 mg/mL for 10-day periods No apparent relationship between drug-induced toxicity (emesis) and embryotoxicity.

[1] Although several additional studies were performed to evaluate various aspects of reproduction, the studies presented form the basis of the safety evaluation of PRIMAXIN®.

Teratology

No evidence of a teratogenic effect was observed in rats or rabbits receiving imipenem or cilastatin sodium alone or in combination. Imipenem alone was evaluated at dosage levels up to 900 mg/kg/day, cilastatin sodium alone at dosage levels up to 1000 mg/kg/day and the two drugs in combination at dosage levels up to 320/320 mg/kg/day in rats.

The characteristic intolerance of rabbits to cephalosporin antibiotics was demonstrated in a teratology study with imipenem alone in this species at a dosage level up to 60 mg/kg/day. Maternotoxicity and feto- and embryotoxicity were observed at 60 mg/kg/day. The embryo- and fetotoxicity is considered to be secondary to the excess maternotoxicity observed in these studies. In the presence of these effects, there was still no evidence of teratogenicity. No evidence of a teratogenic effect was observed in rabbits receiving cilastatin sodium alone at doses up to 300 mg/kg/day.

Monkeys

In a range-finding study imipenem/cilastatin sodium was administered daily by bolus intravenous injection to non-pregnant cynomolgus monkeys for 30 days at doses of 20/20, 60/60, and 120/120 mg/kg/day (4 females per group) in order to establish dosage levels for subsequent studies. Four additional non-pregnant female monkeys were treated with 180/180 mg/kg/day subcutaneously for 30 days and a control group of 4 monkeys were treated intravenously with 0.9% sodium chloride. Emesis or diarrhea were seen on one or two occasions during treatment in some monkeys in the 60/60 and 120/120 mg/kg/day groups. Three animals in the 180/180 mg/kg/day subcutaneous group had occasional diarrhea during treatment.

In a teratology study, a bolus intravenous dose of 40/40 mg/kg/day and a subcutaneous dose of 160/160 mg/kg/day were administered to pregnant cynomolgus monkeys on Days 20 to 50 of gestation (11 and 14 monkeys per group, respectively). A control group of 14 pregnant monkeys were treated with 0.9% sodium chloride I.V. Both doses of imipenem/cilastatin sodium were

maternotoxic and resulted in deaths, reduced appetite, body weight loss, diarrhea, and emesis. In the 40/40 and 160/160 mg/kg/day groups, 7 of 11 and 5 of 14 monkeys lost their embryos. This is considered to reflect the obvious maternotoxicity evident at these dosage levels. There was no evidence of a teratogenic effect in surviving fetuses.

A study was conducted to determine the disposition and metabolism of imipenem/cilastatin sodium in pregnant and non-pregnant cynomolgus monkeys (4-5 monkeys per group). A bolus intravenous dose of 100/100 mg/kg/day was administered for 10 days and the first and last dose contained radioactive imipenem. The data suggest that metabolism or disposition is not directly responsible for the increased sensitivity of pregnant monkeys to imipenem/cilastatin sodium-induced toxicity.

In a teratology study in cynomolgus monkeys, imipenem/cilastatin sodium (100/100 mg/kg/day) was administered to 10 pregnant monkeys per group by slow infusion for 3 consecutive 10-day periods (Days 21-30; 31-40; 41-50). Three groups of 5 pregnant monkeys each were similarly treated with the vehicle. Pregnancy was confirmed by tests for macaque chorionic gonadotropin and the maintenance of pregnancy was assessed through periodic ultrasound examinations. Prior to parturition the fetuses were delivered by cesarean section and examined for malformations. Although there was no evidence of fetal external, visceral or skeletal malformations, there was an increase in the incidence of embryonic/fetal loss in the drug-treated monkeys (7 of 30, 23%) compared to the controls (0 of 15, 0%). Maternotoxicity (emesis and/or gagging during or after treatment) was observed in 4 of the 7 monkeys with embryonic/fetal loss.

Gestation and Postnatal Development

The effect of imipenem/cilastatin sodium during gestation and the postnatal period was studied in rats at doses up to 320/320 mg/kg/day. Imipenem/cilastatin sodium had no effect on growth or survival of offspring.

Genotoxicity

No evidence of drug-induced genetic toxicity was seen in the tests performed with imipenem or cilastatin sodium; these tests are listed in Table 19.

TABLE 19

PRINCIPAL GENETIC TOXICITY STUDIES WITH PRIMAXIN®

Type of Study	Species, Number/Sex/ Group	Dosage Levels (mg/kg/day)	Principal Effects Observed
Studies with Imipenem Alone			
Mutagenic	V-79 cells	3, 10, 20, 36 mM final concentration in medium	No evidence of mutagenic activity
Studies with Cilastatin Sodium Alone			
Mutagenic	Microbial Mutagenesis *(S. typhimurium)*	With and without S-9:** 30, 100, 300, 1000, 2,000 µg/plate	Negative
Studies with Imipenem and Cilastatin Sodium in Combination (PRIMAXIN®)			
Mutagenic	V-79 cells	With S-9: 1,3,4,5,7,9,11 mM Without S-9: 3,5,10,15 mM	No mutagenic activity detected
Mutagenic	Unscheduled DNA synthesis, Rat hepatocytes	3,10,14,22 mM final concentration in medium	No increase in labelled nuclei
Mutagenic	*In vivo* cytogenetic mouse bone marrow	59, 197, 590 mg/kg	No chromosomal aberration seen
Mutagenic	*In vitro* cytogenetic (range-finding)	With and without S-9: 0.2, 0.67, 2.0, 6.7, 20 mM and 2.0, 6.7, 20.0, 67 µM	Increased incidence of sister chromatid exchanges; study repeated and *in vitro* and *in vivo* sister chromatid exchange studies performed (below).
Mutagenic	*In vitro* chromosomal aberration assay	With S-9: 8.5, 6.4, 4.2, 2.1, 1.1 mM; Without S-9: 21.2 1.2 17.0, 12.7, 8.5, 4.2 mM	Negative

** Rat liver microsomal activation system

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