CILANEM

(Imipenem and Cilastatin for Injection USP)

COMPOSITION

CILANEM 250 mg Each vial contains:	
Imipenem Ph. Eur. (Sterile) equivalent to anhydrous Imipenem	250 mg
Cilastatin Sodium Ph. Eur. (Sterile) equivalent to Cilastatin	250 mg
Sodium Bicarbonate USP (Sterile)	added as buffer

CILANEM 500 mg Each vial contains	
Imipenem Ph. Eur. (Sterile) equivalent to anhydrous Imipenem	500 mg
Cilastatin Sodium Ph. Eur. (Sterile) equivalent to Cilastatin	500 mg
Sodium Bicarbonate USP (Sterile)	added as buffer

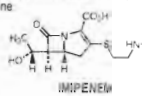
DESCRIPTION

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

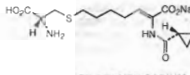
Imipenem (N-formimidoyl thienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. It is chemically designated as (*5R,6S*)-6-[(*R*)-1-hydroxyethyl]-3-[[2-[(iminomethyl) aminolethyl]sulphanyl]-7-oxo- 1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. The empirical formula for imipenem is $C_{12}H_{17}N_3O_4S{\cdot}H_2O$, and its molecular weight is 317.4.

Cilastatin sodium is the sodium salt of a derivative heptenoic acid. It is chemically designated as sodium (*Z*)-7-[[(*R*)-2-amino-2-carboxyethyl] sulphanyl]-2-[[(*1S*)-2,2 dimethylcyclopropyl]carbonyl] amino]hept-2-enoate. The empirical formula for cilastatin sodium is $C_{17}H_{25}N_2NaO_5S$, and its molecular weight is 380.4.

Imipenem, when administered alone, is metabolized in the kidneys by dehydropeptidase I resulting in relatively low levels in urine. Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine.



IMIPENEM



CILASTATIN SODIUM

STRUCTURAL FORMULAE

PHARMACOLOGY

- **Mechanism of action**

The bactericidal activity of imipenem results from the inhibition of cell wall synthesis. Its greatest affinity is for penicillin-binding proteins (PBPs) 1A, 1B, 2, 4, 5 and 6 of *Escherichia coli* and 1A, 1B, 2, 4 and 5 of *Pseudomonas aeruginosa*. The lethal effect is related to binding to PBP 2 and PBP 1B. Imipenem has a high degree of stability in the presence of beta-lactamases, including penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. It is a potent inhibitor of beta-lactamases from certain gram-negative bacteria, which are inherently resistant to many beta-lactam antibiotics, e.g., *Pseudomonas aeruginosa*, *Serratia* spp. and *Enterobacter* spp.

Cilastatin sodium is a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme that metabolises and inactivates imipenem. Cilastatin sodium is devoid of intrinsic antibacterial activity itself and does not affect the antibacterial activity of imipenem.

- **Pharmacokinetics**

Intravenous infusion of imipenem-cilastatin over 20 minutes results in peak plasma levels of imipenem antimicrobial activity that range from 14 to 24 µg/mL for the 250 mg dose, from 21 to 58 µg/mL for the 500 mg dose, and from 41 to 83 µg/mL for the 1000 mg dose. At these doses, plasma levels of imipenem antimicrobial activity decline to below 1 µg/mL or less in 4 to 6 hours. Peak plasma levels of cilastatin following a 20-minute intravenous infusion of imipenem-cilastatin, range from 15 to 25 µg/mL for the 250 mg dose, from 31 to 49 µg/mL for the 500 mg dose, and from 56 to 88 µg/mL for the 1000 mg dose.

The plasma half-life of each component is approximately 1 hour. The binding of imipenem to human serum proteins is approximately 20% and that of cilastatin is approximately 40%. Approximately 70% of the administered imipenem is recovered in the urine within 10 hours after which no further urinary excretion is detectable. Urine concentrations of imipenem in excess of 10 µg/mL can be maintained for up to 6 hours with intravenous imipenem-cilastatin at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of imipenem-cilastatin IV.

No accumulation of imipenem-cilastatin in plasma or urine is observed with regimens administered as frequently as every 6 hours in patients with normal renal function.

In healthy elderly volunteers (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of imipenem 500 mg and cilastatin 500 mg administered intravenously over 20 minutes are consistent with those expected in subjects with slight renal impairment for which no dosage alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin are 91 ± 7.0 minutes and 69 ± 15 minutes, respectively. Multiple dosing has no effect on the pharmacokinetics of either imipenem or cilastatin, and no accumulation of imipenem-cilastatin is observed.

After a 1 gram dose of imipenem-cilastatin administered intravenously, measurable levels of imipenem were found in various tissues and fluids including vitreous humor, aqueous humor, lung tissue, sputum, pleural fluid, peritoneal fluid, bile, CSF (uninflamed), CSF (inflamed), fallopian tubes, endometrium, myometrium, bone, interstitial fluid, skin and fascia.

Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.

- **Antimicrobial spectrum**

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms.

Imipenem has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections treated with imipenem-cilastatin sodium in intravenous formulation:

Gram-positive aerobes: *Enterococcus faecalis* (formerly *S. faecalis*), (Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*]), *Staphylococcus aureus* including penicillinase-producing strains, *Staphylococcus epidermidis* including penicillinase-producing strains (Methicillin-resistant staphylococci should be reported as resistant to imipenem), *Streptococcus agalactiae* (Group B streptococci), *Streptococcus pneumoniae*, *Streptococcus pyogenes*

Gram-negative aerobes: *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Gardnerella vaginalis*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella* spp., *Morganella morganii*, *Proteus vulgaris*, *Providencia rettgeri*, *Pseudomonas aeruginosa* (Note: Imipenem is inactive *in vitro* against *Xanthomonas* (*Pseudomonas*) *maltophilia* and some strains of *P. cepacia*.), *Serratia* spp. including *S. marcescens*

Gram-positive anaerobes: *Bifidobacterium* spp., *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp., *Peptostreptococcus* spp., *Propionibacterium* spp.

Gram-negative anaerobes: *Bacteroides* spp. including *B. fragilis*, *Fusobacterium* spp.

The following *in vitro* data are available, but their clinical significance is unknown:

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

Gram-positive aerobes: *Bacillus* spp., *Listeria monocytogenes*, *Nocardia* spp., *Staphylococcus saprophyticus*, Group C streptococci, Group G streptococci, Viridans group streptococci

Gram-negative aerobes: *Aeromonas hydrophila*, *Alcaligenes* spp., *Capnocytophaga* spp., *Haemophilus ducreyi*, *Neisseria gonorrhoeae* including penicillinase-producing strains, *Pasteurella* spp., *Providencia stuartii*

Gram-negative anaerobes: *Prevotella bivia*, *Prevotella disiens*, *Prevotella melaninogenica*, *Veillonella* spp.

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

INDICATIONS

CILANEM (imipenem and cilastatin) is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

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

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

(3) **Intra-abdominal infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*, *Staphylococcus epidermidis*, *Citrobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Morganella morganii**, *Proteus* species, *Pseudomonas aeruginosa*, *Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species*, *Bacteroides* species including *B. fragilis*, *Fusobacterium* species

(4) **Gynecologic infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains)*, *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B streptococci), *Enterobacter* species*, *Escherichia coli*, *Gardnerella vaginalis*, *Klebsiella* species*, *Proteus* species, *Bifidobacterium* species*, *Peptococcus* species*, *Peptostreptococcus* species, *Propionibacterium* species*, *Bacteroides* species including *B. fragilis**

(5) **Bacterial septicemia.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Serratia* species*, *Bacteroides* species including *B. fragilis**

(6) **Bone and joint infections.** *Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis*, *Enterobacter* species, *Pseudomonas aeruginosa*

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

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

(9) **Polymicrobic infections. CILANEM** is indicated for polymicrobic infections including those in which *S. pneumoniae* (pneumonia, septicemia), *S. pyogenes* (skin and skin structure), or nonpenicillinase-producing *S. aureus* is one of the causative organisms. However, monobacterial infections due to these organisms are usually treated with narrower spectrum antibiotics, such as penicillin G. **CILANEM** (imipenem and cilastatin) is not indicated in patients with meningitis because safety and efficacy have not been established.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, **CILANEM** (imipenem and cilastatin) is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

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

As with other beta-lactam antibiotics, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with **CILANEM** (imipenem and cilastatin). During therapy of *Pseudomonas aeruginosa* infections, periodic susceptibility testing should be done when clinically appropriate.

Infections resistant to other antibiotics, for example, cephalosporins, penicillin, and aminoglycosides, have been shown to respond to treatment with **CILANEM** (imipenem and cilastatin).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **CILANEM** (imipenem and cilastatin) and other antibacterial drugs, **CILANEM** (imipenem and cilastatin) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

DOSAGE AND ADMINISTRATION

Adults: The dosage recommendations for CILANEM (imipenem and cilastatin) represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 250 mg, or 500 mg dose should be given by intravenous administration over 20 to 30 minutes. Each 750 mg or 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.

The total daily dosage for intravenous imipenem-cilastatin should be based on the type or severity of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s), renal function, and body weight. Adult patients with impaired renal function, as judged by creatinine clearance ≤ 70 mL /min/1.73 m², require adjustment of dosage as described below.

Intravenous Dosage Schedule for Adults with Normal Renal Function and Body Weight > 70 kg

Dosage regimens in column A of Table I are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of Table I are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa*.

Table I: Intravenous dosage schedule for adults with normal renal function (creatinine clearance of ≥ 71 mL/min/ 1.73 m²) and body weight ≥70 kg

Type or Severity of Infection	A Fully susceptible organisms including gram-positive and gram-negative aerobes and anaerobes	B Moderately susceptible organisms, primarily some strains of *P. aeruginosa*
Mild	250 mg q6h (Total Daily Dose = 1.0g)	500 mg q6h (Total Daily Dose = 2.0g)
Moderate	500 mg q8h (Total Daily Dose = 1.5g) or 500 mg q6h (Total Daily Dose = 2.0g)	500 mg q6h (Total Daily Dose = 2.0g) or 1 g q8h (Total Daily Dose = 3.0g)
Severe, life threatening only	500 mg q6h (Total Daily Dose = 2.0g)	1 g q8h (Total Daily Dose = 3.0g) or 1 g q6h (Total Daily Dose = 4.0g)
Uncomplicated urinary tract infection	250 mg q6h (Total Daily Dose = 1.0g)	250 mg q6h (Total Daily Dose = 1.0g)
Complicated urinary tract infection	500 mg q6h (Total Daily Dose = 2.0g)	500 mg q6h (Total Daily Dose = 2.0g)

Due to the high antimicrobial activity of intravenous imipenem-cilastatin, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower. There is no evidence that higher doses provide greater efficacy. However, patients over twelve years of age with cystic fibrosis and normal renal function have been treated with intravenous imipenem-cilastatin at doses up to 90 mg/kg/day in divided doses, not exceeding 4.0 g/day.

Reduced Intravenous Schedule for Adults with Impaired Renal Functionand/or Body Weight <70 kg

Patients with creatinine clearance of ≤ 70 mL/min/1.73 m² and/or body weight less than 70 kg require dosage reduction of CILANEM (imipenem and cilastatin) as indicated in the tables below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

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

Cl$_{cr}$ (Females) = 0.85 × above value

To determine the dose for adults with impaired renal function and/or reduced body weight:

1. Choose a total daily dose from Table I based on infection characteristics.
2. a) If the total daily dose is 1.0 g, 1.5 g, or 2.0 g, use the appropriate subsection of Table II and continue with step 3.
   b) If the total daily dose is 3.0 g or 4.0 g, use the appropriate subsection of Table III and continue with step 3.
3. From Table II or III:
   a) Select the body weight on the far left which is closest to the patient's body weight (kg).
   b) Select the patient's creatinine clearance category.
   c) Where the row and column intersect is the reduced dosage regimen.

Table II: Reduced intravenous dosage of intravenous imipenem-cilastatin in adult patients with impaired renal function (creatinine clearance ≤ 70 mL/min/1.73 m²) and/or body weight <70 kg

and Body Weight (kg) is:	If Total Daily Dose from Table I is: 1.0 g/day — and creatinine clearance (mL/min/1.73 m²) is:				1.5 g/day — and creatinine clearance (mL/min/1.73 m²) is:				2.0 g/day — and creatinine clearance (mL/min/1.73 m²) is:			
	>71	41-70	21-40	6-20	>71	41-70	21-40	6-20	>71	41-70	21-40	6-20
	Reduced dosage				Reduced dosage				Reduced dosage			
>70	250 q6h	250 q8h	125 q12h	250 q12h	500 q6h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q6h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q6h	250 q8h	250 q8h	250 q12h
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q6h	250 q8h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q6h	250 q8h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q6h	125 q8h	125 q8h	125 q12h

Table III: Reduced intravenous dosage of intravenous imipenem-cilastatin in adult patients with impaired renal function (creatinine clearance ≤ 70 mL/min/1.73 m²) and/or body weight <70 kg

and Body Weight (kg) is:	If Total Daily Dose from Table I is: 3.0 g/day — and creatinine clearance (mL/min/1.73 m²) is:				4.0 g/day — and creatinine clearance (mL/min/1.73 m²) is:			
	>71	41-70	21-40	6-20	>71	41-70	21-40	6-20
	Reduced dosage				Reduced dosage			
≥70	1000 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
60	750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
50	500 q6h	375 q8h	250 q8h	250 q12h	750 q6h	500 q8h	500 q8h	500 q12h
40	500 q6h	250 q8h	250 q8h	250 q12h	500 q6h	500 q8h	250 q8h	250 q12h
30	250 q6h	250 q8h	250 q8h	250 q12h	500 q6h	250 q8h	250 q8h	250 q12h

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m² should be treated with intravenous imipenem-cilastatin 125 mg or 250 mg every 12 hours for most pathogens. There may be an increased risk of seizures in patients who receive 500 mg every 12 hours as administered to these patients.

Patients with creatinine clearance ≤ 5 mL/min/1.73 m² should not receive intravenous imipenem-cilastatin unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of intravenous imipenem-cilastatin for patients undergoing peritoneal dialysis.

Hemodialysis

When treating patients with creatinine clearances of ≤ 5 mL/min/1.73 m² who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6-20 mL/min/1.73 m² (See Table II and Table III). Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive intravenous imipenem-cilastatin 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, intravenous imipenem-cilastatin is recommended only when the benefit outweighs the potential risk of seizures.

Prophylactic use

For prophylaxis against post-surgical infections in adults: 1 g of **CILANEM** (imipenem and cilastatin) should be given intravenously on induction of anaesthesia and 1 g three hours later. For high-risk (i.e. colorectal) surgery, two additional 0.5 g doses can be given at 8 and 16 hours after induction.

Paediatrics: See **PRECAUTIONS, Paediatrics**.

For paediatric patients ≥3 months of age, the recommended dose for non-CNS infections is 15-25 mg/kg/dose administered every six hours. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis.

For paediatric patients ≤3 months of age (weighing ≥1,500 grams), the following dosage schedule is recommended for non-CNS infections:

<1 week of age: 25 mg/kg every 12 hrs

1-4 weeks of age: 25 mg/kg every 8 hrs

4 weeks-3 months of age: 25 mg/kg every 6 hrs

Doses less than or equal to 500 mg should be given by intravenous infusion over 15 to 30 minutes.

Doses greater than 500 mg should be given by intravenous infusion over 40 to 60 minutes.

Intravenous imipenem-cilastatin is not recommended in paediatric patients with CNS infections because of the risk of seizures.

Intravenous imipenem-cilastatin is not recommended in paediatric patients <30 kg with impaired renal function, as no data are available.

DIRECTIONS FOR USE

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

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

*Caution: **THE SUSPENSION IS NOT FOR DIRECT INFUSION.***

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

Benzyl alcohol as a preservative has been associated with toxicity in neonates. While toxicity has not been demonstrated in pediatric patients greater than three months of age, small pediatric patients in this age range may also be at risk for benzyl alcohol toxicity. Therefore, diluents containing benzyl alcohol should not be used when **CILANEM** (imipenem and cilastatin) is constituted for administration to pediatric patients in this age range.

STABILITY AND COMPATIBILITY

Before reconstitution the dry powder should be stored at a temperature below 25°C (77°F).

Solutions of **CILANEM** (imipenem and cilastatin) range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

CILANEM (imipenem and cilastatin) reconstituted with the following diluents (See **DIRECTIONS FOR USE**), maintains satisfactory potency for 4 hours at room temperature (25°C) or for 24 hours under refrigeration (4°C). Solutions of **CILANEM** (imipenem and cilastatin) should not be frozen.

0.9% Sodium Chloride Injection

5% or 10% Dextrose Injection

5% Dextrose and 0.9% Sodium Chloride Injection

5% Dextrose Injection with 0.225% or 0.45% saline solution

5% Dextrose Injection with 0.15% potassium chloride solution

Mannitol 5% and 10%

CILANEM (imipenem and cilastatin) should not be mixed with or physically added to other antibiotics. However, **CILANEM** (imipenem and cilastatin) may be administered concomitantly with other antibiotics, such as aminoglycosides.

PRECAUTIONS

- **General**

CNS adverse experiences such as myoclonic activity, confusional states, and seizures have been reported with intravenous imipenem-cilastatin, especially when the recommended doses were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there were reports in which there was no recognized or documented underlying CNS disorder or compromised renal function.

When recommended doses of intravenous imipenem-cilastatin were exceeded, adult patients with creatinine clearances of < 20 mL/min/1.73m^2, whether or not undergoing hemodialysis, had a higher risk of seizure activity than those without impairment of renal function. Therefore, close adherence to the dosing guidelines for these patients is recommended.

Patients with creatinine clearances of < 5 mL/min/1.73 m^2 should not receive intravenous imipenem-cilastatin unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, intravenous imipenem-cilastatin is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of intravenous imipenem-cilastatin re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of intravenous imipenem-cilastatin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing intravenous imipenem-cilastatin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

- **Warnings**

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

THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. BEFORE INITIATING THERAPY WITH IMIPENEM-CILASTATIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, IMIPENEM-CILASTATIN SHOULD BE DISCONTINUED.

Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, may also be administered as indicated.

Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported during treatment with intravenous imipenem-cilastatin.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including imipenem-cilastatin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

- **Contraindications**

CILANEM (imipenem and cilastatin) is contraindicated in patients who have shown hypersensitivity to any component of this product.

- *Pregnancy*

Pregnancy Category C

Teratology studies with cilastatin sodium at doses of 30, 100, and 300 mg/kg/day administered intravenously to rabbits and 40, 200, and 1000 mg/kg/day administered subcutaneously to rats, up to approximately 1.9 and 3.2 times the maximum recommended daily human dose (on a mg/m^2 body surface area basis) of the intravenous formulation of imipenem-cilastatin sodium (50 mg/kg/day) in the two species, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity was observed in rabbits given imipenem/cilastatin intravenous doses of 15, 30 or 60 mg/kg/day and rats given imipenem at intravenous doses of 225, 450, or 900 mg/kg/day, up to approximately 0.4 and 2.9 times the maximum recommended daily human dose (on a mg/m^2 body surface area basis) in the two species, respectively.

Teratology studies with imipenem-cilastatin sodium at intravenous doses of 20 and 80, and a subcutaneous dose of 320 mg/kg/day, up to 5 times the (mice) to approximately equal to (rats) the highest recommended daily intravenous human dose (on a mg/m^2 body surface area basis) in pregnant rodents during the period of major organogenesis, revealed no evidence of teratogenicity.

Imipenem-cilastatin sodium, when administered subcutaneously to pregnant rabbits at dosages equivalent to the usual human dose of the intravenous formulation and higher (1000-4000 mg/day), caused body weight loss, diarrhea, and maternal deaths. When comparable doses of imipenem-cilastatin sodium were given to non-pregnant rabbits, body weight loss, diarrhea, and deaths were also observed. This intolerance is not unlike that seen with other beta-lactam antibiotics in this species and is probably due to alteration of gut flora.

A teratology study in pregnant cynomolgus monkeys given imipenem-cilastatin sodium at doses of 40 mg/kg/day (bolus intravenous injection) or 160 mg/kg/day (subcutaneous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhea, abortion, and death in some cases. In contrast, no significant toxicity was observed when non-pregnant cynomolgus monkeys were given doses of imipenem-cilastatin sodium up to 180 mg/kg/day (subcutaneous injection). When doses of imipenem-cilastatin sodium (approximately 160 mg/kg/day or approximately 0.6 times the maximum recommended daily human dose of the intravenous formulation) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

No adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered subcutaneously to rats late in gestation at dosages up to 320 mg/kg/day, approximately equal to the highest recommended human dose (on a mg/m^2 body surface area basis).

There are, however, no adequate and well-controlled studies in pregnant women. Intravenous imipenem-cilastatin should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Based on patient body surface area of 1.4m^2 (weight of 60 kg).

- **Lactation**

It is not known whether imipenem-cilastatin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when imipenem-cilastatin is administered to a nursing woman.

Use of intravenous imipenem-cilastatin in paediatric patients, neonates to 16 years of age, is supported by evidence from adequate and well-controlled studies of intravenous imipenem-cilastatin in adults and by the clinical studies and published literature in paediatric patients. In paediatric patients ≥3 months of age (with non-CNS infections), the recommended dose of intravenous imipenem-cilastatin is 15-25 mg/kg/dose administered every six hours. Doses of 25 mg/kg/dose in patients 3 months to <3 years of age, and 15 mg/kg/dose in patients 3-12 years of age were associated with mean trough plasma concentrations of imipenem of 1.1±0.4 µg/mL and 0.6±0.2 µg/mL following multiple 60-minute infusions, respectively; trough urinary concentrations of imipenem were in excess of 10 µg/mL for both doses. These doses have provided adequate plasma and urine concentrations for the treatment of non-CNS infections. Based on studies in adults, the maximum daily dose for treatment of infections with fully susceptible organisms is 2.0 g per day, and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*) is 4.0 g/day. Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis. Based on studies of paediatric patients ≤3 months of age (weighing ≥1,500 gms), the following dosage schedule is recommended for non-CNS infections:

<1 week of age: 25 mg/kg every 12 hrs
1-4 weeks of age: 25 mg/kg every 8 hrs
4 weeks-3 months of age: 25 mg/kg every 6 hrs

In a published dose-ranging study of smaller premature infants (670-1,890 gms) in the first week of life, a dose of 20 mg/kg q12h by 15-30 minutes infusion was associated with mean peak and trough plasma imipenem concentrations of 43 µg/mL and 1.7 µg/mL after multiple doses, respectively. However, moderate accumulation of cilastatin in neonates may occur following multiple doses of intravenous imipenem-cilastatin. The safety of this accumulation is unknown.
Intravenous imipenem-cilastatin is not recommended in paediatric patients with CNS infections because of the risk of seizures.
Intravenous imipenem-cilastatin is not recommended in paediatric patients <30 kg with impaired renal function, as no data are available.

- **Geriatrics**

No overall differences in safety or effectiveness between elderly subjects (≥65 years) and younger subjects have been reported. However, a greater sensitivity of some older individuals cannot be ruled out.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
No dosage adjustment is required based on age. Dosage adjustment in the case of renal impairment is necessary.

- **Carcinogenicity/Mutagenicity/Impairment of fertility**

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin.
Genetic toxicity studies were performed *in a variety* of bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were: V79 mammalian cell mutagenesis assay (imipenem-cilastatin sodium and imipenem alone), Ames test (cilastatin sodium alone and imipenem alone), unscheduled DNA synthesis assay (imipenem-cilastatin sodium) and *in vivo* mouse cytogenetics test (imipenem-cilastatin sodium). None of these tests showed any evidence of genetic alterations.
Reproductive tests in male and female rats were performed with imipenem-cilastatin sodium at dosage levels up to 11 times the maximum daily recommended human dose of the intramuscular formulation (on a mg/kg basis). Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when imipenem-cilastatin sodium was administered to rats late in gestation.

- **Drug Interactions**

Generalized seizures have been reported in patients who received ganciclovir and imipenem-cilastatin. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.
Concomitant administration of imipenem-cilastatin and probenecid results in only minimal increases in plasma levels and half-life of imipenem, with urinary recovery of active imipenem reduced to approximately 60% of the administered dose. However, the plasma levels and half-life of cilastatin are almost doubled. Concomitant administration of probenecid with imipenem-cilastatin is not recommended.
Imipenem-cilastatin should not be mixed with or physically added to other antibiotics. However, imipenem-cilastatin may be administered concomitantly with other antibiotics, such as aminoglycosides.

- **Adverse reactions**

Imipenem-cilastatin is generally well tolerated. Side effects rarely require cessation of therapy and are generally mild and transient; serious side effects are rare.
Local reactions: erythema, local pain and induration, thrombophlebitis.
Allergic: rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, angioedema, toxic epidermal necrolysis (rarely), exfoliative dermatitis, (rarely) candidiasis, fever including drug fever, anaphylactic reactions.
Gastrointestinal: nausea, vomiting, diarrhoea, staining of teeth and/or tongue. Pseudomembranous colitis has been reported.
Blood: eosinophilia, leucopenia, neutropenia including agranulocytosis, thrombocytopenia, thrombocytosis, decreased haemoglobin and prolonged prothrombin time. A positive direct Coombs test may develop.
Liver function: mild increases in serum transaminases, bilirubin and/or serum alkaline phosphatase, hepatitis rarely have been reported.
Renal function: oliguria/anuria, polyuria, acute renal failure (rarely). The role of imipenem-cilastatin in changes in renal function is difficult to assess, since factors predisposing to pre-renal uraemia or to impaired renal function usually have been present. Elevated serum creatinine and blood urea have been seen. A harmless urine discoloration, not to be confused with haematuria, has been seen in children.
Central nervous system: myoclonic activity, psychic disturbances including hallucinations, paraesthesia, confusional states or convulsions have been reported.
Special senses: hearing loss, taste perversion.
Other reported reactions with an unknown causal relationship
Gastrointestinal: haemorrhagic colitis, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation.
Central nervous system: dizziness, somnolence, encephalopathy, vertigo, headache.
Special senses: tinnitus.
Respiratory: chest discomfort, dyspnoea, hyperventilation, thoracic spine pain.
Cardiovascular: hypotension, palpitations, tachycardia.
Skin: flushing, cyanosis, hyperhidrosis, skin texture changes, pruritus vulvae.
Body as a whole: polyarthralgia, asthenia/weakness.
Blood: haemolytic anaemia, pancytopenia, bone marrow depression.
The spectrum of adverse events in pediatric patients has been reported to be similar to that in adults.

OVERDOSAGE

In the case of overdosage, discontinue intravenous imipenem-cilastatin, treat symptomatically, and institute supportive measures as required. Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable.
The acute intravenous toxicity of imipenem-cilastatin sodium in a ratio of 1:1 was studied in mice at doses of 751 to 1359 mg/kg. Following drug administration, ataxia was rapidly produced and clonic convulsions were noted in about 45 minutes. Deaths occurred within 4-56 minutes at all doses. The acute intravenous toxicity of imipenem-cilastatin sodium was produced within 5-10 minutes in rats at doses of 771 to 1583 mg/kg. In all dosage groups, females had decreased activity, bradypnea, and ptosis with clonic convulsions preceding death; in males, ptosis was seen at all dose levels while tremors and clonic convulsions were seen at all but the lowest dose (771 mg/kg). In another rat study, female rats showed ataxia, bradypnea, and decreased activity in all but the lowest dose (550 mg/kg), deaths were preceded by clonic convulsions. Male rats showed tremors at all doses and clonic convulsions and ptosis was seen at the two highest doses (1130 and 1734 mg/kg). Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

STORAGE

The dry powder should be stored below 25°C.
After suspension vial contents must be transferred to 100 ml infusion solution.
After constitution as directed, the solution maintains satisfactory potency for 4 hours at room temperature (25°C) or for 24 hours under refrigeration (4°C).
Solutions of CILANEM should not be frozen.

Keep all medicines out of reach of children

SUPPLY

CILANEM 250 mg: One vial
CILANEM 500 mg: One vial

REFERENCES

1. US Prescribing information of *Primaxin I.V.* Merck & Co. INC., USA, August 2003.
2. ABPI Compendium of Data Sheets and Summaries of Product Characteristics. *PRIMAXIN IV*, Merck Sharp & Dohme Limited, UK, October 2003.

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MADE IN INDIA
RANBAXY
LABORATORIES LIMITED
INDUSTRIAL AREA - 3
DEWAS - 455 001

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