PRESCRIBING INFORMATION

For the Use Only of a Registered Medical Practitioner

CILANEM 500 mg

(Imipenem and Cilastatin for Injection USP)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Imipenem and Cilastatin and other antibacterial drugs, CILANEM 500 mg (Imipenem and Cilastatin Injection) should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

For Intravenous Injection Only

COMPOSITION

Active Ingredients

CILANEM 500 mg

Each vial contains:

Imipenem USP (Sterile)
equivalent to anhydrous Imipenem 500 mg

Cilastatin Sodium USP (Sterile)
equivalent to Cilastatin 500 mg

Excipients: Sodium Bicarbonate USP (Sterile) added as buffer

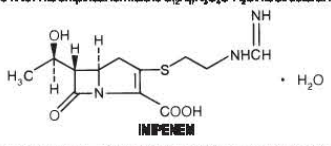
PHARMACEUTICAL FORM AND CONTENTS

Injection for Intravenous use

THERAPEUTIC CLASS / ACTIVITY [1,2]

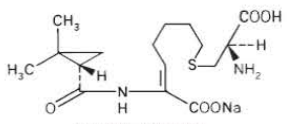
CILANEM 500 mg is a sterile formulation of Imipenem (a thienamycin antibiotic) and cilastatin sodium (the inhibitor of the renal dipeptidase, dehydropeptidase I), with sodium bicarbonate added as a buffer. Imipenem and cilastatin combination is a potent broad spectrum antibacterial for intravenous administration.

Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by *Streptomyces cattleya*. Its chemical name is (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. It has a molecular weight of 317.37. Its empirical formula is $C_{12}H_{17}N_3O_4S{\cdot}H_2O$. Its structural formula is as given below.



IMIPENEM

Cilastatin sodium is the sodium salt of a derivatized heptenoic acid. It is chemically designated as sodium (*Z*)-7[[(*R*)-2-amino-2-carboxyethyl]thio]-2-[(*S*)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It has a molecular weight of 380.43. Its empirical formula is $C_{16}H_{25}N_2O_5SNa$. Its structural formula is as given below.



CILASTATIN SODIUM

Mechanism of Action

Imipenem is a potent inhibitor of bacterial cell wall synthesis and is highly reactive towards penicillin-binding protein. Imipenem is more potent in its bactericidal effect than other antibiotics studied. Imipenem also provides excellent stability to degradative bacterial beta-lactamases. Imipenem is therefore active against a high percentage of organisms resistant to other beta-lactam antibiotics.

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, both 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 most 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 which metabolizes and inactivates Imipenem. Cilastatin sodium is devoid of intrinsic antibacterial activity itself and does not affect the antibacterial activity of imipenem.

Antimicrobial Activity

Imipenem has *in vitro* activity against a wide range of gram-positive and gram-negative organisms. Imipenem has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections treated with the intravenous formulation of imipenem-cilastatin sodium as described in the THERAPEUTIC INDICATIONS sections.

Gram-positive aerobes:
Enterococcus faecalis (formerly *S. faecalis*)
(NOTE: Imipenem is inactive *in vitro* against *Enterococcus faecium* [formerly *S. faecium*])
Staphylococcus aureus including penicillinase-producing strains
Staphylococcus epidermidis including penicillinase-producing strains
(NOTE: 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.

Mechanism(s) of Resistance

For species considered susceptible to Imipenem, resistance was uncommon in surveillance studies in Europe. In resistant isolates, resistance to other antibacterial agents of the carbapenem class was seen in some, but not all isolates. Imipenem is effectively stable to hydrolysis by most classes of beta-lactamases, including penicillinases, cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases. Although effectively stable to beta-lactamase activity, resistance, when seen, is generally due to a combination of decreased permeability and low-level beta-lactamase hydrolysis.

The mechanism of action of imipenem differs from that of other classes of antibiotics, such as quinolones, aminoglycosides, macrolides and tetracyclines. There is no target-based cross-resistance between imipenem and these substances. However, micro-organisms may exhibit resistance to more than one class of antibacterial agents when the mechanism is, or includes, impermeability to some compounds.

Pharmacokinetics

Adults

Intravenous Administration

Intravenous infusion of Imipenem and 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 and 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 upto 8 hours with Imipenem and cilastatin injection at the 500-mg dose. Approximately 70% of the cilastatin sodium dose is recovered in the urine within 10 hours of administration of imipenem and cilastatin injection.

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.

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.

After a 1 gram dose of Imipenem and cilastatin injection, the following average levels of Imipenem were measured (usually at 1 hour post dose except where indicated) in the tissues and fluids listed:

Tissue or Fluid	N	Imipenem Level mg/mL or µg/g	Range
Vitreous Humor	9	3.4 (3.5 hours post dose)	2.88 to 3.8
Aqueous Humor	5	2.99 (2 hours post dose)	2.4 to 3.9
Lung Tissue	8	5.6 (median)	3.5 to 16.5
Sputum	1	2.1	—
Pleural	1	22.0	—
Peritoneal	12	23.8 S.D. ± 5.3 (2 hours post dose)	—
Bile	2	5.3 (2.25 hours post dose)	4.6 to 6.0
CSF (uninflamed)	5	1.0 (4 hours post dose)	0.26 to 2.0
CSF (inflamed)	7	2.6 (2 hours post dose)	0.5 to 5.5
Fallopian Tubes	1	13.6	—
Endometrium	1	11.1	—
Myometrium	1	5.0	—
Bone	10	2.6	0.4 to 5.4
Interstitial Fluid	12	16.4	10.0 to 22.6
Skin	12	4.4	NA
Fascia	12	4.4	NA

Imipenem-cilastatin sodium is hemodialyzable. However, usefulness of this procedure in the overdosage setting is questionable (see OVERDOSAGE AND ITS MANAGEMENT).

THERAPEUTIC INDICATIONS [1,2]

CILANEM 500 mg (Imipenem and Cilastatin Injection) is indicated for the treatment of serious infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- **Lower respiratory tract infections.** *Staphylococcus aureus* (penicillinase-producing strains), *Acinetobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae*, Klebsiella species, Serratia marcescens.*
- **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.*
- **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.
- **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*.*
- **Bacterial septicemia.** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Enterobacter species, Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, Serratia species*, Bacteroides species including B. fragilis*.*
- **Bone and joint infections.** *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Enterobacter species, Pseudomonas aeruginosa.*
- **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*.*
- **Endocarditis.** *Staphylococcus aureus (penicillinase-producing strains).*
- **Polymicrobic infections.** CILANEM 500 mg (Imipenem and Cilastatin Injection) 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.

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

CILANEM 500 mg (Imipenem and Cilastatin Injection) is indicated against **mixed infections** caused by susceptible aerobic and anaerobic bacteria. The majority of these infections are associated with contamination by faecal flora, or flora originating from the vagina, skin, and mouth. In these mixed infections, Imipenem and Cilastatin combination is usually effective against Bacteroides fragilis sp., the most commonly encountered anaerobic pathogen, which is usually resistant to the aminoglycosides, cephalosporins and penicillins.

Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, Imipenem and Cilastatin combination is useful for the treatment of mixed infections and as presumptive therapy prior to the identification of the causative organisms.

Prophylaxis: CILANEM 500 mg (Imipenem and Cilastatin Injection) is also indicated for the prevention of certain post-operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post-operative infection could be especially serious.

CILANEM 500 mg (Imipenem and Cilastatin Injection) is **not** indicated in patients with meningitis or central nervous system infections because safety and efficacy have not been established.

For Pediatric Use Information, see PRECAUTIONS: Pediatric Use; and DOSAGE AND ADMINISTRATION sections.

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 Imipenem and Cilastatin combination. 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 Imipenem and Cilastatin combination.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of anti-bacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Imipenem and Cilastatin combination and other antibacterial drugs, CILANEM 500 mg (Imipenem and Cilastatin Injection) 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.

CONTRAINDICATIONS [1,2]

CILANEM 500 mg (Imipenem and Cilastatin Injection) is contraindicated in patients who have shown hypersensitivity to Imipenem or Cilastatin or to any component / excipient of this product.

WARNINGS [1,2]

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

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA-LACTAM. 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.

Seizure Potential: Seizures and other CNS adverse experiences, such as confusional states and myoclonic activity, have been reported with intravenous Imipenem-cilastatin (see ADVERSE REACTIONS).

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 valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. 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/sodium valproate or divalproex sodium is 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 Imipenem and Cilastatin Injection is necessary, supplemental anticonvulsant therapy should be considered (see DRUG INTERACTIONS).

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Imipenem-cilastatin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Pseudomembranous colitis, reported with virtually all antibiotics, can range from mild to life-threatening in severity. Imipenem-cilastatin combination should be prescribed with caution in patients with a history of gastro-intestinal disease, particularly colitis. Treatment-related diarrhoea should always be considered as a pointer to this diagnosis. While studies indicate that a toxin of Clostridium difficile is one of the primary causes of antibiotic-associated colitis, other causes should be considered.

CILANEM 500 mg (Imipenem and Cilastatin Injection) vial contains 37.5 mg of sodium (1.8 mEq), which should be taken into consideration by patients on a controlled sodium diet.

PRECAUTIONS [1,2]

General

Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon coadministration with Imipenem and Cilastatin Injection. If treatment with Imipenem and Cilastatin Injection is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed.

CNS adverse experiences such as myoclonic activity, confusional states, and seizures have been reported with intravenous Imipenem-cilastatin, especially when the recommended dosages are 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 have been reports of CNS adverse experiences in patients who had 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 (see DOSAGE AND ADMINISTRATION).

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 combination 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.

Laboratory Tests: While intravenous imipenem-cilastatin possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Information for Patients

Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon coadministration with Imipenem and Cilastatin Injection. If treatment with Imipenem and Cilastatin Injection is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed.

Patients should be counseled that antibacterial drugs including intravenous Imipenem-cilastatin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When intravenous Imipenem-cilastatin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy (1) may decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by intravenous Imipenem-cilastatin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Effects on ability to drive and use machines

There are no specific data; however, some of the CNS side-effects, such as dizziness, psychic disturbances, confusion and seizures, may affect the ability to drive or operate machinery.

Pregnancy

US-FDA 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[11] 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 at 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[11] 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 0.5 times[11] (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 to 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 100 mg/kg/day or approximately 0.6 times[11] 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. Imipenem-cilastatin should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

[11]Based on patient body surface area of 1.6m^2 (weight of 60 kg).

Lactation

Imipenem-cilastatin sodium has been detected in human milk. If the use of Imipenem-cilastatin is deemed essential, the mother should stop breast-feeding.

Paediatrics

Use of intravenous Imipenem-cilastatin in pediatric 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 pediatric patients. Based on published studies of 178** pediatric patients ≥ 3 months of age (with non-CNS infections), the recommended dose of intravenous imipenem-cilastatin injection is 15 to 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 to 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 (see Table 1 in DOSAGE AND ADMINISTRATION section). Higher doses (up to 90 mg/kg/day in older children) have been used in patients with cystic fibrosis (see DOSAGE AND ADMINISTRATION).

** Two patients were less than 3 months of age.

Based on studies OF 135*** pediatric 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 to 4 weeks of age: 25 mg/kg every 8 hrs
4 weeks to 3 months of age: 25 mg/kg every 6 hrs.

*** One patient was greater than 3 months of age.

In a published dose-ranging study of smaller premature infants (670 to 1,890 grams) in the first week of life, a dose of 20 mg/kg q12h by 15 to 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 combination is not recommended in pediatric patients with meningitis or CNS infections because of the risk of seizures.

Patients with CNS disorders and/or compromised renal function (accumulation of imipenem-cilastatin may occur) have shown CNS side effects, especially when recommended dosages based on bodyweight and renal function were exceeded. Hence it is recommended that the dosage schedules of Imipenem-cilastatin should be strictly adhered to, and established anticonvulsant therapy continued. If focal tremors, myoclonus or convulsions occur, the patient should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If these symptoms continue, the dosage should be reduced, or imipenem-cilastatin withdrawn completely.

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

Geriatrics

The literature on approximately 800 subjects who were 65 years of age or over, including approximately 300 subjects who were 75 years of age and over show that no overall differences in safety or effectiveness between these elderly subjects and younger subjects have been reported. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but 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 (see DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem-cilastatin. Genetic toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests used were: V79 mammalian cell mutagenesis assay (Imipenem-cilastatin sodium 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 intravenous doses up to 80 mg/kg/day and at a subcutaneous dose of 320 mg/kg/day, approximately equal to the highest recommended human dose of the intravenous formulation (on a mg/m^2 body surface area 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.

DRUG INTERACTIONS [1,2]

Ganciclovir: 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.

Probenecid: Concomitant probenecid has been shown to double the plasma level and half life of cilastatin, but with no effect on its urinary recovery. Concomitant probenecid showed only minimal increases in plasma level and half life of Imipenem, with urinary recovery of active Imipenem decreased to approximately 60% of the administered dose. Since concomitant administration of intravenous Imipenem-cilastatin 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 intravenous imipenem-cilastatin.

Aminoglycosides: 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.

Valproic acid / divalproex: 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 valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. Concomitant use of imipenem and valproic acid/sodium valproate or divalproex sodium is not recommended and alternative antibacterial or anti-convulsant therapies should be considered (see WARNINGS).

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament. The doctor and the pharmacist are the experts in medicines, their benefits and risks. Do not by yourself interrupt the period of treatment prescribed. Do not repeat the same prescription without consulting your doctor. Keep all medicaments out of reach of children.
Council of Arab Health Ministers, Union of Arab Pharmacists.

DOSAGE AND ADMINISTRATION [1,2]

CILANEM 500 mg (Imipenem and Cilastatin Injection) is for intravenous use only and it should not be used intramuscularly.

Adults

The dosage recommendations for CILANEM 500 mg (Imipenem and Cilastatin Injection) represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution. Each 125 mg, 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 m^2, require adjustment of dosage as described below.

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

Doses cited in Table 1 below are based on a patient with normal renal function and a body weight of 70 kg. These doses should be used for a patient with a creatinine clearance of ≥ 71 mL/min/1.73 m^2 and a body weight of ≥ 70 kg. A reduction in dose must be made for a patient with a creatinine clearance of ≤ 70 mL/min/1.73 m^2 and/or a body weight less than 70 kg.

Dosage regimens in column A of Table 1 below are recommended for infections caused by fully susceptible organisms which represent the majority of pathogenic species. Dosage regimens in column B of Table 1 are recommended for infections caused by organisms with moderate susceptibility to imipenem, primarily some strains of *P. aeruginosa*.

Table 1: Intravenous dosage schedule for adults with normal renal function (creatinine clearance of 71 mL/min/ 1.73 m^2) 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 q6h (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 Function and/or Body Weight <70 kg

Patients with creatinine clearance of 70 mL/min/1.73 m^2 and/or body weight less than 70 kg require dosage reduction of CILANEM 500 mg (Imipenem and Cilastatin Injection) as indicated in the tables below. Creatinine clearance may be calculated from serum creatinine concentration by the following equation:

T_{cr} (Males) = $\frac{\text{(wt. in kg)(140 – age)}}{\text{(72)(Creatinine in mg/dL)}}$

T_{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 1 above 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 2 below 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 3 and continue with step 3.
3. From Table 2 or 3:
   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 2: Reduced intravenous dosage of intravenous *imipenem-cilastatin* in adult patients with impaired renal function (creatinine clearance 70 mL/min/1.73 m^2) and/or body weight <70 kg.

If Total Daily Dose from Table 1 is:	1.0 g/day				1.5 g/day				2.0 g/day			
And Body Weight (kg) is:	and creatinine clearance (mL/min/1.73 m^2) is:				and creatinine clearance (mL/min/1.73 m^2) is:				and creatinine clearance (mL/min/1.73 m^2) is:			
	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is				then the reduced dosage regimen (mg) is				than the reduced dosage regimen (mg) is			
≥70	250 q6h	250 q6h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q8h	125 q8h	250 q12h	125 q12h	250 q8h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h
50	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q8h	125 q8h	125 q12h	125 q12h	250 q8h	125 q8h	125 q8h	125 q12h	250 q8h	250 q8h	250 q12h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q8h	125 q8h	125 q8h	125 q12h	250 q8h	125 q8h	125 q8h	125 q12h

Table 3: Reduced intravenous dosage of intravenous *imipenem-cilastatin* in adult patients with impaired renal function (creatinine clearance 70 mL/min/1.73 m^2) and/or body weight <70 kg.

If Total Daily Dose from Table 1 is:	3.0 g/day				4.0 g/day			
And Body Weight (kg) is:	and creatinine clearance (mL/min/1.73 m^2) is:				and creatinine clearance (mL/min/1.73 m^2) is:			
	≥71	41-70	21-40	6-20	≥71	41-70	21-40	6-20
	then the reduced dosage regimen (mg) is				then the reduced dosage regimen (mg) is			
≥70	1000 q8h	500 q8h	500 q8h	500 q12h	1000 q6h	750 q8h	500 q6h	500 q12h
60	750 q8h	500 q8h	500 q8h	500 q12h	1000 q8h	750 q8h	500 q8h	500 q12h
50	500 q6h	500 q8h	250 q8h	250 q12h	750 q8h	500 q8h	500 q8h	500 q12h
40	500 q8h	250 q8h	250 q8h	250 q12h	500 q6h	500 q8h	250 q8h	250 q12h
30	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h

Patients with creatinine clearances of 6 to 20 mL/min/1.73 m^2 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 when doses of 500 mg every 12 hours are administered to these patients.

Patients with creatinine clearance ≤ 5 mL/min/1.73 m^2 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 m^2 who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of 6 to 20 mL/min/1.73 m^2 (See *Reduced Intravenous Dosage Schedule for Adults with Impaired Renal Function and/or Body Weight <70 kg*). 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 (see PRECAUTIONS).

Prophylactic use: For prophylaxis against post-surgical infections in adults, 1 gram of Imipenem-Cilastatin Injection should be given intravenously on induction of anaesthesia and 1 gram three hours later. For high-risk (i.e. colorectal) surgery, two additional 0.5 gram doses can be given at 8 and 16 hours after induction.

Pediatrics

(See PRECAUTIONS: Pediatric patients)

For pediatric patients ≥ 3 months of age, the recommended dose for non-CNS infections is 15 to 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 pediatric 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 to 4 weeks of age: 25 mg/kg every 8 hrs
4 weeks to 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 CILANEM 500 mg (Imipenem and Cilastatin Injection) is not recommended in paediatric patients with meningitis or CNS infections because of the risk of seizures. If meningitis is suspected, then other appropriate antibiotic should be used.

Intravenous CILANEM 500 mg (Imipenem and Cilastatin Injection) is not recommended in paediatric patients <30 kg with impaired renal function, as no data are available.

Use in the elderly

Age does not usually affect the tolerability and efficacy of Imipenem and Cilastatin Injection. The dosage should be determined by the severity of the infection, the susceptibility of the causative organism(s), the patient's clinical condition, and renal function.

Preparation of Solution

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

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

CAUTION: THE SUSPENSION IS NOT FOR DIRECT INFUSION.

Repeat with an additional 10 mL of compatible infusion solution to ensure complete transfer of vial contents to the compatible 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 500 mg (Imipenem and Cilastatin Injection) is constituted for administration to pediatric patients in this age range.

Compatibility and Stability

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

Reconstituted solutions of CILANEM 500 mg (Imipenem and Cilastatin Injection) range from colorless to yellow. Variations of color within this range do not affect the potency of the product.

In keeping with good clinical and pharmaceutical practice, CILANEM 500 mg (Imipenem and Cilastatin Injection) should be administered as a freshly prepared solution. CILANEM 500 mg (Imipenem and Cilastatin Injection) as supplied in single use vials and reconstituted with the below given diluents (see Preparation of Solution above), maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (4°C). Solutions of CILANEM 500 mg (Imipenem and Cilastatin Injection) 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 500 mg (Imipenem and Cilastatin Injection) should not be mixed with or physically added to other antibiotics. However, Imipenem and Cilastatin Injection may be administered concomitantly with other antibiotics, such as aminoglycosides.

CILANEM 500 mg (Imipenem and Cilastatin Injection) is chemically incompatible with lactate and should not be reconstituted with diluents containing lactate.

General

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded.

OVERDOSAGE AND ITS MANAGEMENT [1,2]

No specific information is available on the treatment of overdosage with Imipenem-cilastatin.

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 to 56 minutes at all doses.

The acute intravenous toxicity of imipenem-cilastatin sodium was produced within 5 to 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 were seen at the two highest doses (1130 and 1734 mg/kg). Deaths occurred between 6 and 88 minutes with doses of 771 to 1734 mg/kg.

ADVERSE REACTIONS [1,2]

Adults

Intravenous Imipenem-cilastatin combination is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with intravenous imipenem-cilastatin combination.

Local Adverse Reactions:

*Adverse local clinical reactions that were reported as possibly, probably, or definitely related to therapy with intravenous **Imipenem-cilastatin combination** were:*

Phlebitis / thrombophlebitis — 3.1%
Pain at the injection site — 0.7%
Erythema at the injection site — 0.4%
Vein induration — 0.2%
Infused vein infection — 0.1%

Systemic Adverse Reactions:

*The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to intravenous **Imipenem-cilastatin combination** were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see **PRECAUTIONS**), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).*

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity:

Gastrointestinal — pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment, see WARNINGS), hemorrhagic colitis, hepatitis *(including fulminant hepatitis),* hepatic failure, jaundice, gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, staining of the teeth and/or tongue, heartburn, pharyngeal pain, increased salivation.

Hematologic — pancytopenia, bone marrow depression, thrombocytopenia, thrombocytosis, neutropenia including agranulocytosis, leukopenia, hemolytic anemia.

CNS — encephalopathy, tremor, confusion, myoclonus, myoclonic activity, *paresthesia, vertigo, headache, psychic disturbances including hallucinations.*

Special Senses — hearing loss, tinnitus, taste perversion.

Respiratory — chest discomfort, dyspnea, hyperventilation, thoracic spine pain.

Cardiovascular — palpitations, tachycardia.

Skin — Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, angioneurotic edema, angioedema, anaphylactic reactions, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae.

Body as a whole — polyarthralgia, asthenia / weakness, drug fever.

Renal — acute renal failure, oliguria / anuria, polyuria, urine discoloration. The role of intravenous imipenem-cilastatin combination in changes in renal function is difficult to assess, since *factors predisposing to prerenal azotemia or to impaired renal function usually have been present.*

Granulocytopenic patients: drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with *Imipenem-cilastatin combination.*

Adverse Laboratory Changes:

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were:

Hepatic: Increased ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, and LDH.

Hemic: Increased eosinophils, positive Coombs test, increased WBC, increased platelets, decreased hemoglobin and hematocrit, agranulocytosis, increased monocytes, abnormal / prolonged 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.

Pediatric Patients

In studies of 178 pediatric patients ≥ 3 months of age, the following adverse events were noted:

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence >1%).	
Adverse Experience	No. of Patients (%)
Digestive System	
Diarrhea	7* (3.9)
Gastroenteritis	2 (1.1)
Vomiting	2* (1.1)
Skin	
Rash	4 (2.2)
Infection, I.V. site	2 (1.1)
Urogenital System	
Urine discoloration	2 (1.1)
Cardiovascular System	
Phlebitis	4 (2.2)
*One patient had both vomiting and diarrhea and is counted in each category.	

In studies of 135 patients (newborn to 3 months of age), the following adverse events were noted:

The Most Common Clinical Adverse Experiences Without Regard to Drug Relationship (Patient Incidence >1%).	
Adverse Experience	No. of Patients (%)
Digestive System	
Diarrhea	4 (3.0%)
Oral Candidiasis	2 (1.5%)
Skin	
Rash	2 (1.5%)
Urogenital System	
Oliguria / anuria	3 (2.2%)
Cardiovascular System	
Tachycardia	2 (1.5%)
Nervous System	
Convulsions	8 (5.9%)

Patients (≥ 3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values.		
Laboratory Parameter	Abnormality	No. of Patients With Abnormalities / No. of Patients With Lab Done (%)
Hemoglobin	Age <5 mos.: <10 gm %	19/129 (14.7)
	6 mos. to 12 yrs.: <11.5 gm %	
Hematocrit	Age <5 mos.: <30 vol %	23/129 (17.8)
	6 mos. to 12 yrs.: <34.5 vol %	
Neutrophils	≥ 1000/mm^3 (absolute)	4/123 (3.3)
Eosinophils	≥ 7%	15/117 (12.8)
Platelet Count	≥ 500 the/mm^3	18/119 (13.4)
Urine Protein	≥1	8/97 (8.2)
Serum Creatinine	>1.2 mg/dL	0/105 (0)
BUN	>22 mg/dL	0/108 (0)
AST (SGOT)	>36 IU/L	14/78 (17.9)
ALT (SGPT)	>30 IU/L	10/93 (10.8)

Patients (<3 Months of Age) With Normal Pretherapy but Abnormal During Therapy Laboratory Values.	
Laboratory Parameter	No. of Patients With Abnormalities* (%)
Eosinophil Count↑	11 (9.0%)
Hematocrit ↓	3 (2.0%)
Hematocrit↑	1 (1.0%)
Platelet Count↑	5 (4.0%)
Platelet Count ↓	2 (2.0%)
Serum Creatinine↑	5 (5.0%)
Bilirubin↑	3 (3.0%)
Bilirubin ↓	1 (1.0%)
AST (SGOT) ↑	5 (6.0%)
ALT (SGPT) ↑	3 (3.0%)
Serum Alkaline Phosphate↑	2 (3.0%)
* The denominator used for percentages was the number of patients for whom the test was performed during or post-treatment and, therefore, varies by test.	

Examination of published literature and spontaneous adverse event reports suggested a similar spectrum of adverse events in adult and pediatric patients.

Expiry Date with Warning

The product should not be used after the expiry date mentioned on the pack.

STORAGE

The dry powder should be stored below 25°C.

For Vial **- 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 500 mg (Imipenem and Cilastatin Injection) should not be frozen.

SUPPLY

CILANEM 500 mg (Imipenem and Cilastatin Injection) supplied as a sterile powder mixture in single dose containers vial.

DATE OF LAST REVISION OF PACKAGE LEAFLET

October 2010

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Marketing Authorization Holder:
Sun Pharmaceutical Industries Ltd.
Sun House, 201 B/1, Western Express Highway, Goregaon (East),
Mumbai - 400063, India

Manufactured in India by:
Sun Pharmaceutical Ind. Ltd.
Industrial Area - 3,
Dewas - 455 001