ONEM™ I.V.
INJECTION 500
(Imipenem / Cilastatin) for Injection U.S.P.

اونم آئی وی
انجکشن ۵۰۰

COMPOSITION:
Each vial contains:
Imipenem Monohydrate eq. to Imipenem U.S.P. ..... 500 mg
Cilastatin Sodium eq. to Cilastatin U.S.P. ..... 500 mg
(U.S.P. Specifications)

DESCRIPTION:
Imipenem and Cilastatin for Injection 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 for Injection. is a potent broad spectrum antibacterial agent for intravenous administration. Imipenem (N-formimidoylthienamycin monohydrate) is a crystalline derivative of thienamycin, which is produced by Streptomyces cattleya. Its chemical name is (5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(R)-1- hydroxyethyl] -7- oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate. It is an off-white, nonhygroscopic crystalline compound with a molecular weight of 317.37. It is sparingly soluble in water and slightly soluble in methanol.

Cilastatin sodium is the sodium salt of a derivative heptenoic acid. Its chemical name is sodium (Z)-7[[(R)-2- amino-2-carboxyethyl]thio]-2-[(S)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate. It is off-white to yellowish-white, hygroscopic, amorphous compound with a molecular weight of 380.43. It is very soluble in water and in methanol.
Imipenem and Cilastatin for Injection. is buffered to provide solutions in the pH range of 6.5 to 8.5. There is no significant change in pH when solutions are prepared and used as directed.

CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Mechanism of Action:
Imipenem and cilastatin sodium in a 1:1 ratio by weight.
Imipenem, also referred to as N-formimidoyl-thienamycin, is a semi-synthetic derivative of thienamycin, the parent compound produced by the filamentous bacterium Streptomyces cattleya.
Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).
Cilastatin sodium is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.
Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Similar to other beta-lactam antibacterial agents, the time that imipenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy.
Mechanism of resistance
Resistance to imipenem may be due to the following:
• Decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins)
• Imipenem may be actively removed from the cell with an efflux pump.
• Reduced affinity of PBPs to imipenem.

Pharmacokinetics:
Imipenem
Absorption
In normal volunteers, intravenous infusion of Imipenem and Cilastatin over 20 minutes resulted in peak plasma levels of imipenem ranging from 12 to 20 µg/ml for the 250 mg/250 mg dose, from 21 to 58 µg/ml for the 500 mg/500 mg dose, and from 41 to 83 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of imipenem following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg /1000 mg doses were 17, 39, and 66 µg/ml, respectively. At these doses, plasma levels of imipenem decline to below 1 µ g/ml or less in four to six hours.
Distribution
The binding of imipenem to human serum proteins is approximately 20%.
Biotransformation
When administered alone, imipenem is metabolised in the kidneys by dehydropeptidase-I. Individual urinary recoveries ranged from 5 to 40%, with an average recovery of 15-20% in several studies.
Cilastatin is a specific inhibitor of dehydropeptidase-I enzyme and effectively inhibits metabolism of imipenem so that concomitant administration of imipenem and cilastatin allows therapeutic antibacterial levels of imipenem to be attained in both urine and plasma.
Elimination
The plasma half-life of imipenem was one hour. Approximately 70% of the administered antibiotic was recovered intact in the urine within ten hours, and no further urinary excretion of imipenem was detectable. Urine concentrations of imipenem exceeded 10 µg/ml for up to eight hours after a 500 mg/500 mg dose of Imipenem and Cilastatin for Injection. The remainder of the administered dose was recovered in the urine as antibacterially inactive metabolites, and faecal elimination of imipenem was essentially nil.
No accumulation of imipenem in plasma or urine has been observed with regimens of Imipenem and Cilastatin, administered as frequently as every six hours, in patients with normal renal function.
Cilastatin
Absorption
Peak plasma levels of cilastatin, following a 20 minute intravenous infusion of Imipenem and Cilastatin, ranged from 21 to 26 µg/ml for the 250 mg/250 mg dose, from 21 to 55 µg/ml for the 500 mg/500 mg dose and from 56 to 88 µg/ml for the 1000 mg/1000 mg dose. The mean peak plasma levels of cilastatin following the 250 mg/250 mg, 500 mg/500 mg, and 1000 mg/1000 mg doses were 22, 42, and 72 µg/ml respectively.
Distribution
The binding of cilastatin to human serum proteins is approximately 40%.
Biotransformation and elimination
The plasma half-life of cilastatin is approximately one hour. Approximately 70-80% of the dose of cilastatin was recovered unchanged in the urine as cilastatin within 10 hours of administration of Imipenem and Cilastatin for Injection. No further cilastatin appeared in the urine thereafter. Approximately 10% was found as the N-acetyl metabolite, which has inhibitory activity against dehydropeptidase comparable to that of cilastatin. Activity of dehydropeptidase-I in the kidney returned to normal levels shortly after the elimination of cilastatin from the blood stream.
Pharmacokinetics in special populations
Renal insufficiency
Urinary recovery, renal clearance and plasma clearance of Imipenem and Cilastatin for Injection decrease with decreasing renal function following intravenous administration of Imipenem and Cilastatin for InjectionDose adjustment is necessary for patients with impaired renal function.
Hepatic insufficiency
The pharmacokinetics of imipenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of imipenem, its pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dose adjustment is recommended in patients with hepatic impairment.
Paediatric population
The average clearance (CL) and volume of distribution (Vdss) for imipenem were approximately 45% higher in paediatric patients (3 months to 14 years) as compared to adults. The AUC for imipenem following administration of 15/15 mg/kg per body weight of imipenem/cilastatin to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500 mg/500 mg dose. At the higher dose, the exposure following administration of 25/25 mg/kg imipenem/cilastatin to children was 9% higher as compared to the exposure in adults receiving a 1000 mg/1000 mg dose.
Elderly
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 and Cilastatin 500 mg/500 mg administered intravenously over 20 minutes were consistent with those expected in subjects with slight renal impairment for which no dose alteration is considered necessary. The mean plasma half-lives of imipenem and cilastatin were 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 was observed.

INDICATIONS:
Imipenem and Cilastatin for Injection 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***. Imipenem and Cilastatin for 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.
Imipenem and Cilastatin for Injection is not indicated in patients with meningitis because safety and efficacy have not been established.

DOSAGE AND ADMINISTRATION:
Adults
The dosage recommendations for Imipenem and Cilastatin for 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 Imipenem and Cilastatin for Injection 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 in the succeeding section of these guidelines. Intravenous Dosage Schedule for Adults with Normal Renal Function and Body Weight ≥70 kg Doses cited in Table I 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 m2 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 m2 and/or a body weight less than 70 kg. (See Tables II and III.) 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 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 Imipenem and Cilastatin for Injection, 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 Imipenem and Cilastatinfor Injection 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.

TABLE II
REDUCED INTRAVENOUS DOSAGE OF IMIPENEM AND CILASTATIN FOR INJECTION IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION AND/OR BODY WEIGHT <70 kg

And Body Weight (kg) is:	If TOTAL DAILY DOSE from TABLE I is: 1.0 g/day				1.5 g/day				2.0 g/day			
	and creatinine clearance (mL/min/1.73 m²) is:				and creatinine clearance (mL/min/1.73 m²) is:				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
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	250 q6h	250 q8h	250 q12h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	250 q12h
60	250 q8h	125 q6h	250 q12h	125 q12h	250 q6h	250 q8h	250 q8h	250 q12h	500 q8h	250 q6h	250 q8h	250 q12h
50	125 q6h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h	250 q6h	250 q6h	250 q8h	250 q12h
40	125 q6h	125 q8h	125 q12h	125 q12h	250 q8h	125 q6h	125 q8h	125 q12h	250 q6h	250 q8h	250 q12h	250 q12h
30	125 q8h	125 q8h	125 q12h	125 q12h	125 q6h	125 q8h	125 q8h	125 q12h	250 q8h	250 q6h	125 q8h	125 q12h

TABLE III
REDUCED INTRAVENOUS DOSAGE OF IMIPENEM AND CILASTATIN FOR INJECTION IN ADULT PATIENTS WITH IMPAIRED RENAL FUNCTION 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
	then the reduced dosage regimen (mg) is:				then the reduced dosage regimen (mg) is:			
≥70	1000 q8h	500 q6h	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 q6h	250 q12h	750 q8h	500 q6h	500 q8h	500 q12h
40	500 q8h	250 q6h	250 q8h	250 q12h	500 q6h	500 q8h	250 q6h	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 Imipenem and Cilastatin for Injection125 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 Imipenem and Cilastatin for Injection unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of Imipenem and Cilastatin for Injection 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 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 ONEM I.V. 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, ONEM I.V. is recommended only when the benefit outweighs the potential risk of seizures.

Pediatric Patients

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

<1 wk of age: 25 mg/kg every 12 hrs
1-4 wks of age: 25 mg/kg every 8 hrs
4 wks-3 mos. 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.
ONEM I.V. is not recommended in pediatric patients with CNS infections because of the risk of seizures.
ONEM I.V. is not recommended in pediatric patients <30 kg with impaired renal function, as no data are available.
ONEM I.V., as supplied in single use infusion bottles, vials and MONOVIAL® vials and reconstituted with the following diluents, maintains satisfactory potency for 4 hours at room temperature or for 24 hours under refrigeration (5°C). Solutions of ONEM I.V. 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%

CONTRAINDICATIONS:

Imipenem and Cilastatin for Injection is contraindicated in patients who have shown hypersensitivity to any component of this product.

PRECAUTIONS:

General

CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with Imipenem and Cilastatin for Injection, especially when recommended dosages 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 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 were exceeded, adult patients with creatinine clearances of ≤20 mL/min/1.73 m2, 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 m2 should not receive Imipenem and Cilastatin for Injection unless hemodialysis is instituted within 48 hours. For patients on hemodialysis, Imipenem and Cilastatin for Injection 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 Imipenem and Cilastatin for Injection reexamined to determine whether it should be decreased or the antibiotic discontinued. As with other antibiotics, prolonged use of Imipenem and Cilastatin for Injection 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 Imipenem and Cilastatin for Injection 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.

Information for Patients

Patients should be counseled to inform their physician if they are taking valproic acid or divalproex sodium.

ADVERSE REACTIONS:

Adults Imipenem and Cilastatin for Injection 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 Imipenem and Cilastatin for Injection.

Local Adverse Reactions: Adverse local clinical reactions that were reported as possibly, probably, or definitely related to therapy with Imipenem and Cilastatin for Injection 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 Imipenem and Cilastatin for Injection were nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%), 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), 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, neutropenia, leukopenia, hemolytic anemia.

CNS: encephalopathy, tremor, confusion, myoclonus, 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, angioneurotic edema, 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 Imipenem and Cilastatin for Injectionin changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

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 prothrombin time, increased lymphocytes, increased basophils

Electrolytes: Decreased serum sodium, increased potassium, increased chloride

DRUG INTERACTIONS:

Generalized seizures have been reported in patients who received ganciclovir and ONEM. These drugs should not be used concomitantly unless the potential benefits outweigh the risks.
Since concomitant administration of ONEM 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 ONEM.
ONEM should not be mixed with or physically added to other antibiotics. However, ONEM may be administered concomitantly with other antibiotics, such as aminoglycosides.
The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures.

USE IN SPECIFIC POPULATIONS:

Pregnancy Category C

There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women.
Imipenem and Cilastatin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore it is unlikely that the suckling infant will be exposed to significant quantities. If the use of Imipenem and Cilastatin is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Fertility

There are no data available regarding potential effects of imipenem/cilastatin treatment on male or female fertility.

OVER DOSAGE:

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 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. In the case of overdosage, discontinue Imipenem and 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.

AVAILABILITY:

Onem (Imipenem and Cilastatin) 500 I.V is available in a pack of one vial.

STORAGE:

Store vial below 30°C.
Keep this medicine out of the sight and reach of children.
To be sold on the prescription of a registered medical practitioner only.

خوراک:
۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دوا کو بچوں کی نظر اور پہنچ سے دور رکھیں۔
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