AMANAM 500

INJECTION

Imipenem and Cilastatin sodium

For IV use only

Composition :
The vial contains:
Imipenem equivalent to 500 mg
anhydrous Imipenem and
Cilastatin Sodium equivalent to
500mg Cilastatin, with 21 mg
Sodium Bicarbonate

INDICATIONS :
Broad-spectrum beta-lactam antibiotic.
'Imipenem and Cilastatin for injection' contains:
Imipenem, a member of a class of beta lactam antibiotics-the thienamycins
Cilastatin sodium, a specific enzyme inhibitor that blocks the metabolism of Imipenem in the kidney and substantially increases the concentration of unchanged Imipenem in the urinary tract.
'Imipenem and Cilastatin for injection IV' is bactericidal against an unusually wide spectrum of Gram positive, Gram negative, aerobic and anaerobic pathogens. 'Imipenem and Cilastatin for injection IV' is useful for treating single and polymicrobic infections, and initiating therapy prior to identification of the causative organisms.
'Imipenem and Cilastatin for injection IV' is indicated for the treatment of the following infections due to susceptible organisms:
Lower respiratory tract infections, Intra-abdominal infections, Genito-urinary infections, Gynaecological infections, Septicemia, Bone and joint infections, Skin and soft tissue infections
Note: 'Imipenem and Cilastatin for injection IV' is not indicated against central nervous system infections.
'Imipenem and Cilastatin for injection IV' 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 for injection IV' is usually effective against Bacteroides fragilis sp., the most commonly encountered anaerobic pathogen, which is usually resistant to the aminoglycosides, cephalosporins and penicillins.
Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of 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.
Prophylaxis: 'Imipenem and Cilastatin for injection IV' 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 postoperative infection could be especially serious.

DOASAGE AND METHOD OF ADMINISTRATION :
The total daily dosage and route of administration of 'Imipenem and Cilastatin for injection IV' should be based on the type or severity of infection, consideration of degree of susceptibility of the pathogen(s), renal function and bodyweight. Doses cited are based on a bodyweight of >70 kg. The total daily requirement should be given in equally divided doses.
The dosage recommendations that follow specify the amounts of imipenem to be given. An equivalent amount of cilastatin is provided with this. One vial of 'Imipenem and Cilastatin for injection IV' 500 mg provides the equivalent of 500 mg anhydrous imipenem and 500 mg cilastatin.
Use in the elderly
Age does not usually affect the tolerability and efficacy of 'Imipenem and Cilastatin for injection IV'. 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.

INTRAVENOUS ADMINISTRATION :
This formulation should not be used intramuscularly. The dosage of 'Imipenem and cilastatin for injection IV' should be determined by the severity of the infection, the antibiotic susceptibility of the causative organism(s) and the condition of the patient.
Note: All recommended doses refer to the Imipenem fraction of 'Imipenem and Cilastatin for injection IV'.
Adults (based on 70 kg bodyweight): The usual adult daily dosage is 1-2 g administered in 3-4 equally divided doses (see chart below). In infections due to less sensitive organisms, the daily dose may be increased to a maximum dose of 50 mg/kg/day (not exceeding 4 g daily).
Usual adult intravenous dosage
Each dose of 250 mg or 500 mg should be given by intravenous infusion over 20-30 minutes. Each dose of 1000 mg should be infused over 40-60 minutes. In patients who develop nausea during infusion, the infusion rate may be slowed.

IV administration			
Severity of infection	**Dose**	**Dosage interval**	**Total daily dose**
Mild	250 mg	6 hours	1.0 g
Moderate	500 mg	8 hours	1.5 g
Severe - fully susceptible	500 mg	6 hours	2.0 g
Severe and/or life-threatening infections due to less sensitive organisms (primarily some strains of P.aeruginosa)	1000 mg	8 hours	3.0 g
	1000 mg	6 hours	4.0 g

Imipenem and Cilastatin for injection IV' has been used successfully as monotherapy in immunocompromised cancer patients for confirmed or suspected infections such as sepsis.
Prophylactic use

For prophylaxis against post-surgical infections in adults, 1 g 'Imipenem and Cilastatin for injection IV' should be given intravenously on induction of anaesthesia and 1 g three hours later. For highrisk (i.e. colorectal) surgery, two additional 0.5 g doses can be given at 8 and 16 hours after induction.

In patients with renal insufficiency

As in patients with normal renal function, dosing is based on the severity of the infection. The maximum dosage for patients with various degrees of renal functional impairment is shown in the following table. Doses cited are based on a bodyweight of 70 kg. Proportionate reduction in dose administered should be made for patients with lower bodyweight.

Maximum dosage in relation to renal function				
Renal function	Creatinine clearance (ml/min)	Dose (mg)	Dosage interval (hrs)	Maximum total daily dose* (g)
Mild impairment	31-70	500	6 - 8	1.5 - 2
Moderate impairment	21-30	500	8 - 12	1 - 1.5
Severe** impairment	0-20	250-500	12	0.5 - 1.0

* The higher dose should be reserved for infections caused by less susceptible organisms.

** Patients with creatinine clearance of 620 ml/min should be treated with 250 mg (or 3.5 mg/kg, whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients there may be an increased risk of convulsions.

Patients with a creatinine clearance of ≤5 ml/min should not receive 'Imipenem and Cilastatin for injection IV' unless haemodialysis is started within 48 hours.

'Imipenem and Cilastatin for injection IV' is cleared by haemodialysis. The patient should receive 'Imipenem and Cilastatin for injection IV' immediately after haemodialysis and at 12-hourly intervals thereafter. Dialysis patients, especially those with background CNS disease, should be carefully monitored; patients on haemodialysis should receive 'Imipenem and cilastatin for injection IV' only when the benefit outweighs the potential risk of convulsions

There are currently inadequate data to recommend the use of 'Imipenem and Cilastatin for injection IV' for patients on peritoneal dialysis.

Paediatric dosage			
Age	Dose	Dosage interval	Total daily dose
3 months of age and older (less than 40 kg bodyweight)	15 mg/kg	6 hours	60 mg/kg

The maximum daily dose should not exceed 2 g.

Children over 40 kg bodyweight should receive adult doses.

Clinical data are insufficient to recommend an optimal dose for children under 3 months of age or infants and children with impaired renal function.

'Imipenem and Cilastatin for injection IV' is not recommended for the therapy of meningitis. If meningitis is suspected an appropriate antibiotic should be used.

'Imipenem and Cilastatin for injection IV' may be used in children with sepsis as long as they are not suspected of having meningitis.

DIRECTIONS FOR USE:

Preparation of intravenous solution

The following table is provided for convenience in reconstituting Imipenem and Cilastatin for I.V. for intravenous infusion.

Strength	Volume of diluent added (ml)	Approximate concentration of Imipenem (mg/ml)
Imipenem and Cilastatin for I.V. 500 mg	100	5

Reconstitution of 20 ml vial

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 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.

Compatibility and stability

In keeping with good clinical and pharmaceutical practice, Imipenem and Cilastatin for I.V. should be administered as a freshly prepared solution. On the few occasions where changing circumstances make this impracticable, reconstituted Imipenem and Cilastatin for I.V. retains satisfactory potency for three hours at room temperature (up to 25°C) or 24 hours in a refrigerator (below 4°C) when prepared in any of the following diluents: 0.9% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride; 5% Dextrose and 0.45% Sodium Chloride; 5% and 10% Dextrose in water; 5% and 10% Mannitol.

Imipenem and Cilastatin for I.V. is chemically incompatible with lactate and should not be reconstituted with diluents containing lactate. Imipenem and Cilastatin for I.V. can, however, be administered into an IV tubing through which a lactate solution is being infused.

Imipenem and Cilastatin for I.V. should not be mixed with, or physically added to, other antibiotics.

CONTRAINDICATIONS:

Hypersensitivity to this product.

WARNINGS AND PRECAUTIONS:

Warnings

There is some clinical and laboratory evidence of partial cross-allergenicity between 'Imipenem and Cilastatin for injection IV' and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics.

Before initiating therapy with 'Imipenem and Cilastatin for injection IV', careful inquiry should be made

concerning previous hypersensitivity reactions to beta-lactam antibiotics. If an allergic reaction to 'Imipenem and Cilastatin for injection IV' occurs, the drug should be discontinued and appropriate measures undertaken.

The concomitant use of Imipenem and valproic acid/sodium valproate is not recommended

Pseudomembranous colitis, reported with virtually all antibiotics, can range from mild to life-threatening in severity. 'Imipenem and Cilastatin for injection IV' should be prescribed with caution in patients with a history of gastrointestinal 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.

Paediatric use

'Imipenem and Cilastatin for injection IV': Efficacy and tolerability in infants under 3 months of age have yet to be established; therefore, 'Imipenem and cilastatin for injection IV' is not recommended for use below this age.

Central nervous system: Patients with CNS disorders and/or compromised renal function (accumulation of 'Imipenem and Cilastatin for injection IV' 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 and Cilastatin for injection IV' 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 and Cilastatin for injection IV' withdrawn completely.

Use in patients with renal insufficiency

Patients with creatinine clearances of ≤5 ml/min should not receive 'Imipenem and Cilastatin for injection IV' unless haemodialysis is instituted within 48 hours. For patients on haemodialysis, 'Imipenem and Cilastatin for injection IV' is recommended only when the benefit outweighs the potential risk of convulsions.

INTERACTIONS:

General seizures have been reported in patients who received ganciclovir and 'Imipenem and Cilastatin for injection IV'. These drugs should not be used concomitantly unless the potential benefit outweighs the risk.

Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of Imipenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered.

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.

PREGNANCY AND LACTATION:

Pregnant monkeys showed evidence of maternal and foetal toxicity with bolus injections at doses equivalent to twice the human dose.

The use of 'Imipenem and Cilastatin for injection IV' in pregnant women has not been studied and 'Imipenem and Cilastatin for injection IV' should therefore not be given in pregnancy unless the anticipated benefit to the mother outweighs the possible risk to the foetus.

'Imipenem and Cilastatin for injection IV' has been detected in human milk. If the use of 'Imipenem and Cilastatin for injection IV' is deemed essential, the mother should stop breast-feeding.

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.

UNDESIRABLE EFFECTS:

'Imipenem and Cilastatin for injection IV' 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.

Gastro-intestinal: 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 and Cilastatin for injection IV' in changes in renal function is difficult to assess, since factors predisposing to prerenal 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.

Granulocytopenic patients: drug-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with 'Imipenem and Cilastatin for injection IV'.

Special senses: hearing loss, taste perversion.

Other reported reactions with an unknown causal relationship

Gastro-intestinal: 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.

OVERDOSE:
No specific information is available on the treatment of overdosage with 'Imipenem and Cilastatin for injection IV'.
Imipenem-cilastatin sodium is haemodialysable. However, usefulness of this procedure in the overdosage setting is unknown.

PHARMACOLOGY:
Pharmacotherapeutic group: Antibacterials for systemic use.
ATC code: J01DH51

PHARMACODYNAMICS:
Mechanism of Action
Imipenem is a potent inhibitor of bacterial cell wall synthesis and is highly reactive towards penicillinbinding 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.
Cilastatin sodium is a competitive, reversible, and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem. Cilastatin sodium is devoid of intrinsic antibacterial activity itself and does not affect the antibacterial activity of imipenem.

PHARMACOKINETICS:
The product is administered intravenously, therefore bioavailability data are not relevant.
Imipenem: Peak plasma levels of 36.1 mcg/ml after 500 mg, half-life 62.0 (±3.9) mins, plasma clearance 225.5 (±15.9) ml/min.
Co-administration of cilastatin sodium increases plasma concentrations of imipenem and increases the AUC by about 20%. There is also a decrease in plasma clearance (194.9 ml/min) and an increase in renal clearance, urinary recovery and urinary concentration.

STORAGE:
Store below 25°C.
Once reconstituted store at room temperature (below 25°C) for 3 hours or under refrigeration (below 4°C) for 24 hours
Keep out of the reach and sight of children.

PRESENTATION:
Available in a 20 ml Glass vial.

Manufactured :
SWISS EXPORTS PVT. LTD. INDIA.