Pharma code

XENEM G2DADLL03AESIUS

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XENEM

Imipenem and Cilastatin for Injection USP 500 mg/500 mg

Composition:
Each vial contains:
Imipenem USP Equivalent to anhydrous Imipenem .....500 mg
Cilastatin Sodium USP Equivalent to Cilastatin.....500 mg
Sodium Bicarbonate USP added as buffer.

Dosage Form:
Powder for solution for infusion.

Pharmacological properties
Pharmacodynamic properties:
Pharmacotherapeutic group: Antibacterial for systemic use, Carbapenems,
Mechanism of action:
XENEM consists of two components: 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
•Imipenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-positive and gram-negative bacteria, with the exception of relatively rare carbapenem hydrolysing beta-lactamases. Species resistant to other carbapenems do generally express co-resistance to imipenem. There is no target-based cross-resistance between imipenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes.
Breakpoints
EUCAST MIC breakpoints for imipenem to separate susceptible (S) pathogens from resistant (R) pathogens are as follows (v 1,1 2010-04-27):
•Enterobacteriaceae 1: S ≤2 mg/l, R >8 mg/l
•Pseudomonas spp. 2: S ≤4 mg/l, R >8 mg/l
•Acinetobacter spp.: S ≤2 mg/l, R >8 mg/l
•Staphylococcus spp. 3: Inferred from cefoxitin susceptibility
•Enterococcus spp.: S ≤4 mg/l, R >8 mg/l
•Streptococcus A, B, C, G: The beta-lactam susceptibility of beta-haemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
•Streptococcus pneumoniae 4: S ≤2 mg/l, R >2 mg/l
•Other streptococci 4: S ≤2 mg/l, R >2 mg/l
•Haemophilus influenzae 4: S ≤2 mg/l, R >2 mg/l
•Moraxalla catarrhalis 4: S ≤2 mg/l, R >2 mg/l
•Neisseria gonorrhoeae: There is insufficient evidence that Neisseria gonorrhoeae is a good target for therapy with imipenem.
•Gram-positive anaerobes: S ≤2 mg/l, R >8 mg/l
•Gram-negative anaerobes: S ≤2 mg/l, R >8 mg/l
•Non-species related breakpoints 5: S ≤2 mg/l, R >8 mg/l
[1] Proteus and Morganella species are considered poor targets for imipenem.
[2]The breakpoints for Pseudomonas relate to high dose frequent therapy (1g every 6 hours).
[3]Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
[4]Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.
[5]Non-species related breakpoint have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the overview of species-related breakpoints or footnotes.
Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when thelocal prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species:
Gram-positive aerobes:
Enterococcus faecalis
Staphylococcus aureus (Methicillin-susceptible)*
Staphylococcus coagulase negative (Methicillin-susceptible)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus viridans group
Gram-negative aerobes:
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Serratia marcescens
Gram-positive anaerobes:
Clostridium perfringens**
Peptostreptococcus spp.**
Gram-negative anaerobes:
Bacteroides fragilis
Bacteroides fragilis group
Fusobacterium spp.
Porphyromonas asaccharolytica
Prevotella spp.
Veillonella spp.
Species for which acquired resistance may be a problem:
Gram-negative aerobes:
Acinetobacter baumannii
Pseudomonas aeruginosa
Inherently resistant species:
Gram positive aerobes:
Enterococcus faecium
Gram negative aerobes:
Some strains of Burkholderia cepacia (formerly Pseudomonas cepacia)
Legionella spp.
Stenotrophomonas maltophilia (formerly Xanthomonas maltophilia, formerly Pseudomonas maltophilia)
Others:
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureoplasma urealyticum

* All methicillin-resistant staphylococci are resistant to imipenem/cilastatin.
** EUCAST non-species related breakpoint is used.

Pharmacokinetic properties:
Imipenem
Absorption
In normal volunteers, intravenous infusion of XENEM 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 µg/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 XENEM. 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 XENEM, 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 XENEM, 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 XENEM. 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
Following a single 250 mg/250 mg intravenous dose of XENEM, the area under the curve (AUCs) for imipenem increased 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine Clearance (CrCL) 50-80 ml/min/1.73 m^2), moderate (CrCL 30-<50 ml/min/1.73 m^2), and severe (CrCL <30 ml/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m^2), and AUCs for cilastatin increased 1.6-fold, 2.0-fold, and 6.2-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Following a single 250 mg/250 mg intravenous dose of XENEM given 24 hours after haemodialysis, AUCs for imipenem and cilastatin were 3.7-fold and 16.4-fold higher, respectively, as compared to subjects with normal renal function. Urinary recovery, renal clearance and plasma clearance of imipenem and cilastatin decrease with decreasing renal function following intravenous administration of XENEM. Dose 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 XENEM 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.

Therapeutic indications:
Xenem is indicated for the treatment of the following infections in adults and children 1 year of age and above:
Complicated intra-abdominal infections
Severe pneumonia including hospital and ventilator-associated pneumonia
Intra- and post-partum infections
Complicated urinary tract infections
complicated skin and soft-tissue infections may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Posology and method of administration:
Posology
The dose recommendations for represent the quantity of Imipenem/ Cilastatin to be administered.
The daily dose of should be based on the type of infection and given in equally divided doses based on consideration of degree of susceptibility of the pathogen(s) and the patient's renal function
Adults and adolescents
For patients with normal renal function (creatinine clearance of ≥90 ml/min), the recommended dose regimens are:
500 mg/500 mg every 6 hours OR
1000 mg/1000 mg every 8 hours OR every 6 hours
It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg/1000 mg administered every 6 hours.
A reduction in dose is necessary when creatinine clearance is < 90 ml/min.
The maximum total daily dose should not exceed 4000 mg/4000 mg per day.

To determine the reduced dose for adults with impaired renal function:
1. The total daily dose (i.e. 2000/2000, 3000/3000 or 4000/4000 mg) that would usually be applicable to patients with normal renal function should be selected.
2. From table 1 the appropriate reduced dose regimen is selected according to the patient's creatinine clearance.

Creatinine clearance (mL/min) is:	**If TOTAL DAILY DOSE is: 2000 mg/day**	**If TOTAL DAILY DOSE is: 3000 mg/day**	**If TOTAL DAILY DOSE is: 4000 mg/day**
≥90 (normal)	500 q6h	1000 q8h	1000 q6h
reduced dosage (mg) for patients with renal impairment:			
<90 - ≥60	400 q6h	500 q6h	750 q8h
<60 - ≥30	300 q6h	500 q8h	500 q6h
<30 - ≥15	200 q6h	500 q12h	500 q12h

Patients with a creatinine clearance of <15 ml/min
These patients should not receive unless haemodialysis is instituted within 48 hours.
Patients on haemodialysis
When treating patients with creatinine clearances of <15 ml/min who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 15 to 29 ml/min.
Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, is recommended only when the benefit outweighs the potential risk of seizures.

Hepatic impairment
No dose adjustment is recommended in patients with impaired hepatic function

Elderly population:
No dose adjustment is required for the elderly patients with normal renal function.

(Paediatric population ≥1 year of age:
For paediatric patients ≥1 year of age, the recommended dose is 15/15 or 25/25 mg/kg/dose administered every 6 hours.
It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25/25 mg/kg administered every 6 hours.
Paediatric population <1 year of age:
Clinical data are insufficient to recommend dosing for children less than 1 year of age.Patients on haemodialysis
When treating patients with creatinine clearances of <15 ml/min who are undergoing dialysis use the dose recommendation for patients with creatinine clearances of 15 to 29 ml/min.
Both imipenem and cilastatin are cleared from the circulation during haemodialysis. The patient should receive after haemodialysis and at 12 hour intervals timed from the end of that haemodialysis session. Dialysis patients, especially those with background central nervous system (CNS) disease, should be carefully monitored; for patients on haemodialysis, is recommended only when the benefit outweighs the potential risk of seizures.

Hepatic impairment
No dose adjustment is recommended in patients with impaired hepatic function

Elderly population:
No dose adjustment is required for the elderly patients with normal renal function.

(Paediatric population ≥1 year of age:
For paediatric patients ≥1 year of age, the recommended dose is 15/15 or 25/25 mg/kg/dose administered every 6 hours.
It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25/25 mg/kg administered every 6 hours.
Paediatric population <1 year of age:
Clinical data are insufficient to recommend dosing for children less than 1 year of age.

Paediatric population with renal impairment:
Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine > 2 mg/dl).

Method of administration
Xenem is to be reconstituted and further diluted prior to administration. Each dose of ≤500 mg/500 mg should be given by intravenous infusion over 20 to 30 minutes. Each dose >500 mg/500 mg should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

Contraindications:
Hypersensitivity to the active substances or to any of the excipients (e.g.Sodium bicarbonate).
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

Special warnings and precautions:
General
The selection of imipenem/cilastatin to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with , careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to XENEM occurs, discontinue the therapy immediately.

Interaction:
Generalized seizures have been reported in patients who received ganciclovir and XENEM. These medicinal products should not be used concomitantly unless the potential benefit outweighs the risks.
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.
Oral anti-coagulants
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects.
There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.
Concomitant administration of XENEM and probenecid resulted in minimal increases in the plasma levels and plasma half-life of imipenem. The urinary recovery of active (non-metabolised) imipenem decreased to approximately 60% of the dose when XENEM was administered with probenecid. Concomitant administration of XENEM and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.
Paediatric population
Interaction studies have only been performed in adults.

Fertility, pregnancy and lactation:
Pregnancy
There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women.
Studies in pregnant monkeys have shown reproductive toxicity. The potential risk for humans is unknown.
XENEM 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 XENEM 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.

Undesirable effects
In clinical trials including 1,723 patients treated with imipenem/cilastatin intravenous the most frequently reported systemic adverse reactions that were reported at least possibly related to therapy were nausea (2.0%), diarrhoea (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%). Similarly, the most frequently reported local adverse reactions were phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%) and vein induration (0.2%). Increases in serum transaminases and in alkaline phosphatase are also commonly reported.
The following adverse reactions have been reported in clinical studies or during post-marketing experience.
All adverse reactions are listed under system organ class and frequency: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000) and not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Event
Infections and infestations	Rare	pseudomembranous colitis, candidiasis
	Very rare	gastro-enteritis'
Blood and lymphatic system disorders	Common	eosinophilia
	Uncommon	pancytopenia, neutropenia, leucopenia, thrombocytopenia, thrombocytosis
	Rare	agranulocytosis
	Very rare	haemolytic anaemia, bone marrow depression
Immune system disorders	Rare	anaphylactic reactions
Psychiatric disorders	Uncommon	psychic disturbances including hallucinations and confusional states
Nervous system disorders	Uncommon	seizures, myoclonic activity, dizziness, somnolence
	Rare	encephalopathy, paraesthesia, focal tremor, taste perversion
	Very rare	aggravation of myasthenia gravis, headache
	Not Known	agitation, dyskinesia
Ear and labyrinth disorders	Rare	hearing loss
	Very rare	vertigo, tinnitus
Cardiac disorders	Very rare	cyanosis, tachycardia, palpitations
Vascular disorders	Common	thrombophlebitis
	Uncommon	hypotension
	Very rare	flushing
Respiratory, thoracic and mediastinal disorders	Very rare	dyspnoea, hyperventilation, pharyngeal pain
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea Medicinal product-related nausea and/or vomiting appear to occur more frequently in granulocytopenic patients than in non-granulocytopenic patients treated with XENEM
	Rare	staining of teeth and/or tongue
	Very rare	haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation

System Organ Class	Frequency	Event
Hepatobiliary disorders	Rare	hepatic failure, hepatitis
	Very Rare	fulminant hepatitis
Skin and subcutaneous tissue disorders	Common	rash (e.g. exanthematous)
	Uncommon	urticaria, pruritus
	Rare	toxic epidermal necrolysis, angioedema,
		Stevens-Johnson syndrome,
		erythema multiforme, exfoliative dermatitis
	Very rare	hyperhidrosis, skin texture changes
Musculoskeletal and connective tissue disorders	Very rare	polyarthralgia, thoracic spine pain
Renal and urinary disorders	Rare	acute renal failure, oligurial/anuria, polyuria, urine discoloration (harmless and should not be confused with haematuria) The role of XENEM in changes in renal function is difficult to assess, since factors predisposing
		to pre-renal azotemia or to impaired renal function usually have been present.
Reproductive system and breast disorders	Very rare	pruritus vulvae
General disorders and administration site	Uncommon	fever, local pain and induration at the injection site, erythema at the injection site
conditions	Very rare	chest discomfort, asthenia/weakness
Investigations		increases in serum transaminases,
	Common	increases in serum alkaline phosphatase
	Uncommon	A positive direct Coombs' test, prolonged prothrombin time, decreased haemoglobin, increases in serum bilirubin, elevations in serum creatinine, elevations in blood urea nitrogen

Paediatric population (≥3 months of age)

In studies of 178 paediatric patients ≥3 months of age, the reported adverse reactions were consistent with those reported for adults.

Overdose:
Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, and bradycardia. No specific information is available on treatment of overdose with XENEM. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.

Storage:
Store below 30°C. Protect from light.

Presentation:
1 vial in a carton

LIST I

Manufactured for:
Indoco Remedies Limited
Regd. Office: 166, C.S.T. Road, Mumbai-400098

Perforation

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