Lastinem-500 (Imipenem and Cilastatin Powder for Solution for Infusion 500 mg/ 500mg)

DESCRIPTION

Before Reconstitution: White to pale yellow crystalline powder filled in glass vial.

After Reconstitution: Clear Solution. Appropriate diluents can be used for reconstitution are 0.9% Sodium Chloride Injection, 5% Dextrose Injection

COMPOSITION

Lastinem-500 (Imipenem and Cilastatin Powder for Solution for Infusion 500 mg/ 500mg) Each vial contains:

Sterile Imipenem USP equivalent to Anhydrous Imipenem 500 mg

Sterile Cilastatin Sodium USP equivalent to Cilastatin 500 mg

Sterile Sodium bicarbonate is used as a buffer.

PHARMACODYNAMICS

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):

- Enterobacteriaceae1: 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 pneumoniae4: S ≤2 mg/l, R >2 mg/l
- Other streptococci4: S ≤2 mg/l, R >2 mg/l
- Haemophilus influenzae4: S ≤2 mg/l, R >2 mg/l
- Moraxalla catarrhalis4: 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 breakpoints5: 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 the local 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 pneumonia, 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

PHARMACOKINETICS

Imipenem

Absorption

Intravenous infusion of Imipenem and Cilastatin for Injection 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%. 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 500mg / 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 for Injection, 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 for Injection, 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.

Special Population

Renal insufficiency

Following a single 250 mg/250 mg intravenous dose of Imipenem and Cilastatin for Injection, the area under the curve (AUCs) for imipenem was reported to increase by 1.1-fold, 1.9-fold, and 2.7-fold in subjects with mild (Creatinine Clearance (CrCL) 50-80 ml/min/1.73 m2), moderate (CrCL 30-<50 ml/min/1.73 m2), and severe (CrCL <30 ml/min/1.73 m2) renal impairment, respectively, compared to subjects with normal renal function (CrCL >80 ml/min/1.73 m2), 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 Imipenem and Cilastatin for Injection given 24 hours after haemodialysis, AUCs for imipenem and cilastatin were reported to be 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 Imipenem and Cilastatin for Injection. 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 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 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 higher as compared to the exposure in adults receiving a 1000 mg/1000 mg dose.

Elderly

In healthy elderly (65 to 75 years of age with normal renal function for their age), the pharmacokinetics of a single dose of Imipenem and Cilastatin for Injection 500 mg/500 mg administered intravenously over 20 minutes were reported to be 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 there is no accumulation of imipenem/cilastatin.

INDICATION

The activity of LASTINEM-500 against an unusually broad spectrum of pathogens makes it particularly useful in the treatment of polymicrobic and mixed aerobic/anaerobic infections, as well as initial therapy prior to the identification of the causative organisms.

LASTINEM-500 is indicated for the treatment of the following infections due to susceptible organisms:

- Intra-abdominal infections
- Lower respiratory tract infections
- Gynecological infections
- Septicemia
- Genitourinary tract infections
- Bone and joint infections
- Skin and soft tissue infections
- Endocarditis

LASTINEM-500 is indicated for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria. The majority of these mixed infections are associated with contamination by fecal flora or flora originating from the vagina, skin and mouth. In these mixed infections, Bacteroides fragilis is the most commonly encountered anaerobic pathogen and is usually resistant to aminoglycosides, cephalosporins and penicillins. However, Bacteroides fragilis is usually susceptible to LASTINEM-500.

LASTINEM-500 has demonstrated efficacy against many infections caused by aerobic and anaerobic gram-positive and gram-negative bacteria resistant to the cephalosporins, including cefazolin, cefoperazone, cephalothin, cefoxitin, cefotaxime, moxalactam, cefamandole, ceftazidime and ceftriaxone. Similarly, many infections caused by organisms resistant to aminoglycosides (gentamicin, amikacin, tobramycin) and/or penicillins (ampicillin, carbenicillin, penicillin-G, ticarcillin, piperacillin, azlocillin, mezlocillin) responded to treatment with LASTINEM-500.

LASTINEM-500 is not indicated for the treatment of meningitis.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients
- 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).

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 reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with LASTINEM-500, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, LASTINEM-500 must be discontinued immediately and appropriate alternative therapy instituted.

Hepatic

Hepatic function should be closely monitored during treatment with imipenem/cilastatin due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure and fulminant hepatitis).

Patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin. There is no dose adjustment necessary.

Haematology

A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin.

Antibacterial spectrum

The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. The use of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections are suspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications.

Interaction with valproic acid

The concomitant use of imipenem/cilastatin and valproic acid/sodium valproate is not recommended.

Clostridium difficile

Antibiotic-associated colitis and pseudomembranous colitis have been reported with imipenem/cilastatin and with nearly all other anti-bacterial agents and may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of imipenem/cilastatin. Discontinuation of therapy with imipenem/cilastatin and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Meningitis

LASTINEM-500 is not recommended for the therapy of meningitis.

Renal impairment

Imipenem/cilastatin accumulates in patients with reduced kidney function. CNS adverse reactions may occur if the dose is not adjusted to the renal function.

Central nervous system

CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence close adherence to recommended dose schedules is urged especially in these patients. Anticonvulsant therapy should be continued in patients with a known seizure disorder.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.

If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dose of LASTINEM-500 should be decreased or discontinued.

Paediatric use

LASTINEM-500 is not recommended in children under 1 year of age or paediatric patients with impaired renal function (serum creatinine >2 mg/dl).

Imipenem + Cilastatin contains sodium which should be taken into consideration by patients on a controlled sodium diet.

PREGNANCY AND LACTATION

Pregnancy: There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women. The potential risk for humans is unknown. LASTINEM-500 should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation: 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 + Cilastatin is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

DRUG INTERACTIONS

Generalized seizures have been reported in patients who received ganciclovir and LASTINEM-500. 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 LASTINEM-500 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 LASTINEM-500 was administered with probenecid. Concomitant administration of LASTINEM-500 and probenecid doubled the plasma level and half-life of cilastatin, but had no effect on urine recovery of cilastatin.

MAIN SIDE/ ADVERSE EFFECTS

Most frequently reported adverse reactions were nausea, diarrhoea, vomiting, rash, fever, hypotension, seizures, dizziness, pruritus, urticaria, somnolence, phlebitis/thrombophlebitis, pain at the injection site, erythema at the injection site and vein induration. Increases in serum transaminases and in alkaline phosphatase are also commonly reported.

The following adverse reactions have been reported. 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.

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) *Rare:* staining of teeth and/or tongue

Very rare: haemorrhagic colitis, abdominal pain, heartburn, glossitis, tongue papilla hypertrophy, increased salivation

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)

Reproductive system and breast disorders

Very rare: pruritus vulvae

General disorders and administration site conditions

Uncommon: fever, local pain and induration at the injection site, erythema at the injection site

Very rare: chest discomfort, asthenia/weakness

Investigations

Common: increases in serum transaminases, 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

OVERDOSE AND TREATMENT

Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. No specific information is available on treatment of overdose with Imipenem + Cilastatin.

Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown.

DOSAGE AND ADMINISTRATION

LASTINEM-500 is available as intravenous infusion only.

Posology: The dose recommendations for LASTINEM-500 represent the quantity of imipenem/cilastatin to be administered. An equivalent amount of cilastatin is also present.

The total daily dosage of LASTINEM-500 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) and renal function.

Adults: based on suspected or confirmed pathogen susceptibility as shown in Table 1 below. The dosage recommendations for LASTINEM-500 represent the quantity of imipenem to be administered. An equivalent amount of cilastatin is also present in the solution.

These doses should be used for patients with creatinine clearance of greater than or equal to 90 mL/min. A reduction in dose must be made for patients with creatinine clearance less than 90 mL/min as shown in Table 2. It is recommended that the maximum total daily dosage not exceed 4 g/day.

Table 1: Dosage of LASTINEM-500 in Adult Patients with Creatinine Clearance Greater than or Equal to 90 mL/min

Suspected or Proven Pathogen Susceptibility	Dosage of LASTINEM-500
If the infection is suspected or proven to be due to a susceptible bacterial species	500 mg every 6 hours OR 1000 mg every 8 hours
If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility	1000 mg every 6 hours

Adult Patients with Renal Impairment: Patients with creatinine clearance less than 90 mL/min require dosage reduction of LASTINEM-500 as indicated in Table 2. The serum creatinine should represent a steady state of renal function. Use the Cockroft-Gault method described below to calculate the creatinine clearance:

(weight in kg) × (140-age in years)

Males: ----------
(72)× serum creatinine (mg/100mL)

Females: (0.85)× (value calculated for males)

Table 2: Dosage of LASTINEM-500 for Adult Patients in Various Renal Function Groups Based on Estimated Creatinine Clearance (CLcr)

	Creatinine clearance (mL/min)			
	Greater than or equal to 90	Less than 90 to greater than or equal to 60	Less than 60 to greater than or equal to 30	Less than 30 to greater than or equal to 15
Dosage of LASTINEM-500 If the infection is suspected or proven to be due to a susceptible bacterial species:	500 mg every 6 hours	400 mg every 6 hours	300 mg every 6 hours	200 mg every 6 hours
	OR			
	1000 mg every 8 hours	500 mg every 6 hours	500 mg every 8 hours	500 mg every 12 hours
Dosage of LASTINEM-500 If the infection is suspected or proven to be due to bacterial species with intermediate susceptibility:	1000 mg every 6 hours	750 mg every 8 hours	500 mg every 6 hours	500 mg every 12 hours

Patients with a creatinine clearance of less than 30 to greater than or equal to 15 mL/min: There may be an increased risk of seizures.

Patients with a creatinine clearance less than 15 mL/min: These patients should not receive LASTINEM-500 unless hemodialysis is instituted within 48 hours.

Patients on haemodialysis: When treating patients with creatinine clearances of less than 15 mL/min who are undergoing hemodialysis, use the dosage recommendations for patients with creatinine clearances of less than 30 to greater than or equal to 15 mL/min in Table 2.

Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive LASTINEM-500 after hemodialysis and at 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, LASTINEM-500 is recommended only when the benefit outweighs the potential risk of seizures.

Patients on peritoneal dialysis: There is inadequate information to recommend usage of LASTINEM-500.

Pediatric Patients (3 months or older): LASTINEM-500 is not recommended in pediatric patients with CNS infections because of the risk of seizures. LASTINEM-500 is not recommended in pediatric patients <30 kg with renal impairment, as no data are available.

The maximum total daily dose in pediatric patients should not exceed 4 g/day. The recommended dosage for pediatric patients with non-CNS infections is shown in Table 3 below:

Table 3: Recommended LASTINEM-500 Dosage in Pediatric Patients for Non-CNS Infections

Age	**Dose (mg/kg)**	**Frequency (hours)**
Greater than or equal to 3 Months of Age		
	15-25 mg/kg	Every 6 hours
Less than or equal to 3 months of age (Greater than or equal to 1,500g body weight)		
4 weeks to 3 months of age	25 mg/kg	Every 6 hours
1 to 4 weeks of age	25 mg/kg	Every 8 hours
Less than 1 week of age	25 mg/kg	Every 12 hours

Method of administration: LASTINEM-500 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.

For patients with renal insufficiency, a reduced dose of LASTINEM-500 will be administered according to the patient's CrCl, as determined from Table 4. Prepare 100 mL of infusion solution as directed above. Select the volume (mL) of the final infusion solution needed for the appropriate dose of LASTINEM-500 as shown in Table 4.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

Table 4: Preparation of LASTINEM-500 Doses

Creatinine Clearance (mL/min)	**Dosage of LASTINEM-500 (imipenem/cilastatin (mg))**	**Volume (mL) of Solution to be Removed and Discarded from Preparation**	**Volume (mL) of Final Infusion Solution Needed for Dosage**
Greater than or equal to 90	500/500	NA	100
Less than 90 to greater than or equal to 60	400/400	20	80
Less than 60 to greater than or equal to 30	300/300	40	60
Less than 30 to greater than or equal to 15	200/200	60	40

PREPARATION AND DIRECTIONS FOR USE

LASTINEM-500 is supplied as a dry powder in a single dose vial that must be reconstituted and further diluted using aseptic technique prior to IV infusion as outlined below.

To prepare the infusion solution, contents of the vial must be reconstituted by adding approximately 10 mL of the appropriate diluent to the vial. List of appropriate diluents are as follows:

- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection

Withdraw 20 mL (10 mL x 2) of diluent from the appropriate infusion bag and constitute the vial with 10 mL of the diluent.

CAUTION: THE RECONSTITUTED SUSPENSION MUST NOT BE ADMINISTERED BY DIRECT IV INFUSION.

After reconstitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.

Add the additional 10 mL of infusion solution to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.

Reconstituted solutions of LASTINEM-500 range from clear and colorless to yellow. Variations of color within this range do not affect the potency of the product.

- Do not freeze the reconstituted solution.
- Each vial is for single use only.
- Discard any unused portion immediately after use.
- From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

Incompatibilities

This medicinal product is chemically incompatible with lactate and should not be reconstituted in diluents containing lactate. However, it can be administered into an I.V. system through which a lactate solution is being infused.

This medicinal product must not be mixed with other medicinal products.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage:

Unopened Vial: Store below 30°C. Protect from light and moisture.

After Reconstitution and Dilution: The reconstituted Solution is Stable for 2 hours When stored at 25ºC.

Presentation/ Packing: Vial of 500mg

Product Registration Holder / Marketing Authorization Holder:

Unimed Sdn Bhd

53, Jalan Tembaga SD 5/2B, Bandar Sri

Damansara, 52200, Kuala Lumpur, Malaysia

Manufactured by:

VENUS REMEDIES LIMITED

Hill Top Industrial Estate, Jharmajri, EPIP

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