120.00 mm

230.00 mm

PACKAGE INSERT

Cefepime Injection IP 1000mg

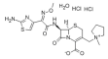
SUPERPIME™-1000

Single Dose Vial

FOR I.M./I.V. USE

COMPOSITION:
Each vial contains:-
Cefepime Hydrochloride (Sterile) IP
Eq. to Anhydrous Cefepime 1000mg
(A Sterile mixture of Cefepime Hydrochloride IP & Arginine IP)
This pack also contains one FFS ampoule of sterile water for injection I.P. 10ml.

PROPERTIES:
Cefepime is a fourth-generation cephalosporin antibiotic used in the treatment of infections caused by susceptible bacteria, such as pneumonia, urinary tract infections, and skin infections. Its emperical formula is $C_{19}H_{24}C_2N_6O_5S_2$ and molecular weight is 571.5g/mol. Structural formula is as shown:



CLINICAL PHARMACOLOGY:
Pharmacodynamics
Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Fourth-generation cephalosporins, ATC code: J01DE01
Mechanism of action
Cefepime is a broad-spectrum, bactericidal antibiotic, with activity against a wide range of Gram-positive and Gram-negative bacteria, including many strains resistant to aminoglycosides or third generation cephalosporins.
It is highly resistant to hydrolysis caused by most beta-lactamases. It has a reduced affinity for beta-lactamases changed via chromosomes and has a rapid penetration in the cells of the Gram-negative bacteria.
Pharmacokinetics
Absorption
Cefepime is completely absorbed after IM administration.
Distribution
Adults: Average plasma concentrations of cefepime observed in the male adult, after a single IV infusion (30 minutes) or after the IM injection of doses of 500 mg, 1 g and 2 g. After theintramuscular administration, cefepime is completely absorbed. The binding of cefepime to serum proteins is, on average, 16.4% and is independent of the serum concentration.
Biotransformation
Cefepime is metabolised in N-methylpyrrolidinium, being converted quickly in N-oxide. About 85% of the administered dose is eliminated unchanged; high concentrations of unchanged cefepime are detected in urine. Less than 1% of the administered dose is eliminated in urine as N-methylpyrrolidinium, 6.8% as N-oxide and 2.5% as cefepimeepimer.
Elimination
The elimination average half-life of cefepime is about 2 hours, and is independent of the dose for the range of 250 mg to 2 g. There is no evidence of accumulation in the healthy individuals receiving doses up to 2 g IV every 8 hours for 9 days. The total body clearance is 120 ml/min. The average renal clearance of cefepime is 110 ml/min, suggesting an elimination almost exclusively via the kidneys, mainly by glomerular filtration.
Special populations
Renal dysfunction: The elimination half-life is increased in patients with several degrees of renal failure, so the dosage adjustment is recommended. *Liver dysfunction:* Cefepime pharmacokinetics was not changed in patients with hepatic insufficiency that received a dose of 1 g. It is not necessary to change the posology of Cefepime in this population.
Elderly: healthy voluntary individuals of 65 years old or more that received a single dose of 1 g IV of cefepime presented higher AUC values and lower renal clearance values when compared with younger adults. It is recommended the dose adjustment in the elderly patient with renal function impairment. From the more than 6400 adults treated with cefepime in clinical studies, 35% were aged 65 years old or more and 16% were aged 75 years old or more. In clinical studies when the elderly patient received the recommended dose for the adult patient, the clinical efficacy and safety were comparable to the clinical efficacy and safety in the non-elderly adult patient, unless the patient had renal failure. There was a mild increase in the elimination half-life time and lower renal clearance values when compared with those seen in younger individuals. Dose adjustments are recommended if the renal function is impaired. *Children:* Cefepime pharmacokinetics with single and multiple doses was assessed in patients aged between 2.1 months and 11.2 years, with doses 50 mg/kg in IV infusion or IM injection; multiple doses were administered with inter vals of 8 or 12 hours for at least 48 hours. After the single IV administration, the total clearance was 3.3 ml/min/kg, with a distribution value of 0.3 l/kg. The elimination half-life was 1.7 hour, with an average recovery in urine of unchanged cefepime around 60.4% of the administered dose, being the renal clearance the main route of elimination (2.0 ml/min/kg). The average plasma concentrations of cefepime in steady state after the administration of multiple IV doses were similar to those seen after the 1st dose, only with mild accumulation after repeated doses. After the IM administration in steady state conditions, maximum cefepime plasma concentrations around 68 micrograms/ml were obtained in average in 0.75 hours. The bioavailability was in average 82% after intramuscular administration. *Other:* clinical improvement was seen with cefepime in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. Pharmacokinetics of cefepime did not change in patients with hepatic function impairment which received a single dose of 1 g and in patients with cystic fibrosis. No dose adjustment of cefepime is required in this population.
INDICATIONS:
Cefepime is indicated in the treatment of infections caused by bacteria that are cefepime-sensitive:
- lower respiratory tract infections, including nosocomial pneumonia and community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis and secondary bacterial infection of acute bronchitis;
- uncomplicated and complicated urinary tract infections, including pyelonephritis;
- skin and subcutaneous infections;
- intra-abdominal infections, including peritonitis and biliary tract infections;
- gynaecological infections;
- bacterial meningitis in infants and children;
- In combination with other antibacterial agents 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.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
DOSAGE AND ADMINISTRATION:
Cefepime can be administered via intravenous use or intramuscular use. The usual dose and the route of administration vary in accordance with the severity of the infection, the renal function and the general conditions of the patient. The IV route of administration is preferable in the patients with severe infections or in a life-threatening situation, particularly if there is the possibility of shock. Adults and children weighing > 40 kg with normal renal function:

Severity of the infection	Dosage and route of administration	Interval between the doses
Mild to moderate urinary tract infections (UTI)	500 mg to 1 g IV or IM	every 12 h
Other mild to moderate infections (non UTI)	1 g IV or IM	every 12 h
Severe infections	2 g IV	every 12 h
Very severe or life- threatening infections	2 g IV	every 8 h

The usual treatment duration is 7 to 10 days; more severe infections can require a more prolonged treatment. In the empirical treatment of febrile neutropenia, the usual treatment duration should not be less than 7 days or until the resolution of the neutropenia. In patients weighing ≤ 40 kg, the posology indicated for the children is recommended.
Elderly:
No dose adjustment is required in patients with normal renal function; the dose adjustment is recommended in patients with impaired renal function. Adults with renal insufficiency: The cefepime dose should be adjusted to compensate the slower renal elimination rate. In adult patients with mild to moderate renal insufficiency, the initial dose of cefepime recommended should be the same as for patients with normal renal function. The recommended maintenance dose should be in accordance with the instructions of the table below. When only the serum creatinine values are available, the (Cockcroft and Gault) formula can be used to calculate the creatinine clearance. The serum creatinine should represent a steady-state of renal function: Man: Creatinine clearance (ml/min) = weight (kg) x (140 - age) 72 x serum creatinine (mg/dl) Woman: 0.85 x value calculated using the man formula

Creatinine clearance(ml/min)	Recommended maintenance dose			
> 50	Usual dose, no dose adjustment is required			
	2 g, 3x day	2 g, 2x day	1 g, 2x day	500 mg, 2x day
30 to 50	2 g, 2x day	2 g, 1x day	1 g, 1x day	500 mg, 1x day
11 to 29	2 g, 1x day	1 g, 1x day	500 mg, 1x day	500 mg, 1x day
< 10	1 g, 1x day	500 mg, 1x day	250 mg, 1x day	250 mg, 1x day
Haemodialysis*	500 mg, 1x day	500 mg, 1x day	500 mg, 1x day	500 mg, 1x day

he pharmacokinetic models indicate that it is necessary to reduce the dose in these patients. In patients receiving cefepime and doing haemodialysis, the dose is 1 gram as loading dose in the first day of treatment followed by 500 mg daily for all the infections, except febrile neutropenia which is 1 gram daily. In the dialysis days, cefepime should be administered after dialysis. Cefepime should be administered, whenever possible, at the same time every day.
Patients doing dialysis
In the patient doing dialysis, about 68% of the total quantity of cefepime present in the body in the beginning of the dialysis will be removed during a 3 hour dialysis. In the patient doing continuous ambulatory peritoneal dialysis, cefepime can be administered in the same dosages that are recommended for the patients with normal renal function, i.e. 500 mg, 1 g or 2 g, depending on the severity of the infection, but with an interval of 48 hours between doses.
Children with normal renal function
In the child, the usual recommended dose is:
- Pneumonia, urinary tract infection, skin and subcutaneous tissue infection:
Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 12 hours for 10 days; in more severe infections, 8 hours interval between the intakes should be done.
- Bacteraemia that occurs in association with infections, bacterial meningitis and empirical treatment of febrile neutropenia: Children aged more than 2 months and weighing ≤ 40 kg: 50 mg/kg every 8 hours for 7 to 10 days. The experience in children aged less than 2 months is limited. Despite the experience having been obtained with the 50 mg/kg dose, data from pharmacokinetic models obtained in children aged more than 2 months suggest that, in children from 1 month to 2 months old, a dose of 30 mg/kg every 12 or 8 hours can be considered. The administration of Cefepime in these patients should be carefully monitored. In the child weighing > 40 kg, it is recommended to use the dose indicated for adults. The maximum recommended dose for adults (2 g every 8 hours) should not be exceeded. The experience with the intramuscular use in children is limited. Children with renal insufficiency: As renal excretion is the main route of elimination of cefepime, the dose should be adjusted in children with renal insufficiency. A dose of 50 mg/kg in children from 2 months to 12 year old and a dose 30 mg/kg in children 1 month to 2 months are comparable to a 2 g dose in the adult. The same interval between the doses is recommended or the same dose reduction indicated for the renal insufficient adult.
Patients with hepatic function impairment:
No dose adjustment is required in patients with hepatic insufficiency.
CONTRAINDICATIONS:
Hypersensitivity to cefepime, to any other cephalosporin or to any of the excipients History of severe hypersensitivity reaction (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).
WARNING AND PRECAUTIONS:
Hypersensitivity reactions
As with all beta-lactam antibacterial agents, severe and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefepime must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefepime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefepime is given to patients with a histoy of non-severe hypersensitivity to other beta-lactam agents. Cefepime should be administered with caution to patients with a history of asthma or allergic diathesis. The patient must be carefully monitored during the first administration. If an allergic reaction occurs, treatment must be discontinued immediately. Serious hypersensitivity reactions may require epinephrine and other suppor tive therapy. Antibiotics should be administered with caution to patients that have shown some for m of allergy, particularly to drugs. If there is an allergic reaction to Cefepime, the medicine should be stopped and adequate treatment applied.
Antibacterial activity of cefepime
Due to the relatively limited spectrum of antibacterial activity of cefepime it is not suitable for the treatment of some 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 with cefepime. As with other antibiotics, the use of Cefepime can lead to the development of resistant micro-organisms. If superinfection occurs during treatment, adequate measures should be taken.
Renal impairment
In patients with impaired renal function, such as reduction of urinary output because of renal insufficiency (creatinine clearance ≤ 50 mL/min) or other conditions that may compromise renal function, the dosage of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection and susceptibility of the causative organisms.
During post-marketing surveillance, the following serious adverse events have been reported: reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures (including non-convulsive status epilepticus), and/or renal failure. Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommendations. In general, symptoms of neurotoxicity resolved after discontinuation of cefepime and/or after haemodialysis, however, some cases included a fatal outcome.
Clostridium difficile associated diarrhoea
Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including cefepime and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of cefepime. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including cefepime, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation. It is known that cefepime is excreted substantially by the kidney and the risk of toxic reactions to this drug can be higher in the patients with renal insufficiency. Because elderly patients are more susceptible to have a decreased renal function, caution should be taken in the selection of the dose and renal function should be monitored. In elderly patients with renal failure to whom the usual dose of cefepime was administered, severe adverse events occurred including reversible encephalopathy (conscience disturbance, including confusion, hallucinations, stupor and coma), myoclonus, convulsions (including non-convulsive status epilepticus) and/or renal failure.
Interference with serological testing
A positive Coombs test, without evidence of haemolysis, has been described in patients treated with cefepime twice daily.
Cephalosporin antibiotics may produce a false-positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.
DRUG INTERACTIONS:
Concomitant treatment with bacteriostatic antibiotics may interfere with the action of beta-lactam antibiotics. The monitoring of renal function is recommended during the treatment with Cefepime if other drugs that have nephrotoxic potential are administered (i.e., aminoglycosides and potent diuretics). Cephalosporins can potentiate the action of coumarin anticoagulants. *Interaction with diagnostic tests* In patients treated with Cefepime positive Coombs test was described with no evidence of haemolysis. In the glycosuria test, a false positive result may occur due to reduction of copper (the enzymatic method should preferably be used).
PREGNANCY AND LACTATION:
Pregnancy
In what concerns cefepime there are no sufficient data on its exposure in pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, labour or post-natal development. This medicinal product should only be prescribed to pregnant women with great caution.
Breastfeeding
Cefepime is excreted in human milk in very low quantities, so caution is recommended when administered to the breast-feeding woman.
Fertility
There are no data on the use of cefepime in human fertility. Reproduction studies in animals did not reveal any effects on fertility.
SIDE EFFECTS:
The frequency of adverse reactions listed below, reported during the clinical experience or post-marketing experience is defined using the following convention:
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) andNot known (cannot be estimated from the available data).
The side effects are presented by decreasing order of severity within each class of frequency.
Infections and Infestations
Uncommon: Oral candidiasis, vaginal infection
Rare: Candidiasis
Blood and lymphatic system disorders
Common: Anaemia, eosinophilia
Uncommon: Thrombocytopenia, leukopenia, neutropenia
Not known: Aplastic anaemia, haemolytic anaemia, agranulocytosis
Immune system disorders
Rare: Anaphylactic reaction, angioedema
Not known: Anaphylactic shock
Psychiatric disorders
Not known: State of confusion, hallucination
Nervous system Disorders
Uncommon: Headaches
Rare: Convulsions, paraesthesia, digeusia, dizziness
Not known: Coma, stupor, encephalopathy, altered state of conscience, myoclonus
Vascular disorders
Common: Phlebitis at the infusion site
Rare: Vasodilatation
Not known: Haemorrhage
Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea
Gastrointestinal Disorders
Common: Diarrhoea
Uncommon: Pseudomembranous colitis, colitis, nausea, vomiting
Rare: Abdominal pain, constipation
Not known: Gastrointestinal disorder
Skin and subcutaneous tissue disorders
Common: Skin rash
Uncommon: Erythema, urticaria, pruritus
Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Renal and urinary disorders
Uncommon: blood urea increased, blood creatinine increased
Not known: Renal failure, toxic nephropathy
Reproductive system and breast disorders
Rare: Genital pruritus
General disorders and administration site conditions
Common: Infusion site reaction, injection site inflammation and pain
Uncommon: Pyrexia, infusion site inflammation
Rare: Chills
Investigations
Very common: Positive Coombs test
Common: Alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, prothrombin time prolonged, partial thromboplastin time prolonged
Not known: False positive glycosuria

OVERDOSE:
In case of severe overdose, especially in patients with renal function impairment, haemodialysis can help remove cefepime from the body (peritoneal dialysis is not useful).
Accidental overdose occurred with the administration of high doses to patients with decreased renal function.

STORAGE CONDITIONS:
Store at a temperature not exceeding 30°C. Protect from light.

SHELF LIFE: Refer vial label

Reconstituted solution for injection, reconstituted with water for injection:
The in use physical and chemical stability was demonstrated for 18 hours at room temperature (15 - 25°C) and for 7 days in a refrigerator (2 - 8°C).
From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use time and storage conditions prior to administration are users responsibility and, usually, should not exceed 24 hours at 2°-8° C, unless reconstitution has occurred under validated aseptic controlled conditions.

DOSAGE FORM AND PACKAGING AVAILABLE:

Cepefime for Injection IP 1000mg is supplied in 20ml clear colorless glass vial with grey bromobutyl rubber stopper and aluminium flip off seal.Such 1 vial is packed in a

mono carton along with one 10ml FFS ampoule of sterile water for Injection IP with package insert.

MANUFACTURED BY:
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