Cefipex®Benta

Cefepime HCl

FORMS AND PRESENTATION

Cefipex®1000 Benta; IM/IV; 1 Vial.

COMPOSITION

Cefipex®1000 Benta: Each vial contains Cefepime HCl equivalent to Cefepime 1000mg.

Excipients: L-Arginine.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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.

Pharmacokinetic properties

Absorption

The average plasma concentrations of Cefepime observed in healthy adult male volunteers at various times following single 30-minute infusion (IV) of Cefepime are summarized in the Table below. Elimination of Cefepime is principally via renal excretion with an average (±SD) half-life of 2 (±0.3) hours and total body clearance of 120 (±8) mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250mg to 2g. There is no evidence of accumulation in healthy adult male volunteers receiving clinically relevant doses for a period of 9 days.

Average plasma concentrations of Cefepime (µg/ml)

Cefepime dose	0.5 h	1 h	2 h	4 h	8 h	12 h
1 g IV	78.7	44.5	24.3	10.5	2.4	0.6
1 g IM	14.8	25.9	26.3	16.0	4.5	1.4

Distribution

The average steady-state volume of distribution of Cefipime is 18.0 (±2.0)L. The serum protein binding of Cefepime is approximately 20% and is independent of its concentration in serum. Cefepime is excreted in human milk. A nursing infant consuming approximately 1000mL of human milk per day would receive approximately 0.5mg of Cefepime per day.

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 Cefepime epimer.

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.

INDICATIONS

Cefipex® Benta is indicated in the treatment of infections caused by susceptible strains of the designated microorganisms.

- Pneumonia
- Empiric therapy for febrile neutropenic patients
- Uncomplicated and complicated urinary tract infections
- Uncomplicated skin and skin structure infections
- Complicated intra-abdominal infections

CONTRAINDICATIONS

Cefipex® Benta is contraindicated in patients who have had previous hypersensitivity reactions to any component of the formulation, the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

PRECAUTIONS

Hypersensitivity: Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particulary to drugs. If an allergic reaction to Cefepime occurs, discontinue the drug and treat the patient appropriately. Serious immediate hypersensitivity reactions may require epinephrine and other supportive therapy.

Pseudomembranous Colitis: Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including Cefepime; therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Mild cases of colitis may respond to drug discontinuation alone; moderate to severe cases may require more elaborate management.

Use of Cefepime injection may result in overgrowth of no susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Hepatic Impairment: The pharmacokinetics of Cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose. Therefore, dosage adjustments are not required in patients with hepatic impairment.

Renal Impairment: Renal function should be monitored carefully if drugs with nephrotoxic potential, such as aminoglycosides and potent diuretics, are administered with Cefepime injection.

Geriatrics: Cefepime is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored. Serious adverse events, including reversible encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma) myoclonus, seizures (including nonconvulsive status epilepticus), and/or renal failure have occurred in geriatric patients with renal insufficiency given the usual dose of Cefipime.

Effects on ability to drive and use machines

The effects of the medicinal product on the ability to drive and use machines have not been studied. However, possible adverse reactions like altered state of consciousness, dizziness, confusional state or hallucinations may alter the ability to drive and use machines.

FERTILITY, 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.

DRUG INTERACTIONS

Cefepime injection exhibits physical or chemical incompatibility when admixed with vancomycin HCl, gentamycin sulfate, netilmycin sulfate and aminophylline.

In patients treated with Cefepime, false positive urinary tests for glucose may result when reducing agents are employed. False positives are not seen with glucose-oxidase methods.

ADVERSE EFFECTS

In clinical trials, the more common adverse events were gastrointestinal symptoms and hypersensitivity reactions. 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) and Not known (cannot be estimated from the available data).

Very common

• Positive Coombs test

Common

• Anaemia, eosinophilia
• Phlebitis at the infusion site
• Diarrhoea
• Skin rash
• Infusion site reaction, injection site inflammation and pain
• Alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, prothrombin time prolonged, partial thromboplastin time prolonged

Uncommon

• Oral candidiasis, vaginal infection
• Thrombocytopenia, leukopenia, neutropenia
• Headaches
• Pseudomembranous colitis, colitis, nausea, vomiting
• Erythema, urticaria, pruritus
• Blood urea increased, blood creatinine increased
• Pyrexia, infusion site inflammation

Rare

• Candidiasis
• Anaphylactic reaction, angioedema
• Convulsions, paraesthesia, digeusia, dizziness
• Vasodilatation
• Dyspnoea
• Abdominal pain, constipation
• Genital pruritus
• Chills

Not known

• Aplastic anaemia, haemolytic anaemia, agranulocytosis
• Anaphylactic shock
• State of confusion, hallucination
• Coma, stupor, encephalopathy, altered state of conscience, myoclonus
• Haemorrhage
• Gastrointestinal disorder
• Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
• Renal failure, toxic nephropathy
• False positive glycosuria

DOSAGE AND ADMINISTRATION

Dosage

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.

Recommended dosage schedule for Cefepime in patients with CrCL greater than 60mL/min.

Site and type of infection	Dose (g)	Frequency	Duration (days)
Moderate to Severe pneumonia due to S.pneumoniae, P.aeruginosa, K.pneumonia or Enterobacter species.	1-2g IV	Every 12 hours	10
Empiric therapy for febrile neutropenic patients.	2g IV	Every 8 hours	7
Mild to Moderate uncomplicated or complicated urinary tract infections, including pyelonephritis, due to E.coli, K.pneumoniae or P.mirabilis.	0.5-1g IV/IM	Every 12 hours	7-10
Severe uncomplicated or complicated urinary tract infections, including pyelonephritis, due to E.coli or K.pneumoniae	2g IV	Every 12 hours	10
Moderate to Severe uncomplicated skin and skin structure infections due to S.aureus or S.pyogenes.	2g IV	Every 12 hours	10
Complicated intra-abdominal infections (used in combination with metronidazole) caused by E.coli, viridans group streptococci, P. aeruginosa, K. pneumonia, Enterobacter species or B.fragilis.	2g IV	Every 12 hours	7-10

Patients with hepatic impairment

No adjustment is necessary for patients with hepatic impairments.

Patients with renal insufficiency

In patients with creatinine clearance less than or equal to 60 mL/min, the dose of Cefepime should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of Cefepime should be the same as in patients with normal renal function except in patients undergoing hemodialysis.

Recommended dosing schedule for Cefepime in adult patients (Normal Renal function, Renal impairment, Hemodialysis)

Creatinine clearance (mL/min)	Recommended maintenance schedule			
Greater than 60 normal recommended dosing schedule	500mg Every 12 hours	1g Every 12 hours	2g Every 12 hours	2g Every 8 hours
30-60	500mg Every 24 hours	1g Every 24 hours	2g Every 24 hours	2g Every 12 hours
11-29	500mg Every 24 hours	500mg Every 24 hours	1g Every 24 hours	2g Every 24 hours
Less than 11	250mg Every 24 hours	250mg Every 24 hours	500mg Every 24 hours	1g Every 24 hours
CAPD	500mg Every 48 hours	1g Every 48 hours	2g Every 48 hours	2g Every 48 hours
Hemodialysis	1g on day 1, then 500mg Every 24 hours thereafter			1g Every 24 hours

In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime may be administered at normally recommended doses at a dosage interval of every 48 hours.

Method of administration

- *Intravenous Infusion:* constitute the vial, and add an appropriate quantity of the resulting solution to an intravenous container with one of the compatible intravenous fluids. The resulting solution should be administered over approximately 30 minutes in an IV administration set with filter.
- *Intramuscular Administration*: For intramuscular administration, Cefepime should be constituted with one of the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride, 5% Dextrose Injection, 0.5% or 1.0% Lidocaine HCl, or Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol.

OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of Cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.

STORAGE CONDITIONS

Store below 30°C. Protect from light. Do not freeze.
Reconstitution solution of Cefepime for IM or IV use are stable for 24 hours at a temperature of 15-30°C or 7 days in the refrigerator (2-8°C).

Date of Revision: December 2020.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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Dbayeh - Lebanon