Cefipex® Benta

Cefepime

FORMS AND PRESENTATION

Cefipex® 1000 Benta: IM/IV, 1 Vial of dry powder.

COMPOSITION:

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

Excipients: L-Arginine.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Cefepime is a semi-synthetic broad spectrum cephalosporin antibiotic intended for IM or IV administration. Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. It has a broad spectrum of activity against a wide range of gram-positive and gram-negative bacteria.

Pharmacokinetic Properties

The average plasma concentrations of Cefepime in normal adult males at various times following single 30-minute infusions and single IM injections of 500 mg and 1 g are summarized in Table 1.

Table 1: Mean Plasma Concentrations of Cefepime (µg/ml)

Cefepime Dose	0.5 h	1 h	2 h	4 h	8 h	12 h
IV						
500 mg	38.2	21.6	11.6	5.0	1.4	0.2
1 g	78.7	44.5	24.3	10.5	2.4	0.6
IM						
500 mg	8.2	12.5	12.0	6.9	1.9	0.7
1 g	14.8	25.9	26.3	16.0	4.5	1.4

The average elimination half-life of Cefepime is approximately 2 hrs, and does not vary with respect to dose over the range of 250 mg to 2 g. There was no accumulation in healthy subjects receiving doses up to 2 g IV every 8 hrs for a period of 9 days. Total body clearance averages 120 ml/minute. The average renal clearance of Cefepime is 110 ml/minute, suggesting that the compound is eliminated almost exclusively by renal mechanisms, primarily glomerular filtration.

Urinary recovery of unchanged Cefepime represents approximately 85% of dose, resulting in high concentrations of Cefepime in the urine. The serum protein binding of Cefepime averages 16.4% and is independent of its concentration in the serum. The average steady-state volume of distribution is 18 l.

Following IM administration, Cefepime is completely absorbed. The pharmacokinetics of Cefepime administered IM are linear over the range of 500 mg to 2 g and do not vary with respect to treatment duration.

INDICATIONS

In the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Adults:

Acute exacerbations of chronic bronchitis caused by Str. pneumoniae and H. influenzae.

Peritonitis due to gangrenous and perforated appendicitis caused by E. coli.

Bacterial septicemia caused by E. coli, S. pneumoniae and K. pneumoniae.

In patients who are at risk of infection due to an anaerobic organism, concurrent initial therapy with an antianaerobic agent such as metronidazole or clindamycin is recommended before the causative organism(s) is (are) known. When such concomitant treatment is appropriate, the recommended doses of both antibiotics should be given according to the severity of the infection and the patient's condition.

Common indications for adults and children:

Lower respiratory tract infections: nosocomial and community acquired pneumonia caused by P. aeruginosa, S. aureus (methicillin-susceptible strains), S. pneumoniae, E. coli, and H. influenzae.

Uncomplicated and complicated urinary tract infections, including pyelonephritis caused by P. aeruginosa, E. coli, K. pneumoniae, and P. mirabilis.

Skin and skin structure infections caused by S. aureus (methicillin-susceptible strains), S. pyogenes (Group A streptococci), and P. aeruginosa.

Empiric Therapy in Febrile Neutropenic Patients: Cefipex® Benta as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of Cefipex® Benta monotherapy in such patients.

CONTRAINDICATIONS

In patients who have had previous hypersensitivity reactions to Cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

PRECAUTIONS

General: As with other antibiotics, prolonged use of Cefepime may result in overgrowth of nonsusceptible microorganisms. Cefepime should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Hypersensitivity: Before therapy with Cefepime is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to Cefepime, cephalosporins, penicillins or other beta-lactam antibiotics. If an allergic reaction to Cefepime occurs, discontinue the drug and institute supportive treatment. 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. Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia.

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: In patients with impaired renal function (Cl_{cr} ≤ 50 ml/min), the dose 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.

Children: The safety and effectiveness of Cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia (nosocomial and community acquired), and as empiric therapy in febrile neutropenic patients, have been established in the age groups 2 months up to 12 years. Use of Cefepime in these age groups is supported by evidence from adequate and well-controlled studies of Cefepime in adults with additional pharmacokinetic and safety data from pediatric trials. Safety and effectiveness in pediatric patients below the age of 2 months have not been established.

Geriatrics: When elderly patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nonelderly adult patients unless the patients had renal insufficiency.

PREGNANCY AND LACTATION

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk. Cefepime is excreted in human breast milk in very low concentrations (0.5µg/ml). Caution should be used when Cefepime is administered to a nursing woman.

DRUG INTERACTIONS

Although there is no evidence that Cefepime adversely affects renal function at normal therapeutic doses, the usual precautions, such as the monitoring of renal function, should be applied if drugs with nephrotoxic potential (such as aminoglycosides and potent diuretics) are administered with Cefepime.

Compatibility: Cefepime, prepared in 0.9% sodium chloride or 5% dextrose injection at a concentration of 4 mg of Cefepime/ml, is stable for 7 days under refrigeration (2-8°C) when admixed with: heparin (10 or 50 U/ml), potassium chloride (10 or 40 mEq/l), theophylline (0.8 mg/ml in 5% dextrose injection).

Cefepime at a concentration of 40 mg/ml in 0.9% sodium chloride solution or 5% dextrose injection was found to be compatible with amikacin (6 mg/ml).

Solutions of Cefepime, like solutions of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40mg/ml, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with Cefepime is indicated, each of these antibiotics can be administered separately to the same patient.

As with all parenteral products, IV admixtures should be inspected visually for clarity, particulate matter, precipitation, discoloration and leakage prior to administration whenever solution and container permit.

ADVERSE EFFECTS

Cefepime is generally well tolerated. In clinical trials (n=5598), the most common adverse effects were gastrointestinal symptoms and hypersensitivity reactions. Adverse effects that occurred at an incidence of >0.1 to 1% (except where noted) were:

Hypersensitivity: rash (1.8%), pruritus, urticaria.

Gastrointestinal symptoms: nausea, vomiting, oral moniliasis, diarrhea (1.2%), colitis (including pseudomembranous colitis).

Central Nervous System: headache.

Other: fever, vaginitis, erythema.

Adverse effects that occurred between 0.05 to 0.1% were: abdominal pain, constipation, vasodilation, dyspnea, dizziness, paresthesia, genital pruritus, taste perversion, chills, unspecified moniliasis, vaginal moniliasis, urogenital infection and vaginitis.

Adverse effects of clinical significance that occurred at an incidence of <0.05% included anaphylaxis and seizures.

Local reactions at the site of IV infusion occurred in 5.2% of patients; these included phlebitis (2.9%) and inflammation (0.1%). IM administration of Cefepime was very well tolerated with 2.6% of patients experiencing pain or inflammation at the injection site.

DOSAGE AND ADMINISTRATION

Guidelines for dosage of Cefipex® Benta in adults and children weighing > 40 kg with normal renal function are provided in Table 2.

Table 2: Recommended Dosage Schedule for Adults and Children weighing > 40 kg With Normal Renal Function

Site and Type of Infection	Dose (g)	Route	Frequency	Duration (days)
Mild to moderate urinary tract infection (uncomplicated and complicated), including pyelonephritis	0.5-1	IV or IM	q12h	7-10
Mild to moderate infections including pneumonia, bronchitis and skin and skin-structure infections	1	IV or IM	q12h	10
Severe infections including pneumonia, septicemia and complicated intra-abdominal infections	2	IV	q12h	10
Empiric therapy in febrile neutropenic patients[a]	2	IV	q8h	7[b]

[a] Cefipex®Benta has also been used in combination with an aminoglycoside or a glycopeptide in patient populations which excluded high risk patients.

[b] Or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.

The usual duration of therapy is 7 to 10 days; however, more severe infections may require longer treatment.

Pediatrics (aged 2 months up to 12 years with normal renal function): Usual Recommended Dosages:

Empiric treatment of febrile neutropenia: Patients >2 months of age with body weight ≤ 40 kg: 50 mg/kg IV q8h for 7 to 10 days.

Pneumonia, urinary tract infections, skin and skin structure infections: Patients >2 months of age with body weight ≤ 40 kg: 50 mg/kg IV q12h for 10 days.

Experience with the use of Cefipex® Benta in pediatric patients <2 months of age is limited.

For pediatric patients with body weights >40 kg, adult dosing recommendations apply (see Table 2). Dosage in pediatric patients should not exceed the maximum recommended dosage in adults (2 g q8h). Experience with IM administration in pediatric patients is limited.

Impaired Hepatic Function: No adjustment is necessary for patients with impaired hepatic function.

Impaired Renal Function: There is no need to adjust dosage in the elderly unless renal impairment is present. Cefipex®Benta is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (Cl_{cr} ≤ 50 ml/min), the dose of Cefipex®Benta should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of Cefipex® Benta in patients with mild to moderate renal impairment should be the same as in patients with normal renal function. An estimate of Cl_{cr} should be made to determine the appropriate maintenance dose. The recommended initial dose for patients on hemodialysis and maintenance doses of Cefipex® Benta in patients with renal insufficiency are presented in Table 3.

Table 3: Maintenance Dosing Schedule in Adult Patients with Renal Impairment

Cl_{cr}		Normal Recommended Maintenance Schedule			
(ml/min/1.73 m2)	(ml/s/1.73 m2)	500 mg q12h	1 g q12h	2 g q12h	2 g q8h
>50	>0.8	Usual maintenance dose, no adjustment necessary			
30-50	0.5-0.8	500 mg q24h	1 g q24h	2 g q24h	2 g q12h
11-29	0.18-0.48	500 mg q24h	500 mg q24h	1 g q24h	2 g q24h
≤ 10	≤ 0.17	250 mg q24h	250 mg q24h	500 mg q24h	1 g q24h
Hemodialysisa		500 mg q24h	500 mg q24h	500 mg q24h	500 mg q24h

[a] Pharmacokinetic modeling indicates that reduced dosing for these patients is necessary. Patients receiving Cefipex®Benta who are undergoing concomitant hemodialysis should be dosed as follows: 1 g loading dose on the first day of Cefipex®Benta therapy and 500 mg per day thereafter. On dialysis days, Cefipex®Benta should be administered following dialysis. Whenever possible Cefipex® Benta should be administered at the same time each day.

Children with Impaired Renal Function: Since urinary excretion is the primary route of elimination of Cefipex® Benta in pediatric patients, an adjustment of the dosage of Cefipex® Benta should also be considered in this population. A dose of 50 mg/kg in patients aged 2 months up to 12 years is comparable to a dose of 2 g in an adult (Table 3).

Dialysis Patients: In patients undergoing hemodialysis, approximately 68% of the total amount of Cefipex® Benta present in the body at the start of dialysis will be removed during a 3-hr dialysis period. The recommended initial dose and maintenance schedule for patients on hemodialysis are presented in Table 3. In patients undergoing continuous ambulatory peritoneal dialysis, Cefipex® Benta may be administered at the same doses recommended for patients with normal renal function, i.e., 500 mg, 1 g or 2 g (depending on the severity of the infection) at a dosage interval of every 48 hrs.

Route of Administration:

IV: The IV route of administration is preferable for patients with severe or life-threatening infections, particularly if the possibility of shock is present.

For direct IV injection, the solution reconstituted as recommended should be slowly injected directly into the vein over a period of 3 to 5 minutes. Alternatively, the injection can be made into the tubing of an administration set while the patient is receiving a compatible IV fluid.

For continuous IV infusion, reconstitute the 0.5 or 1 g vial as recommended and add an appropriate quantity of the resulting solution to one of the compatible IV fluids in an IV administration set. The resulting solution should be administered over a period of approximately 30 minutes.

For intermittent IV infusion, a Y-tube administration set can be used with compatible solutions. However, during infusion of a solution containing Cefipex® Benta, it is desirable to discontinue the other solution.

IM: Reconstituted as recommended to a final concentration of 280 mg/ml and given by deep IM injection into a large muscle mass (such as the upper outer quadrant of the gluteus maximus).

Although Cefipex® Benta can be constituted with 0.5 or 1% lidocaine HCl, it is usually not required since Cefipex®Benta causes little or no pain upon IM administration.

Reconstitution:

IM Injection: The following diluents may be used for constituting Cefipex®Benta for IM injection: sterile water for injection, 0.9% sodium chloride injection, 5% dextrose injection, bacteriostatic water for injection with paraben(s), bacteriostatic water for injection with benzyl alcohol, 0.5 or 1% lidocaine HCl (see Table 4).

Table 4: Reconstitution for IM Injection

Vial Size	Volume of Diluent to be Added	Approximate Cefepime Concentration
0.5 g	1.3 ml	280 mg/ml
1 g	2.4 ml	280 mg/ml

Direct IV Injection: Constitute Cefipex® Benta with 10 ml of sterile water for injection, 5% dextrose injection or 0.9% sodium chloride injection (see Table 5).

Table 5: Reconstitution for Direct IV Injection

Vial Size	Volume of Diluent to be Added	Approximate Cefepime Concentration
0.5 g	5 ml	100 mg/ml
1 g	10 ml	100 mg/ml

IV Infusion: Constitute the vials as recommended and add an appropriate quantity of the resulting solution to one of the compatible IV fluids in an IV administration set.

At concentrations between 1 and 40 mg/ml, Cefipex® Benta is compatible with the following IV infusion fluids: 0.9% sodium chloride injection, 5% or 10% dextrose injection, M/6 sodium lactate injection, 5% dextrose and 0.9% sodium chloride injection, Lactated Ringers and 5% dextrose injection and Normosol-R and Normosol-M in 5% dextrose injection.

OVERDOSAGE

Symptoms: Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy, myoclonus, seizures , and neuromuscular excitability.

Treatment: Cefepime is eliminated primarily by the kidneys. In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of Cefepime from the body. Peritoneal dialysis is of no value.

STORAGE CONDITIONS

Store below 30°C. Protect from light.

Reconstituted solutions 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).

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Manufactured by

Virchow Healthcare Private Limited, India

Packed by

Benta S.A.L.,

Lebanon.

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

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