DEFEPIM
(Cefepime)
For Injection U.S.P.

500mg, 1g/vial
For I.V./I.M. use
after reconstitution

QUALITATIVE AND QUANTITATIVE COMPOSITION

DEFEPIM For Injection U.S.P. 500mg
Each vial contains: Cefepime hydrochloride equivalent to 500mg Cefepime (with L-Arginine).
DEFEPIM For Injection U.S.P. 1g
Each vial contains: Cefepime hydrochloride equivalent to 1g Cefepime (with L-Arginine).

DESCRIPTION

DEFEPIM (Cefepime Hydrochloride, U.S.P) is a semi-synthetic, cephalosporin antibacterial for parenteral administration. DEFEPIM is a sterile, dry mixture of cefepime hydrochloride and L-arginine. Freshly constituted solutions of DEFEPIM will range in color from pale yellow to amber.

CLINICAL PHARMACOLOGY

Mechanism of Action: Cefepime is a cephalosporin antibacterial drug.
Pharmacokinetics: 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. **Absorption:** Following intramuscular (IM) administration, cefepime is completely absorbed. **Distribution:** The average steady-state volume of distribution of cefepime is 18 (±2) L.
Metabolism and Excretion: Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide).

INDICATIONS AND USAGE

Pneumonia: DEFEPIM is indicated in the treatment of pneumonia (moderate to severe) caused by susceptible strains of Streptococcus pneumoniae, bacteremia, Pseudomonas aeruginosa, Klebsiella pneumoniae, or Enterobacter species. **Empiric Therapy for Febrile Neutropenic Patients:** DEFEPIM as monotherapy is indicated for empiric treatment of febrile neutropenic patients. **Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis):** DEFEPIM is indicated in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis) caused by susceptible isolates of Escherichia coli or Klebsiella pneumoniae, when the infection is severe, or caused by Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these bacteria. **Uncomplicated Skin and Skin Structure Infections:** DEFEPIM is indicated in the treatment of uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible isolates only) or Streptococcus pyogenes. **Complicated Intra-Abdominal Infections (used in combination with metronidazole):** DEFEPIM is indicated in the treatment of complicated intra-abdominal infections (used in combination with metronidazole) in adults caused by susceptible isolates of *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species, or Bacteroides fragilis*. **Usage:** To reduce the development of drug-resistant bacteria and maintain the effectiveness of DEFEPIM and other antibacterial drugs, DEFEPIM should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

CONTRAINDICATIONS

DEFEPIM is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other beta-lactam antibiotics.

INTERACTIONS

Drug/Laboratory Test Interactions: The administration of cefepime may result in a false-positive reaction for glucose in the urine with certain methods. **Aminoglycosides:** Monitor renal function if aminoglycosides are to be administered with DEFEPIM. **Diuretics:** Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

USE IN SPECIFIC POPULATION

Pregnancy Category B: There are no adequate and well-controlled studies of cefepime use in pregnant women. **Labor and Delivery:** Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated. **Nursing Mothers:** Cefepime is excreted in human breast milk. Caution should be exercised when cefepime is administered to a nursing woman. **Pediatric Use:** The safety and effectiveness of cefepime have been established in the age groups 2 months up to 16 years. Safety and effectiveness in pediatric patients below the age of 2 months have not been established. **Geriatric Use:** Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. **Renal Impairment:** Adjust the dose of DEFEPIM in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination.
Hepatic Impairment: No dose adjustment is necessary for patients with impaired hepatic function.

PRECAUTIONS

Hypersensitivity Reactions: Patient should be checked for hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other beta-lactams before start of therapy.
Neurotoxicity: Encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status. ***Clostridium difficile* Associated Diarrhea:** *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including DEFEPIM, and may range in severity from mild diarrhea to fatal colitis. **Development of Drug-Resistant Bacteria:** Prolonged use of DEFEPIM may result in overgrowth of nonsusceptible microorganisms. **Ability to perform tasks that require judgment, motor or cognitive skills:** Caution is necessary as cefepime cause dizziness and disturbance of consciousness.

DRUG/LABORATORY TEST INTERACTIONS

Urinary Glucose: The administration of cefepime may result in a false-positive reaction for glucose in the urine when using some methods. **Coombs' Tests:** Positive direct Coombs' tests have been reported during treatment with DEFEPIM. **Prothrombin Time:** Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

ADVERSE REACTIONS

Hypersensitivity Reactions, Neurotoxicity and Clostridium difficile-Associated Diarrhea. **Cephalosporin-Class Adverse Reactions:** Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.
Side effects: Fever, headache, nausea, vomiting, anemia, phlebitis, pain and/or inflammation, rash, pruritus.

DOSAGE AND ADMINISTRATION

Dosage for Adults: Administer DEFEPIM intravenously over approximately 30 minutes. The recommended adult dosages and routes of administration for patients with creatinine clearance, greater than 60mL/min are as follows:

Recommended Dosage Schedule for DEFEPIM in Adult Patients with Creatinine Clearance (CrCL) Greater Than 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration(days)
Adults	Intravenous (IV)/ Intramuscular (IM)		
Moderate to Severe Pneumonia	1 to 2 g IV	Every 8 to 12 hours	10
Empiric therapy for febrile neutropenic patients	2 g IV	Every 8 hours	7*
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	0.5 to 1 g IV/IM**	Every 12 hours	7 to 10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	2 g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2 g IV	Every 12 hours	10
Complicated Intra-abdominal Infections †(used in combination with metronidazole)	2 g IV	Every 8 to 12 hours	7 to 10

*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. **Intramuscular route of administration is indicated only for mild to moderate, uncomplicated or complicated UTIs due to *E. coli*. §For *P. aeruginosa,* use 2 g IV every 8 hours. **Pediatric Patients (2 months up to 16 years):** The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for durations as given above for adults is:
•50 mg per kg per dose, administered every 12 hours for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia.•For moderate to severe pneumonia due to P. aeruginosa give 50 mg per kg per dose, every 8 hours. •50 mg per kg per dose, every 8 hours for febrile neutropenic patients.
Dosage Adjustments in Patients with Renal Impairment: Adult Patients Adjust the dose of DEFEPIM in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination. In these patients, the recommended initial dose of DEFEPIM should be the same as in patients with CrCL greater than 60 mL/min except in patients undergoing hemodialysis. The recommended doses of DEFEPIM in patients with renal impairment are presented are as follows:

Recommended Dosing Schedule for DEFEPIM in Adult Patients With Creatinine Clearance Less Than or Equal to 60 mL/min

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule			
Greater than 60	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30 to 60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11 to 29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24hours	1g every 24 hours
Continuous Ambulatory Peritoneal Dialysis (CAPD)	500 mg every 48 hours	1 g every 48 hours	2 g every 48 hours	2 g every 48 hours
Hemodialysis*	1 g on day 1, then 500 mg every 24 hours thereafter			1 g every 24 hours

*On hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day. In patients undergoing Continuous Ambulatory Peritoneal Dialysis (CAPD), DEFEPIM may be administered at the recommended doses at a dosage interval of every 48 hours. In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3-hour dialysis period. The dosage of DEFEPIM for hemodialysis patients is 1 g on Day 1 followed by 500 mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1 g every 24 hours. DEFEPIM should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days.
Preparation of DEFEPIM for Intravenous Infusion Vials
1) Constitute the 0.5 gram, or 1 gram vial, of DEFEPIM with the one of the following diluents:
• Sterile Water for Injection
• 0.9% Sodium Chloride Injection
• 5% Dextrose Injection
• 0.5% or 1% Lidocaine Hydrochloride Injection
• Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol
2) Dilute the reconstituted solution with one of the following compatible infusion solutions prior to intravenous infusion:
• 0.9% Sodium Chloride Injection
• 5% and 10% Dextrose Injection
• M/6 Sodium Lactate Injection
• 5% Dextrose and 0.9% sodium Chloride Injection
• Lactated Rings and 5% Dextrose Injection
• Multiple Electrolytes Injection Type-I U.S.P., Multiple Electrolytes + 5% Dextros Injection Type-I U.S.P. in 5% Dextrose Injection.
3) Parenteral drugs should be inspected visually for particulate matter before administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.
4) Administer the resulting intravenous infusion over approximately 30 minutes.
5) Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing cefepime, it is desirable to discontinue the other solution.
Preparation for Intramuscular Administration
Constitute DEFEPIM vials 0.5 gram or 1 gram with one of the following diluents:
• Sterile Water for Injection,
• 0.9% Sodium Chloride,
• 5%Dextrose Injection,
• 0.5% or 1% Lidocaine Hydrochloride,
• Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol.
Parenteral drugs should be inspected visually for particulate matter before administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Preparation of Reconstituted Solutions of DEFEPIM for Injection

Single-Dose Vials for Intravenous (IV)/ Intramuscular (IM) Administration	Amount of Diluent to be added (mL)	Approximate Cefepime Concentration (mg/mL)	Amount of Reconstituted Volume to be Withdrawn (mL)
Cefepime vial content			
500 mg (IV)	5	100	5
500 mg (IM)	1.5	280	1.8
1 g (IV)	10	100	10.5
1 g (IM)	3	280	3.6
2 g (IV)	10	160	12.5

COMPATIBILITY AND STABILITY

Intravenous Infusion Compatibility: DEFEPIM vials are compatible at concentrations between 1 mg per mL and 40 mg per mL with the above mentioned intravenous infusion fluids. These solutions may be stored up to 24 hours at controlled room temperature 20°C to 25°C or 7 days in a refrigerator 2°C to 8°C.
Admixture Compatibility
DEFEPIM admixture compatibility is as follows:

Cefepime Admixture Stability

DEFEPIM Concentration	Admixture and Concentration	Intravenous (IV) Infusion Solutions	RT/L (20° to 25°C)	Refrigeration (2° to 8°C)
40 mg/mL	Amikacin 6 mg/mL	NS or D5W	24 hours	7 days
40 mg/mL	Amikacin 1mg/mL	D5W	8 hours	8 hours
40 mg/mL	Amikacin 10mg/mL	D5W	2 hours	8 hours
40 mg/mL	Amikacin 1 mg/mL	NS	24 hours	48 hours
40 mg/mL	Amikacin 10 mg/mL	NS	8 hours	48 hours
4mg/mL	Amikacin 40 mg/mL	NS	8 hours	8 hours
4 to 40 mg/mL	Clindamycin Phosphate 0.25 to 6 mg/mL	NS or D5W	24 hours	7 days
4 mg/mL	Heparin 10 to 50 units/mL	NS or D5W	24 hours	7 days
4 mg/mL	Potassium Chloride 10 to 40 mEq/L	NS or D5W	24 hours	7 days
4 mg/mL	Theophylline 0.8 mg/mL	D5W	24 hours	7 days
1 to 4 mg/mL	na	Aminoacid II 4.25% with electrolytes and calcium	8 hours	3 days
0.125 to 0.25mg/ml	na	Inpersol with 4.25% dextrose	24 hours	7 days

NS = 0.9% Sodium Chloride Injection.
D5W = 5% Dextrose Injection. na = not applicable.
RT/L = Ambient room temperature and light.
DEFEPIM Admixture Incompatibility: Do not add solutions of DEFEPIM, to solutions of ampicillin at a concentration greater than 40 mg per mL, or to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate, or aminophylline because of potential interaction. However, if concurrent therapy with DEFEPIM is indicated, each of these antibiotics can be administered separately. **Intramuscular DEFEPIM:** DEFEPIM constituted as directed is stable for 24 hours at controlled room temperature 20°C to 25°C or for 7 days in a refrigerator 2°C to 8°C with the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Sterile Bacteriostatic, Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine Hydrochloride. **Intramuscular and Intravenous DEFEPIM:** As with other cephalosporins, the color of DEFEPIM powder, as well as its solutions tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.
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. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability and nonconvulsive status epilepticus.

INSTRUCTIONS:

Dosage as directed by the physician. Store below 30°C. Protect from heat, light & moisture.
Reconstitute before intramuscular use. Dilute before Intravenous Infusion. Keep all medicines out of the reach of children.
Injection should not be used if container is leaking, solution is cloudy or it contains un-dissolved particles.
Do not remove unit carton until the product is to be used or administered.

WARNING:

To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

DEFEPIM (Cefepime Hydrochloride) 500mg For Injection U.S.P is available as 1 glass vial packed along with 1 ampoule of 5mL water for Injection and insert.
DEFEPIM (Cefepime Hydrochloride) 1g For Injection U.S.P is available as 1 glass vial packed along with 1 ampoule of 10mL water for Injection and insert.

For detailed information please contact:
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