Fectopime™

(C e f e p i m e)

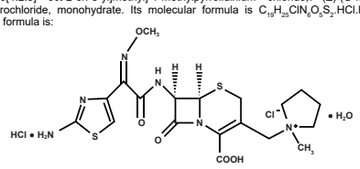
فیکٹوپائم

IV/IM Powder for Injection

500mg, 1g and 2g

DESCRIPTION

Fectopime contains active substance Cefepime Hydrochloride which is a semi-synthetic, cephalosporin antibacterial for parenteral administration. The chemical name of Cefepime Hydrochloride is 1-[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride,7²-(Z)-(O-methyloxime), monohydrochloride, monohydrate. Its molecular formula is $C_{19}H_{25}ClN_6O_5S_2.HCl.H_2O$ and the structural formula is:



Cefepime Hydrochloride

QUALITATIVE & QUANTITATIVE COMPOSITION

Fectopime (Cefepime) Powder for Injection is available for administration as:

Fectopime IV/IM Powder for Injection 500mg
Each vial contains:
Sterile Cefepime HCl USP with L-Arginine equivalent to Cefepime…500mg

Fectopime IV/IM Powder for Injection 1g
Each vial contains:
Sterile Cefepime HCl USP with L-Arginine equivalent to Cefepime…1g

Fectopime IV Powder for Injection 2g
Each vial contains:
Sterile Cefepime HCl USP with L-Arginine equivalent to Cefepime…2g

CLINICAL PHARMACOLOGY

Mechanism of Action

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of in vitro activity that encompasses a wide range of both gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally encoded β-lactamases. Cefepime is highly resistant to hydrolysis by most β-lactamases and exhibits rapid penetration into gram-negative bacterial cells. Within bacterial cells, the molecular targets of Cefepime are the penicillin binding proteins (PBP).

Microbiology

Cefepime has been shown to be active against most strains of the following microorganisms:

Aerobic Gram-Negative Microorganisms:
Enterobacter spp
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus pyrogenes (Lancefield's Group A streptococci)
Viridans group streptococci

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for Cefepime against isolates of similar genus or organism group. However, the efficacy of Cefepime in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible isolates only)
Staphylococcus saprophyticus
Streptococcus agalactiae (Lancefield's Group B streptococci)
NOTE: Most isolates of *Listeria* and *Enterococci*, e.g., *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to Cefepime.

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus subsp. Lwoffii
Aeromonas Spp
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilus influenza (including β-lactamase producing strains)
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis (including β-lactamase producing strains)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens
NOTE: Cefepime is inactive against many isolates of *Burkholderia cepacia, Legionella and Stenotrophomonas maltophilia.*

Anaerobic Microorganisms:
NOTE: Cefepime is inactive against most strains of *Clostridium difficile.*

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 500mg, 1g and 2g are summarized in table below:

Average plasma concentrations of Cefepime (µg/ml)

Cefepime dose	0.5 h	1h	2h	4h	8h	12h
500mg IV	38.2	21.6	11.6	5	1.4	0.2
1g IV	78.7	44.5	24.3	10.5	2.4	0.6
2g IV	163.1	85.8	44.8	19.2	3.9	1.1
500mg IM	8.2	12.5	12	6.9	1.9	0.7
1g IM	14.8	25.9	26.3	16	4.5	1.4
2g IM	36.1	49.9	51.3	31.5	8.7	2.3

Cefepime concentrations in specific tissues and biological fluids are in table below. The binding of Cefepime to serum proteins is, on average, 16.4% and is independent of the serum concentration.

Average concentrations of Cefepime in several tissues (µg/g) and biological fluids (µg/g)

Tissue or fluid	Dose (IV)	Time after the collection (h)	Average concentration
Urine	500mg	0 - 4	292
	1g	0 - 4	926
	2g	0 - 4	3120
Bile	2g	9.4	17.8
Peritoneal fluid	2g	4.4	18.3
Blister Fluid	2g	1.5	81.4
Bronchial mucosa	2g	4.8	24.1
Expectoration	2g	4	7.4
Prostate	2g	1	31.5
Appendix	2g	5.7	5.2
Gall bladder	2g	8.9	11.9

Metabolism

Cefepime is metabolised in N-methylpyrrolidinium, being converted quickly in Noxide. 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 250mg to 2g.

Special Populations

Patients with Renal impairment

Cefepime pharmacokinetics have been investigated in patients with various degrees of renal impairment. The average half-life in patients requiring hemodialysis was 13.5 (±2.7) hours and in patients requiring continuous peritoneal dialysis was 19 (±2) hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients.

Geriatric patients

Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men and women whose mean (SD) creatinine clearance was 74 (±15) mL/min. There appeared to be a decrease in Cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of Cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60mL/min or less.

Pediatric patients

Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to 11 years of age following single and multiple doses on every 8 hours and every 12 hours schedules. Following a single intravenous dose, total body clearance and the steady-state volume of distribution averaged 3.3(±1)mL/min/kg and 0.3(±0.1)L/kg, respectively. The urinary recovery of unchanged Cefepime was 60.4 (±30.4)% of the administered dose, and the average renal clearance was 2(±1.1)mL/min/kg. No accumulation was seen when Cefepime was given at 50mg/kg every 12 hours, while C_{max}, AUC, and $t_{½}$ were increased about 15% at steady state after 50mg/kg every 8 hours. The exposure to Cefepime following a 50mg/kg intravenous dose in a pediatric patient is comparable to that in an adult treated with a 2g intravenous dose. The absolute bioavailability of Cefepime after an dose of 50mg/kg was 82.3(±15)%.

THERAPEUTIC INDICATION

Fectopime (Cefepime) is indicated in the treatment of following 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.
- Gynecological 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 bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Culture and susceptibility testing should be performed where appropriate to determine the susceptibility of the causative microorganism to Fectopime (Cefepime).
Therapy with the Fectopime (Cefepime) may be instituted before results of susceptibility testing are known; however once these results become available, the antibiotic treatment should be adjusted accordingly.

DOSAGE AND ADMINISTRATION

The recommended adult dosages and routes of administration are outlined in table below for patients with creatinine clearance greater than 60mL/min. Administer Fectopime (Cefepime) intravenously over approximately 30 minutes.

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

Site and Type of Infection	Dose	Frequency	Duration (days)
Adults		**Intravenous (IV)/Intramuscular (IM)**	
Moderate to Severe Pneumonia§	1 to 2g IV	Every 8 to 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	0.5 to 1g IV/IM**	Every 12 hours	7-10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis	2g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2g IV	Every 12 hours	10
Complicated Intra-abdominal Infections§ (used in combination with metronidazole)	2g IV	Every 8 to 12 hours	7-10
Other mild to moderate infections (non UTI)	1g IV or IM	Every 12 hours	7-10
Severe infections	2g IV	Every 12 hours	7-10
Very severe or life threatening infections	2g IV	Every 8 hours	7-10

*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 2g 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 40kg in weight for durations as given above for adults is:

- 50mg/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 50mg/kg per dose, every 8 hours.
- 50mg/kg per dose, every 8 hours for febrile neutropenic patients.
- 50mg/kg every 8 hours for 7 to 10 days for Bacteremia that occurs in association with infections and bacterial meningitis.

Special Population

Dosage Adjustments in Patients with Renal Impairment

Adult Patients

Adjust the dose of Fectopime (Cefepime) in patients with creatinine clearance less than or equal to 60mL/min to compensate for the slower rate of renal elimination. In these patients, the recommended initial dose of Fectopime (Cefepime) should be the same as in patients with CrCL greater than 60mL/min except in patients undergoing hemodialysis. The recommended doses of Fectopime (Cefepime) in patients with renal impairment are presented in table below.
When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

Recommended Dosing Schedule for Fectopime (Cefepime) in Adult Patients With Creatinine Clearance Less Than or Equal to 60 mL/min

Creatinine Clearence (mL/min)	Recommended Maintenance Schedule			
Greater than 60	500mg every 12 hours	1g every 12 hours	2g every 12 hours	2g every 8 hours
30 to 60	500mg every 24 hours	1g every 24 hours	2g every 24 hours	2g every 12 hours
11 to 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
Continuous Ambulatory Peritoneal Dialysis (CAPD)	250mg 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

**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), Fectopime (Cefepime) may be administered at the recommended doses at a dosage interval of every 48 hours (see above table).
- 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 Fectopime (Cefepime) for hemodialysis patients is 1g on Day 1 followed by 500mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1g every 24 hours.

- Fectopime (Cefepime) should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (See table above).

Pediatric Patients
Data in pediatric patients with impaired renal function are not available; however, since Cefepime pharmacokinetics are similar in adults and pediatric patients, changes in the dosing regimen proportional to those in adults (see Tables above) are recommended for pediatric patients.

Directions for Reconstitution
As a general rule the solution should be used immediately after preparation. Reconstituted solutions may be stored up to 24 hours at 25°C or 7 days in a refrigerator 2°C to 8°C.
The color of Fectopime (Cefepime) 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.
Freshly reconstituted solutions of Fectopime (Cefepime) will range in color from pale yellow to amber.
Parenteral drugs should be inspected visually for particulate matter before administration. If particulate matter is evident in reconstituted solution, the drug solution should be discarded.

Preparation of Fectopime (Cefepime) for IV / IM Injection
Fectopime (Cefepime) may be given intravenously or by deep intramuscular injection into a large muscle mass (such as the upper quadrant of the gluteus maximus). Reconstitute Fectopime (Cefepime) 500mg, 1g and 2g with Sterile Water for Injection. The amount of diluent to be added to each vial is shown in table below:

Route of Administration	Dosage	Volume of Diluent to be Added
IV	500mg vial	5mL
IV	1g vial	10mL
IV	2g vial	10mL
IM	500mg vial	1.5mL
IM	1g vial	3mL

Preparation of Fectopime (Cefepime) for IV Infusion
Reconstitute Fectopime (Cefepime) 500mg, 1g and 2g with Sterile Water for Injection as mentioned in table above. 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, Ringer Lactate Injection, Ringer Lactate with 5% Dextrose Injection.
Administer the resulting intravenous infusion over approximately 30 minutes. 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.

Special Instructions
Do not add solutions of Fectopime (Cefepime) to solutions of ampicillin at a concentration greater than 40mg/mL, or to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate, or aminophylline because of potential interaction. However, if concurrent therapy with Fectopime (Cefepime) is indicated, each of these antibacterial drugs can be administered separately.

ADVERSE REACTIONS
Very Common: Positive Coombs' test.
Common: Anemia, eosinophilia, phlebitis at the infusion site, diarrhea, 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 and 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 and infusion site inflammation.
Rare: Candidiasis, anaphylactic reaction, angioedema, convulsions, paresthesia, digeusia, dizziness, vasodilatation, dyspnea, abdominal pain, constipation, genital pruritus and chills.
Not Known: Aplastic anemia, hemolytic anemia, agranulocytosis, anaphylactic shock, state of confusion, hallucination, coma, stupor, encephalopathy, altered state of conscience, myoclonus, hemorrhage, gastrointestinal disorder, toxic epidermal necrolysisa, Stevens-Johnson syndrome, erythema multiforme, renal failure, toxic nephropathy and false positive glycosuria.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATION
Cefepime is contraindicated in patients who have shown immediate hypersensitivity reactions to Cefepime or the cephalosporin class of antibacterial drugs, penicillin or other beta-lactam antibacterial drugs.

PRECAUTIONS
Hypersensitivity Reactions
Before therapy with Cefepime for Injection 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-lactams. Exercise caution if this product is to be given to penicillin-sensitive patients. If an allergic reaction to Cefepime occurs, discontinue the drug and institute appropriate supportive measures.

Neurotoxicity
Serious adverse reactions have been reported including life-threatening or fatal occurrences of encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus. If neurotoxicity associated with Cefepime therapy occurs, discontinue Cefepime and institute appropriate supportive measures.

Clostridioides difficile-Associated Diarrhea
Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefepime, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Development of Drug-Resistant Bacteria
Prescribing Cefepime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. As with other antimicrobials, prolonged use of Cefepime may result in overgrowth of non-susceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Urinary Glucose
The administration of Cefepime may result in a false-positive reaction for glucose in the urine when using some methods (e.g. Clinitest™ Tablets, Benedict's or Fehling's Solution).

Coombs' Tests
Positive direct Coombs' tests have been reported during treatment with Cefepime. In patients who develop hemolytic anemia, discontinue the drug and institute appropriate therapy. Positive Coombs' test may be observed in newborns whose mothers have received cephalosporin antibacterial drugs before parturition.

Prothrombin Time
Many cephalosporins, including Cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, Cefepime should be discontinued immediately and an alternative treatment should be considered.

Pseudomembranous colitis and delaying peristalsis
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It is important to consider this diagnosis in patients who develop diarrhea in association with the use of Cefepime. Drugs which delay peristalsis may prolong and/or worsen the condition and should not be used.

Effects on ability to drive and use machines
During treatment with Cefepime undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines. Patients should be cautious when driving or operating machinery.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Cefepime should only be prescribed to pregnant women with great caution.

Nursing Mother
Cefepime is present in human breast milk at low concentrations (approximately 0.5mcg/mL) following a single intravenous dose of 1000mg. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cefepime and any potential adverse effects on the breastfed child from Cefepime or from the underlying maternal condition.

DRUG INTERACTIONS
Laboratory Test Interactions
It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Aminoglycosides
Monitor renal function if aminoglycosides are to be administered with Cefepime because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs.

Diuretics
Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. Monitor renal function when Cefepime is concomitantly administered with potent diuretics.

Coumarin Anticoagulant
Cephalosporins can potentiate the action of coumarin anticoagulants.

OVERDOSAGE
Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability and nonconvulsive status epilepticus. 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.

STORAGE
Do not store above 30°C.
Protect from light & moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Fectopime IV/IM (Cefepime) Powder for Injection 500mg is available in unit pack size of 1 vial along with a 5mL ampoule of Sterile Water for Injection.

Fectopime IV/IM (Cefepime) Powder for Injection 1g is available in unit pack size of 1 vial along with a 10mL ampoule of Sterile Water for Injection.

Fectopime IV (Cefepime) Powder for Injection 2g is available in unit pack size of 1 vial along with a 10mL ampoule of Sterile Water for Injection.

Keep out of the reach of children.

To be sold on prescription of registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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