Cefepime HCl Rx

Axera®

500 mg, 1 g and 2 g Powder for Injection
Intravenous / Intramuscular
ANTIBACTERIAL

FORMULATIONS
Each vial contains:
Cefepime (as hydrochloride).....500 mg, 1 g or 2 g

PRODUCT DESCRIPTION
Cefepime is a sterile white or yellowish crystalline powder, consisting of a dry mixture of cefepime hydrochloride and L-arginine. The L-arginine is added only to control the pH of the reconstituted solution at 4 to 6.

When reconstituted, the powder dissolves completely into a clear, pale to light yellow solution.

The product is packaged in a clear, colorless Type I glass vial, and plugged with gray rubber stopper and sealed with flip off cap.

PHARMACODYNAMICS
Cefepime is a semi-synthetic, broad spectrum, fourth generation cephalosporin for parenteral administration which is active against a wide range of Gram-positive, Gram-negative aerobic organisms and certain anaerobes. It exerts bactericidal effect by inhibiting the synthesis of the bacterial cell wall. Its activity against Gram-positive cocci is similar to that of cefotaxime and includes staphylococci (but not methicillin-resistant *Staphylococcus aureus*) and streptococci. It has a broader spectrum of activity against *Enterobacteriaceae* than other cephalosporins, including organisms that produce chromosomally mediated beta-lactamases such as *Enterobacter* species and *Proteus vulgaris*. It has a similar or slightly less activity than ceftazidime against *Pseudomonas aeruginosa*, although it may be active against some strains resistant to ceftazidime.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Cefepime has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections:

Aerobic Gram-Positive	Aerobic Gram-Negative
Staphylococcus aureus (methicillin-susceptible strains only) *Streptococcus pneumoniae* *Streptococcus pyogenes* (Lancefield's Group A streptococci) Viridans group streptococci	*Enterobacter* *Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa*

Cefepime has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown:

Aerobic Gram-Positive	Aerobic Gram-Negative
Staphylococcus epidermidis (methicillin-susceptible strains only) *Staphylococcus saprophyticus* *Streptococcus agalactiae* (Lancefield's Group B streptococci)	*Acinetobacter calcoaceticus* subsp. *lwoffii* *Citrobacter diversus* *Citrobacter freundii* *Enterobacter agglomerans* *Haemophilus influenzae* (including beta-lactamase producing strains) *Hafnia alvei* *Klebsiella oxytoca* *Moraxella catarrhalis* (including beta-lactamase producing strains) *Morganella morganii* *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Serratia marcescens*

Most strains of enterococci, e.g., *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to cefepime.

Cefepime is inactive against many strains of *Stenotrophomonas* (formerly *Xanthomonas maltophilia* and *Pseudomonas maltophilia).*

Cefepime is inactive against most strains of *Clostridium difficile.*

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS
Cefepime is rapidly and almost completely absorbed after intramuscular (IM) injection. After 1.5 hours of 500 mg and 1 g doses, mean peak plasma concentrations in adults are 14 and 30 mcg/mL, respectively. Peak plasma concentrations of about 40 and 80 mcg/mL are reported within 30 minutes of similar intravenous (IV) doses. In children 2 months to 16 years old who received a single 50 mg/kg IM dose, average plasma concentrations are 76, 75.2, 64, and 4.8 mcg/mL at 0.5, 0.75, 1, and 8 hours, respectively. Intravenous administration of a single 50 mg/kg dose of cefepime in pediatric patients results in cefepime concentrations similar to adults after IV administration of a single 2 g dose of the drug.

Cefepime is widely distributed into tissues and fluids, including blister fluid, bronchial mucosa, sputum, bile, peritoneal fluid, appendix, gall bladder, prostate and cerebrospinal fluid. The average steady state volume of distribution of cefepime is 18 (± 2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is metabolized to *N*-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide. Elimination of cefepime is principally via the kidneys with an average (± SD) half-life of 2 (±0.3) hours and total body clearance of 120 (±8) mL/min in healthy volunteers. About 85% of the dose is recovered unchanged in the urine.

Studies in adults with renal impairment indicate that pharmacokinetics (PK) of cefepime are affected by the degree of renal impairment and that total body clearance of the drug decreases in proportion to decreases in creatinine clearance. Patients with renal dysfunction and those undergoing hemodialysis require dosing adjustment. Hepatic impairment does not affect pharmacokinetics of cefepime.

Cefepime is removed by hemodialysis and peritoneal dialysis.

INDICATIONS
For the treatment of the following infections caused by susceptible microorganisms:

- Lower respiratory tract infections, including pneumonia (moderate to severe) and bronchitis
- Uncomplicated and complicated urinary tract infections (UTIs), including pyelonephritis
- Skin and skin structure infections
- Complicated intra-abdominal infections, including peritonitis and biliary tract infections
- Empiric therapy for febrile neutropenic patients
- Septicemia

DOSAGE AND ADMINISTRATION

- For IV or IM administration.
- Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms and the patient's condition. The IV route is preferable for patients with severe or life-threatening infections, particularly if the possibility of shock is present.

Usual Dose in Adults and Children ≥ 2 months old with Normal Renal Function

Infection	Recommended IV Dose		Frequency	Duration
	Adults & Children > 40 kg	Children ≤ 40 kg		
Moderate to severe pneumonia	1 to 2 g	50 mg/kg body weight per dose	Every 12 hours	10 days
Mild to moderate uncomplicated or complicated UTIs, including pyelonephritis and/or concurrent bacteremia*	500 mg to 1 g	50 mg/kg body weight per dose	Every 12 hours	7-10 days
Severe uncomplicated or complicated UTIs, including pyelonephritis and/or concurrent bacteremia	2 g	50 mg/kg body weight per dose	Every 12 hours	10 days
Moderate to severe uncomplicated skin and skin structure infections	2 g	50 mg/kg body weight per dose	Every 12 hours	10 days
Complicated intra-abdominal infections (used in combination with metronidazole)	2 g	50 mg/kg body weight per dose	Every 12 hours	7-10 days
Empiric therapy for febrile neutropenic patients	2 g	50 mg/kg body weight per dose	Every 8 hours	7 days 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.
Very severe or life-threatening infections	2 g	50 mg/kg body weight per dose	Every 8 hours	Usual duration of treatment is 7-10 days; however, more severe infections may require longer treatment.
Pediatric dosage should not exceed the recommended adult dose.				

*Intramuscular route of administration is indicated only for mild to moderate, uncomplicated or complicated UTIs due to *E. coli* when the IM route is considered to be a more appropriate route of drug administration.

Dose in Adults with Renal Impairment:

- **Initial Dose:** The same as in patients with normal renal function except in patients undergoing hemodialysis.
- Adjust cefepime maintenance dose to compensate for the slower rate of renal elimination

Recommended Maintenance Dosing Schedule in Adults with Renal Impairment or Undergoing Hemodialysis

Creatinine Clearance (mL/min)	Mild to moderate UTI	Mild to moderate infections other than UTI	Severe infections	Very severe or life-threatening infections
30-60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11-29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
<11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g 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 for all infections except febrile neutropenia, which is 1 g every 24 hours. • On hemodialysis days, cefepime should be administered after hemodialysis. Whenever possible, cefepime should be administered at the same time each day.			

When only serum creatinine is available, the following formula may be used to estimate creatinine clearance in adults. Serum creatinine should represent a steady state of renal function:

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x value calculated using the above formula

Dose in Children with Renal impairment: Data is not available on dosing in children with renal impairment; however, reduction in dose and increase in dosing interval may follow the same recommendations for adults.

When only serum creatinine is available, creatinine clearance in children may be estimated using either of the following methods:

$$\text{Creatinine clearance (mL/min/1.73m}^2\text{)} = \frac{0.55 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

Or

$$\text{Creatinine clearance (mL/min/1.73m}^2\text{)} = \frac{0.52 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

-3.6

Or, as prescribed by a physician.

Directions for Use, Compatibility and Stability

Cefepime powder for injection may be reconstituted with the following compatible diluents:

- Sterile Water for Injection
- Dextrose 5% Injection
- Sodium chloride 0.9% Injection
- Lidocaine 0.1% Injection

Preparation of Cefepime Solutions

Cefepime Single Dose Vials for IV/IM Administration	Volume of Diluent to be added (mL)	Approximate Available Volume (mL)	Approximate Cefepime Concentration (mg/mL)
500 mg (IV)	5	5.6	100
500 mg (IM)	1.3	1.8	280
1g (IV)	10	11.3	100
1g (IM)	2.4	3.6	280
2g (IV)	10	12.5	160

Reconstituted solutions at concentrations of 100 mg/mL or 280 mg/mL are stable for 24 hours at 20 to 25°C or for 7 days at 2 to 8°C. Reconstituted solution with concentration of 160 mg/mL should be used immediately after reconstitution.

For IM Administration: The resulting solution is administered by deep IM injection into a large mass (such as the upper outer quadrant of the gluteus maximus).

For Direct IV Administration: The resulting solution should be injected directly into the vein over 3 to 5 minutes or injected into a tubing of an administration set while the patient is receiving a compatible IV fluid.

For IV Infusion: Reconstitute cefepime powder for injection as noted above for direct IV administration, and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids. The resulting solution for IV infusion should be administered over approximately 30 minutes.

- *Prior to administration, parenteral products should be inspected visually for particulate matter and discoloration.*
- *Shake the reconstituted solution before use.*
- *Observe strict aseptic technique when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.*
- *Like some other cephalosporins, cefepime powder for injection and solutions of the drug tend to darken, depending on storage conditions; however, such discoloration does not indicate loss of potency.*

Incompatibility

As with most beta-lactam antibiotics, solutions of cefepime should not be added to solutions of metronidazole, vancomycin, gentamicin, tobramycin sulfate, or netilmicin sulfate because of physical or chemical incompatibility. However, if concomitant treatment with cefepime is indicated, each of these antibiotics can be administered separately.

CONTRAINDICATIONS

Known hypersensitivity to cefepime, cephalosporins, penicillins, other beta-lactam antibiotics or any component of the product.

WARNINGS AND PRECAUTIONS

- **Careful inquiry should be made concerning previous immediate hypersensitivity to cephalosporins, penicillins, or other drugs before initiating therapy with cefepime. If cefepime is given to penicillin-sensitive patients, caution should be exercised since cross-hypersensitivity among beta-lactam antibiotics has been clearly documented. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.**

  Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, IV fluids and IV antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

- *Clostridium difficile*-associated diarrhea (CDAD) and colitis have been reported with the use of nearly all antibacterial agents, including cefepime, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.

- Since high or prolonged serum cefepime concentrations can occur if usual dosage is used in patients with renal impairment or other conditions that may compromise renal function, the maintenance dosage of cefepime should be decreased in patients with renal impairment (i.e., creatinine clearance 60 mL/minute or less). Continued dosage should be determined by the degree of renal impairment, severity of infection and susceptibility of the causative organisms.
  Serious adverse events, including life-threatening or fatal encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures and/or renal failure, have been reported in patients receiving cefepime during postmarketing surveillance.
  Most cases occurred in patients with renal impairment who received cefepime dosage that exceeded the recommended dosage schedules. However, some cases of encephalopathy occurred in patients who received dosage adjusted for renal impairment. In most patients, symptoms of neurotoxicity were reversible and resolved after discontinuance of cefepime and/or after hemodialysis.

  If seizures associated with cefepime therapy occur, the drug should be discontinued.

- Antimicrobial monotherapy may not be appropriate in patients at high risk of severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying malignancy, or with severe or prolonged neutropenia). Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.

- Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.

- 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 development of drug-resistant bacteria.

- As with other antibacterial agents, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Aminoglycosides:** Monitor renal function carefully if high doses of aminoglycosides are to be administered with cefepime because of increased potential of nephrotoxicity and ototoxicity.
- **Diuretics:** Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

Interference with Laboratory Tests:

Cephalosporins can cause false-positive results in urine glucose determinations using cupric sulfate solution (Benedict's reagent, Clinitest®). It is recommended to use glucose oxidase methods (e.g., Clinistix®).

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category B) Reproductive studies in mice, rats and rabbits showed no evidence of fetal damage. However, since there are no adequate and well-controlled studies using cefepime in pregnant women, cefepime should only be used during pregnancy when clearly needed and when the benefits justify the potential risks.

Lactation: Cefepime is excreted in human milk in very low concentrations. Use with caution in breastfeeding women.

Children: The safety and efficacy of cefepime have been established in children 2 months up to 16 years old.

However, there are insufficient clinical data to support the use of cefepime in patients under 2 months old or for the treatment of serious infections in pediatric patients of any age where the suspected or proven pathogen is *Haemophilus influenzae* type b (Hib).

An alternative agent with demonstrated clinical efficacy should be used in patients with meningeal seeding from a distant infection site or when meningitis is suspected or documented.

Elderly: Elderly patients are more likely to have decreased renal function, therefore, care should be taken in dose selection and renal function should be monitored.

Serious adverse events occur in elderly patients with renal insufficiency given unadjusted doses of cefepime including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, seizures and/ or renal failure.

Renal Impairment: The dose of cefepime in patients with impaired renal function should be adjusted to compensate for the slower rate of renal elimination [see **Dosage and Administration**].

Hepatic Impairment: The PK of cefepime is unaltered in patients with hepatic impairment who received a single 1 g dose. The PK of cefepime does not change to a clinically significant degree in cystic fibrosis patients. It is not necessary to alter the dosage of cefepime in these patient groups.

UNDESIRABLE EFFECTS

Cefepime is generally well tolerated. The most common adverse effects reported were gastrointestinal (GI) symptoms and hypersensitivity reactions.

Dermatologic / Hypersensitivity Reactions: Local reactions, including phlebitis, pain and/or inflammation; erythema, unspecified moniliasis, pruritus, urticaria, rash, anaphylaxis including anaphylactic shock

GI: Diarrhea, nausea, vomiting, oral moniliasis, colitis (including pseudomembranous colitis), abdominal pain, constipation

Nervous System: Headache, dizziness, paresthesia, taste perversion; encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (including nonconvulsive status epilepticus) have been reported in patients with renal impairment who received unadjusted doses of cefepime.

Cardiovascular: Vasodilation

Renal / Genitourinary: Renal failure; vaginitis, genital pruritus, urogenital infection

Hepatic: Hepatic failure (although a causal relationship to cefepime therapy has not been determined)

Hematologic: As with other cephalosporins, transient leukopenia, neutropenia, agranulocytosis, and thrombocytopenia have been reported.

Laboratory Abnormalities: Positive Coombs' test (without hemolysis), elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), eosinophils, prothrombin time (PT), partial thromboplastin time (PTT), alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine, calcium, phosphorus, potassium, total bilirubin; decreased levels of phosphorus, calcium (particularly in elderly patients), hematocrit

Other Adverse Effects: Fever, dyspnea, chills

The following adverse effects have also been reported for cephalosporin-class antibiotics: Hypersensitivity reactions including eosinophilia, joint pain or inflammation, edema, facial edema, genital and anal pruritus, angioedema, shock, hypotension, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, and exfoliative dermatitis; anaphylaxis including a few fatalities; thrombocythemia, leukocytosis, granulocytosis, monocytosis, lymphocytopenia, basophilia, anemia, aplastic anemia, pancytopenia, hemolytic anemia, epistaxis or hemorrhage; renal dysfunction, toxic nephropathy; vaginal candidiasis, menstrual irregularities; transient increase in γ-glutamyl transferase concentration; increased serum bilirubin and/or lactate dehydrogenase; decreased serum albumin and/or total protein; hepatic dysfunction including cholestasis; thrombophlebitis; malaise, fatigue, nightmares, vertigo, hyperactivity, nervousness or anxiety, agitation, hallucinations, insomnia, somnolence, weakness, hot flushes, alteration in color perception, confusion, hypertonia; chest pain, pleural effusion, pulmonary infiltrate, respiratory distress, cough, rhinitis; increased or decreased serum glucose concentration

OVERDOSE AND TREATMENT
Accidental overdosing has occurred when large doses of cefepime were given to patients with impaired renal function. Symptoms include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability.

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.

STORAGE CONDITIONS

- Cefepime powder for injection should be stored at temperatures not exceeding 30°C.
- Protect from light.
- Keep the product out of sight and reach of children.

AVAILABILITY
Cefepime (Axera®) 500 mg, 1 g and 2 g colorless Type I glass vials in box of 1's.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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PT. DARYA VARIA LABORATORIA TBK
Jl. Lanbau Liobaru RT.007 RW.009, Kel.
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