CINAVEROS
Cefepime 0.5 gm
Cefepime 1 gm

Powder for solution for
I.M & I.V injection

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefepime and other antibacterial drugs, CINAVEROS should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

CLINICAL PHARMACOLOGY

Cefepime is an antibacterial agent belonging to the cephalosporin class of antibacterials with *in vitro* antibacterial activity against facultative Gram-positive and Gram-negative bacteria

Absorption

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous (IV) administration are portrayed in Table 1.

Table 1: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intravenous Administration

	Cefepime		
Parameter	**500 mg IV**	**1 g IV**	**2 g IV**
0.5 h	38.2	78.7	163.1
1 h	21.6	44.5	85.8
2 h	11.6	24.3	44.8
4 h	5	10.5	19.2
8 h	1.4	2.4	3.9
12 h	0.2	0.6	1.1
C_{max}, mcg/mL	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, h•mcg/mL	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single intramuscular injection are summarized in Table 1. The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g intramuscularly and do not vary with respect to treatment duration.

Table 1: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intramuscular Administration

CINAVEROS Parameter	**500 mg IM**	**1 g IM**	**2 g IM**
0.5 h	8.2	14.8	36.1
1 h	12.5	25.9	49.9
2 h	12	26.3	51.3
4 h	6.9	16	31.5
8 h	1.9	4.5	8.7
12 h	0.7	1.4	2.3
C_{max}, mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)

T_{max}, h	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, h•mcg/mL	60 (8)	137 (11)	262 (23)
Number of subjects (male)	6	6	12

Distribution

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 excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day. (See **PRECAUTIONS: Nursing Mothers**.)

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 3.

Table 3: Average Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)

Tissue or Fluid	Dose/Route	Average Time of Sample Post-Dose (h)	Average Concentration
Blister Fluid	2 g IV	1.5	81.4 mcg/mL
Bronchial Mucosa	2 g IV	4.8	24.1 mcg/g
Sputum	2 g IV	4	7.4 mcg/mL
Urine	500 mg IV	0 to 4	292 mcg/mL
	1 g IV	0 to 4	926 mcg/mL
	2 g IV	0 to 4	3120 mcg/mL
Bile	2 g IV	9.4	17.8 mcg/mL
Peritoneal Fluid	2 g IV	4.4	18.3 mcg/mL
Appendix	2 g IV	5.7	5.2 mcg/g
Gallbladder	2 g IV	8.9	11.9 mcg/g
Prostate	2 g IV	1	31.5 mcg/g

Data suggest that cefepime does cross the inflamed blood-brain barrier.

Metabolism and Excretion

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See**DOSAGE AND ADMINISTRATION**.)

Specific Populations

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 creatinne clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients. (See **DOSAGE AND ADMINISTRATION**.)

Hepatic impairment: The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1 g dose.

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 60 mL/min or less. (See **DOSAGE AND ADMINISTRATION**.)

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. There were no significant effects of age or gender (25 male vs 17 female) on total body clearance or volume of distribution, corrected for body weight. No accumulation was seen when cefepime was given at 50 mg per kg every 12 hours, while C_{max}, AUC, and $t_{½}$ were increased about 15% at steady state after 50 mg per kg every 8 hours. The exposure to cefepime following a 50 mg per kg intravenous dose in a pediatric patient is comparable to that in an adult treated with a 2 g intravenous dose. The absolute bioavailability of cefepime after an intramuscular dose of 50 mg per kg was 82.3 (±15)% in eight patients.

Microbiology

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 Gram-positive and Gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into Gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Cefepime has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Gram-Negative bacteria :
Enterobacter spp.
Escherichia coli

Klebsiella pneumonia
Proteus mirabilis
Pseudomonas aeruginosa
Gram-Positive bacteria :

Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus pneumoniae
Streptococcus pyogenes

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. However, the efficacy of cefepime in treating clinical infections due to these bacteria has not been established in adequate and well-controlled trials.

Gram-Positive bacteria :

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Staphylococcus saprophyticus

Streptococcus agalactiae

NOTE: Most isolates of enterococci, eg, *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to cefepime.

Gram-Negative bacteria :

Acinetobacter calcoaceticus subsp. *lwoffii*

Citrobacter diversus

Citrobacter freundii

Enterobacter agglomerans

Haemophilus influenzae

Hafnia alvei

Klebsiella oxytoca

Moraxella catarrhalis

Morganella morganii

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Serratia marcescens

NOTE: Cefepime is inactive against many isolates of *Stenotrophomonas maltophilia* .

INDICATIONS AND USAGE

CINAVEROS is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see also **PRECAUTIONS: Pediatric Use** and **DOSAGE AND ADMINISTRATION**):

Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.

Empiric Therapy for Febrile Neutropenic Patients. Cefepime 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 cefepime monotherapy in such patients.

Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *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 microorganisms.

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) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides fragilis*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CINAVEROS and other antibacterial drugs, CINAVEROS should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

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

Hypersensitivity to the active substance , to other cephalosporins or to any of the excipients . previous immediate and/ or severe hypersensitivity reaction to a penicillin or to any other .

WARNINGS

Special warning and precautions for use
Special caution is required to determine any other type of previous hypersensitivity reactions to penicillin or to other betalactam medicinal products because patients hypersensitive to these medications may be hypersensitive to cefepime as well (cross-allergy) .

Hypersensitivity Reactions to Cefepime, Cephalosporins, Penicillins, or Other Drugs
Before therapy with CINAVEROS is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other drugs. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to CINAVEROS occurs, discontinue the drug.

Use in Patients with Renal Impairment
In patients with creatinine clearance less than or equal to 60 mL/min, adjust the dose of CINAVEROS (cefepime hydrochloride) to compensate for the slower rate of renal elimination [see **DOSAGE AND ADMINISTRATION**]. Because high and prolonged serum cefepime concentrations can occur from usual dosages in patients with renal impairment, the cefepime dosage should be reduced when it is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

Neurotoxicity
During postmarketing surveillance, serious adverse reactions have been reported including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and nonconvulsive status epilepticus (see **ADVERSE REACTIONS**). Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with cefepime therapy occurs, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment.
***Clostridium difficile* Associated Diarrhea**

Clostridium 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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

Prescribing CINAVEROS 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 CINAVEROS may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.
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.

Positive direct Coombs' tests have been reported during treatment with Cefepime . In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

CINAVEROS (cefepime hydrochloride) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of Cefepime . The effect of lower doses is not presently known.

Information for Patients

Before therapy with CINAVEROS is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefepime, cephalosporins, penicillins, or other drugs. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to CINAVEROS occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, corticosteroids, intravenous fluids, intravenous antihistamines, pressor amines, and airway management, as clinically indicated.

Patients should be counseled that antibacterial drugs including CINAVEROS should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold).

When CINAVEROS is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CINAVEROS or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be advised of neurological adverse events that could occur with CINAVEROS use. Patients should be instructed to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures and nonconvulsive status epilepticus . for immediate treatment, dosage adjustment, or discontinuation of CINAVEROS .

Drug Interactions

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with CINAVEROS because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide.

Pregnancy
There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Cefepime is excreted in human breast milk in very low concentrations (0.5 mcg/mL). Caution should be exercised when cefepime is administered to a nursing woman.
Labor and Delivery
Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.
Pediatric Use
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, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of CINAVEROS 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. There are insufficient clinical data to support the use of CINAVEROS in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b.
IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED.
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. (See **WARNINGS** and **ADVERSE REACTIONS**.)
This drug 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. (See **CLINICAL PHARMACOLOGY: Special Populations**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

Table 4: Adverse Reactions Cefepime Multiple-Dose Dosing Regimens

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions, including phlebitis , pain and/or inflammation *; rash
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, erythema, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting, anemia

At the higher dose of 2 g every 8 hours, the incidence of probably-related adverse events was higher among the patients who received this dose of cefepime. They consisted of rash, diarrhea, nausea, vomiting, pruritus, fever, and headache.

Table 5: Adverse Laboratory Changes Cefepime Multiple-Dose Dosing Regimens

INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs' test (without hemolysis) ; decreased phosphorus; increased ALT/SGPT, AST/SGOT, eosinophils ; abnormal PTT, PT
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

* Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.

Postmarketing Experience

Encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and nonconvulsive status epilepticus have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules, some cases of neurotoxicity occurred in patients receiving an appropriate dosage adjustment for their degree of renal impairment. If neurotoxicity associated with cefepime therapy occurs, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment. (See **WARNINGS**).

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported.

Cephalosporin-Class Adverse Reactions

In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

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. (See **WARNINGS**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**.)

DOSAGE AND ADMINISTRATION

The recommended adult and pediatric dosages and routes of administration are outlined in the following table.

Table 6. Recommended Dosage Schedule for CINAVEROS in Patients with CrCL Greater Than 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration (days)
Moderate to Severe Pneumonia due to S. pneumoniae*, P. aeruginosa§, K. pneumoniae, or Enterobacter species	1 to 2 g IV	Every 8 to 12 hours	10
Empiric therapy for febrile neutropenic patients (See INDICATIONS AND USAGE)	2 g 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 to 1 g IV/IM***	Every 12 hours	7 to 10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli* or *K. pneumoniae**	2 g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections due to *S. aureus* or *S. pyogenes*	2 g IV	Every 12 hours	10
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *E. coli*, viridans group streptococci, *P. aeruginosa*§, *K. pneumoniae*, *Enterobacter* species, or *B. fragilis*.	2 g IV	Every 8 to 12 hours	7 to 10
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 uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg per kg per dose, administered every 12 hours (50 mg per kg per dose, every 8 hours for febrile neutropenic patients), for durations as given above.			

†Adjust dose in patients with CrCL less than or equal to 60 mL/min
*including cases associated with concurrent bacteremia
**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 when the intramuscular route is considered to be a more appropriate route of drug administration.

§For *Pseudomonas aeruginosa*, use 2 g IV every 8 hours (50 mg per kg per dose in pediatric patients 2 months up to 16 years)

Patients with Hepatic Impairment

No adjustment is necessary for patients with hepatic impairment.

Patients with Renal Impairment

In patients with creatinine clearance less than or equal to 60 mL/min, the dose of CINAVEROS should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended doses of CINAVEROS in patients with renal impairment are presented in Table below.
When only serum creatinine is available, the following formula (Cockcroft and Gault equation)4 may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: Creatinine Clearance (mL/min) =

$$\frac{\text{Weight (kg) x (140–age)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 × above value

Table 7 : Recommended Dosing Schedule for CINAVEROS in Adult Patients (Normal Renal Function, Renal Impairment, and Hemodialysis)

Creatinine Clearance (mL/min)	**Recommended Maintenance Schedule**			
Greater than 60 Normal recommended dosing schedule	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 gm every 24 hours	2 gm every 24 hours	2 gm every 12 hours
11 to 29	500 mg every 24 hours	500 mg every 24 hours	1 gm every 24 hours	2 gm every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 gm every 24 hours
CAPD	500 mg every 48 hours	1 gm every 48 hours	2 gm every 48 hours	2 gm every 48 hours
Hemodialysis*	1 g on day 1, then 500 mg every 24 hours thereafter			1 gm 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, CINAVEROS may be administered at normally 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 CINAVEROS 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.

CINAVEROS should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days .

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients (see **CLINICAL PHARMACOLOGY**), changes in the dosing regimen proportional to those in adults are recommended for pediatric patients.

Administration

For Intravenous Infusion, Dilute with a suitable parenteral vehicle prior to intravenous infusion. Constitute the 500 mg, 1 g, or 2 g vial, and add an appropriate quantity of the resulting solution to an intravenous container with one of the compatible intravenous fluids listed in the **Compatibility and Stability** subsection. **THE RESULTING SOLUTION SHOULD BE ADMINISTERED 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.

Intramuscular Administration: For intramuscular administration, CINAVEROS (cefepime hydrochloride) should be constituted with one of the following diluent : sterile water for injection Preparation of CINAVEROS solutions is summarized in Table

Preparation of Solutions of CINAVEROS

Single-Dose Vials for Intravenous/Intramuscular Administration	**Amount of Diluent to be added (mL)**	**Approximate Available Volume (mL)**	**Approximate Cefepime Concentration (mg/mL)**
cefepime vial content			
500 mg (IV)	5	5.6	100
500 mg (IM)	1.3	1.8	280
1 g (IV)	10	11.3	100
1 g (IM)	2.4	3.6	280
2 g (IV)	10	12.5	160
ADD-Vantage			
1 g vial	50	50	20
1 g vial	100	100	10
2 g vial	50	50	40
2 g vial	100	100	20

Compatibility and Stability

Intravenous: CINAVEROS is compatible at concentrations between 1 mg per mL and 40 mg per mL with the following intravenous infusion fluids: 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, M/6 Sodium Lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection, Normosol™-R, and Normosol™-M in 5% Dextrose Injection. These solutions may be stored up to 24 hours at controlled room temperature not exceeding 30°C or 7 days in a refrigerator 2°C to 8°C .

CINAVEROS admixture compatibility information is summarized in The following Table.

Table: Cefepime Admixture Stability

CINAVEROS Concentration	Admixture and Concentration	IV Infusion Solutions	RT/L (not exceeding 30°C)	Refrigeration (2° to 8°C)
40 mg/mL	Amikacin 6 mg/mL	NS or D5W	24 hours	7 days
40 mg/mL	Ampicillin 1 mg/mL	D5W	8 hours	8 hours
40 mg/mL	Ampicillin 10 mg/mL	D5W	2 hours	8 hours
40 mg/mL	Ampicillin 1 mg/mL	NS	24 hours	48 hours
40 mg/mL	Ampicillin 10 mg/mL	NS	8 hours	48 hours
4 mg/mL	Ampicillin 40 mg/mL	NS	8 hours	8 hours
4 to 40 mg/mL	Clindamycin Phosphate .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	Aminosyn™ II 4.25% with electrolytes and calcium	8 hours	3 days
0.125 to 0.25 mg/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

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

Intramuscular: CINAVEROS (cefepime hydrochloride) constituted as directed is stable for 24 hours at controlled room temperature not exceeding 30°C or for 7 days in a refrigerator 2°C to 8°C with the following diluent: sterile water for injection.

NOTE: 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.

As with other cephalosporins, the color of CINAVEROS 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.

Cinaveros 1 gm vial contains :
Cefepime hydrochloride 1152.1 mg Eq. to 1000 mg cefepim base+L arginine 725 mg /vial

Cinaveros 0.5 gm vial contains :
Cefepime hydrochloride 576.05 mg Eq. to 500 mg cefepim base+L arginine 362.5 mg /vial

HOW SUPPLIED/STORAGE AND HANDLING

Cinaveros 1 gm vial pack & staorage :
Carton box containing 15ml transparent glass (type 1) vial containing 1877.1 mg powder closed with rubber stopper and capped by aluminum sheet provided with polyethylene disc + 2 polyethylene bottle of 5 ml sterile water for injection + inner leaflet .

To be stored at temperature not exceeding 30˚C in dry place & used after reconstitution at a week to be stored at a temperature of 2 - 8˚C

Cinaveros 0.5 gm vial pack & storage :
Carton box containing 15ml transparent glass (type 1) vial containing powder for 5 ml solution closed with rubber stopper and capped by aluminum sheet provided with polyethylene disc + 2 polyethylene bottle of 5 ml sterile water for injection + inner leaflet.

Manufactured by: T3A Industrial for Averroes Pharma for pharmaceutical industries