SUMMARY OF PRODUCT CHARACTERISTICS

1.**Name of the medicinal product**

Cefepime for Injection USP 1000 mg

2.**Qualitative and quantitative composition**

Each vial contains:

Cefepime Hydrochloride USP

Equivalent to Cefepime ……..1000 mg

(Sterile mixture of Cefepime HCl & L-Arginine)

3. Pharmaceutical form

Dry Powder for Injection

White to pale yellow powder contained in 20ml flint USP type III glass vials sealed with 20 mm grey butyl rubber stopper and 20 mm pink colored flip off aluminum seal.

4.**Clinical particulars**

4.1**Therapeutic indications**

Cefepime for injection is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Pneumonia (moderate to severe): caused by Streptococcus pneumonia, including cases associated with concurrent bacteremia, Pseudomonas aeruginosa, Klebsiella pneumonia, 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 pneumonia, when the infection is severe, or caused by Escherichia coli, Klebsiella pneumonia, 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 pneumonia, Enterobacter species, or Bacteroides fragilis.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefepime for injection and other antibacterial drugs, Cefepime for injection 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.

4.2 Posology and method of administration

Dosage for Adults:

The recommended adult dosages and routes of administration are outlined in Table 1 below for patients with creatinine clearance greater than 60 mL/min. Administer CEFEPIME intravenously over approximately 30 minutes.

Table 1: Recommended Dosage Schedule for Cefepime in Adult Patients with Creatinine Clearance (CrCL) Greater Than 60 mL/min Duration

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 cefepimemum 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 (see below).
- 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 CEFEPIME 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 CEFEPIME should be the same as in patients with CrCL greater than 60 mL/min except in patients undergoing hemodialysis. The recommended doses of CEFEPIMEPIME in patients with renal impairment are presented in Table 2.

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:

Males: weight in kg) x (140 – age)

(72) x serum creatinine (mg/100 mL)

Females: (0.85) x (above value)

Table 2: Recommended Dosing Schedule for CEFEPIME in Adult Patients With Creatinine Clearance Less Than or Equal to 60 mL/min Creatinine Recommended Maintenance Schedule Clearance (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 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			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), CEFEPIME may be administered at the recommended doses at a dosage interval of every 48 hours (see Table 2).

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 CEFEPIME 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.

CEFEPIME should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see Table 2).

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 1 and 2) are recommended for pediatric patients.

Reconstitution:

Intravenous Infusion:

Constitute the 1 or 2 g piggy back (100 ml) bottle with 50 or 100 ml of a compatible IV fluid. Intermittent IV 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 IM administration, CEFICAD (Cefepime HCl) should be constituted with one of the following diluents: sterile water for injection, 0.9% sodium chloride, 5% dextrose injection, 0.5% or 1.0% lidocaine hydrochloride, or sterile bacteriostatic water for injection with parabens or benzyl alcohol. In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime Hydrochloride may be administered at normally recommended doses at a dosage interval of every 48 hours

Compatibility and Stability:

Intravenous:

CEFICAD (Cefepime HCl) is compatible at concentrations between 1 mg/ml and 40 mg/ml with the following IV infusion fluids: 0.9% sodium chloride, 5 % and 10% dextrose injection, M/6 sodium lactate injection, 5% dextrose and 0.9% sodium chloride injection, lactated ringers and 5% dextrose injection. These solutions may be stored up to 24 hours at controlled room temperature 20-25°C (68-77°F) or 7 days in a refrigerator 2-8°C (36-46°F). Solutions of cefepime HCl, like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/ml, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with CEFICAD (Cefepime HCl) is indicated, each of these antibiotics can be administered separately.

Intramuscular:

CEFICAD (Cefepime Hydrochloride) constituted as directed is stable for 24 hours at controlled room temperature 20-25°C (68-77°F) or for 7 days in a refrigerator 2-8°C (36-46°F).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy.

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 the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus. 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, discontinue cefepime and institute appropriate supportive measures.

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 antibacterial drug 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 antibacterial drug 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.

Development of Drug-Resistant Bacteria:

Prescribing CEFEPIME in the absence of a proven or strongly suspected bacterial infection 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 nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

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 (e.g. Clinitest™ tablets).

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 antibiotics 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.

Nonclinical Toxicology:

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal carcinogenicity studies have been conducted with cefepime. In chromosomal aberration studies, cefepime was positive for clastogenicity in primary human lymphocytes, but negative in Chinese hamster ovary cells. In other in vitro assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes, and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Moreover, in vivo assessments of cefepime in mice (2 chromosomal aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a body surface area basis).

Use in Specific Populations:

Pregnancy:

Pregnancy Category B: There are 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.

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a body surface area basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a body surface area basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum human dose calculated on a body surface area basis).

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 in very low quantities. Caution should be exercised when cefepime is administered to a nursing woman.

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 CEFEPIME in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and

safety data from pediatric trials.

Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of CEFEPIME in pediatric patients for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is H. 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:

Of the more than 6400 adults treated with CEFEPIME in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in non-geriatric adult patients. 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.

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.

Renal Impairment:

Adjust the dose of CEFEPIME 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 adjustment is necessary for patients with hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Drug/Laboratory Test Interactions: The administration of cefepime may result in a false-positive reaction for glucose in the urine with certain methods. 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.

4.6 Pregnancy and lactation

Pregnancy:

Pregnancy Category B: There are 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.

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a body surface area basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a body surface area basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum human dose calculated on a body surface area basis).

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.

4.7 Effects on ability to drive and use machines

Be careful driving or operating machinery until you know how cefepime injection affects you. Cefepime injection generally does not cause any problems with your ability to drive a car or operate machinery. However as with other medicines, cefepime injection may cause dizziness, drowsiness or tiredness in some people.

4.8 Undesirable effects

The following adverse reactions are discussed in the Warnings and Precautions section and below:

- Hypersensitivity Reactions
- Neurotoxicity
- Clostridium difficile-Associated Diarrhea

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g intravenous every 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse reactions. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse reactions was similar at daily doses of 500 mg, 1 g, and 2 g every 12 hours (0.8%, 1.1%, and 2%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses.

The following adverse reactions were identified in clinical trials conducted in North America (n=3125 cefepime-treated patients).

Adverse Reactions in Cefepime Multiple-Dose Dosing Regimens Clinical Trials in North America	
Incidence equal to or greater than 1%	Local adverse reactions (3%), including phlebitis(1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)

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 adverse reactions was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%).

The following adverse laboratory changes, with cefepime, were seen during clinical trials conducted in North America.

Adverse Laboratory Changes in Cefepime Multiple-Dose Dosing Regimens Clinical Trials in North America	
Incidence equal to or greater than 1%	Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased Alanine Transaminase (ALT) (2.8%), Aspartate Transaminase (AST) (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), Prothrombin Time (PT) (1.4%)
Incidence less than 1% but greater than 0.1%	Increased alkaline phosphatase, Blood Urea Nitrogen (BUN), calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, White Blood Cells (WBC)
* Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.	

A similar safety profile was seen in clinical trials of pediatric patients.

Postmarketing Experience:

The following adverse reactions have been identified during post-approval use of CEFEPIME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In addition to the adverse reactions reported during the North American clinical trials with cefepime, the following adverse reactions have been reported during worldwide postmarketing experience. Encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia, myoclonus, seizures, and nonconvulsive status epilepticus have been reported.

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 antibacterial drugs:

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

cholestasis, and pancytopenia.

4.9 Overdose

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.

5. Pharmacological properties 5.1

Pharmacodynamic properties

Mechanism of Action:

Cefepime is a cephalosporin antibacterial drug. Cefepime is a bactericidal drug 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. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Pharmacodynamics:

Similar to other beta-lactam antimicrobial agents, the time that the unbound plasma concentration of cefepime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamics relationship for cefepime has not been evaluated in patients.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters for cefepime in healthy adult male volunteers (n=9) following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in the following table. 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 over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n=7) receiving clinically relevant doses for a period of 9 days.

Mean Pharmacokinetic Parameters for Cefepime (±SD), Intravenous Administration			
Parameter	500 mg IM	1 g IM	2 g IM
Cmax, 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

Pharmacokinetic parameters for cefepime following a single intramuscular injection are summarized in the following table. 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.

Mean Pharmacokinetic Parameters for Cefepime (±SD), Intramuscular Administration			
Parameter	500 mg IM	1 g IM	2 g IM

Cmax, mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
Tmax, 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

Absorption:

Following intramuscular (IM) administration, cefepime is completely absorbed.

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 at a concentration of 0.5 mcg/mL. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day.
Concentrations of cefepime achieved in specific tissues and body fluids are listed in the the table below.

Mean Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g) Mean Time of Sample Mean Tissue or Fluid Dose/Route # of Patients Post-Dose Concentration				
Tissue or Fluid	Dose/Route	# of Patients	Mean Time of Sample Post-Dose (h)	Mean Concentration
Blister Fluid	2 g IV	6	1.5	81.4 mcg/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 mcg/g
Sputum	2 g IV	5	4	7.4 mcg/mL
Urine	500 mg IV	8	0 to 4	292 mcg/mL
	1 g IV	12	0 to 4	926 mcg/mL
	2 g IV	12	0 to 4	3120 mcg/mL
Bile	2 g IV	26	9.4	17.8 mcg/mL
Peritoneal Fluid	2 g IV	19	4.4	18.3 mcg/mL
Appendix	2 g IV	31	5.7	5.2 mcg/g
Gallbladder	2 g IV	38	8.9	11.9 mcg/g
Prostate	2 g IV	5	1	31.5 mcg/g

Data suggest that cefepime does cross the inflamed blood-brain barrier. The clinical relevance of these data is uncertain at this time.

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.

Specific Populations:

Patients with Renal impairment:

Cefepime pharmacokinetics have been investigated in patients with various degrees of renal impairment (n=30). 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.

Patients with Hepatic impairment:

The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1 g dose (n=11).

Geriatric Patients:

Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men (n=12) and women (n=12) 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.

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 (n=29) and every 12 hours (n=13) 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 (n=13), while Cmax, AUC, and t½ 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 drug 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. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Antimicrobial Activity:

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

Gram-negative Bacteria:

Enterobacter spp.

Escherichia coli

Klebsiella pneumoniae

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 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.

Gram-positive Bacteria:

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Staphylococcus saprophyticus

Streptococcus agalactiae

NOTE: Most isolates of enterococci, e.g., 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.

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar). The MIC should be interpreted according to criteria provided below in the table following Diffusion Techniques.

DiffusionTechniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. This procedure uses paper discs impregnated with 30 mcg cefepime to test the susceptibility of microorganisms to cefepime. The disk diffusion interpretive criteria are provided below.

Susceptibility Test Interpretive Criteria for Cefepime[¥]

Pathogen	Minimum Inhibitory Concentrations (mcg/ml)					Diameters
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae	≤2	4 to 8*	≥16	≥25	19 to 24*	≤18
Pseudomonas aeruginosa[§]	≤8	-	≥16	≥18	-	≤17
Streptococcus pneumoniae[b] non-meningitis isolates	≤1	2	≥4	-	-	-
Streptococcus pyogenes	≤0.5	-	-	≥24	-	-
Viridans group streptococci	≤1	2	≥4	≥24	22 to 23	≤21

[¥]For patients with renal impairment see Dosage and Administration.
*For isolates of *Enterobacteriaceae* with intermediate susceptibility, use a dose of 2 g every 8 hours in patients with normal renal function.

[§]For *P. aeruginosa,* use 2 g IV every 8 hours in patients with normal renal function
[b]For non-meningitis isolates, a penicillin MIC of < 0.06 mcg/ml (or oxacillin zone > 20 mm) can predict susceptibility to cefepime. Susceptibility of staphylococci to cefepime may be deduced from testing only penicillin and either cefoxitin or oxacillin.

A report of Susceptible (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of Intermediate (I) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test. Standard cefepime powder should provide the following range of MIC values noted in the table below. For the diffusion technique using the 30 mcg disc, the criteria in the following table should be achieved.

Acceptable Quality Control Ranges for Cefepime

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Escherichia coli ATCC 25922	0.015 to 0.12	31 to 37
Staphylococcus aureus ATCC 29213	1 to 4	-
Staphylococcus aureus ATCC 25923	-	23 to 29
Pseudomonas aeruginosa ATCC 27853	0.5 to 4	24 to 30
Streptococcus pneumoniae ATCC 49619	0.03 to 0.25	28 to 35

Haemophilus influenzae ATCC 49247	0.5 to 2	25 to 31
Neisseria gonorrhoeae ATCC 49226	0.015 to 0.06	37 to 46

Clinical Studies:

Febrile Neutropenic Patients:

The safety and efficacy of empiric cefepime monotherapy of febrile neutropenic patients have been assessed in two multicenter, randomized trials comparing cefepime monotherapy (at a dose of 2 g intravenously every 8 hours) to ceftazidime monotherapy (at a dose of 2 g intravenously every 8 hours). These studies comprised 317 evaluable patients. The following table describes the characteristics of the evaluable patient population.

Demographics of Evaluable Patients (First Episodes Only)

	Cefepime	Ceftazidime
Total	164	153
Median age (yr)	56 (range, 18 to 82)	55 (range, 16 to 84)
Male	86 (52%)	85 (56%)
Female	78 (48%)	68 (44%)
Leukemia	65 (40%)	52 (34%)
Other hematologic malignancies	43 (26%)	36 (24%)
Solid tumor	54 (33%)	56 (37%)
Median ANC nadir (cells/microliter)	20 (range, 0 to 500)	20 (range, 0 to 500)
Median duration of neutropenia (days)	6 (range, 0 to 39)	6 (range, 0 to 32)
Indwelling venous catheter	97 (59%)	86 (56%)
Prophylactic antibiotics	62 (38%)	64 (42%)

Bone marrow graft	9 (5%)	7 (5%)
SBP less than 90 mm Hg at entry	7 (4%)	2 (1%)
ANC = absolute neutrophil count; SBP = systolic blood pressure		

The following table describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

Pooled Response Rates for Empiric Therapy of Febrile Neutropenic Patients

	% Response	
	Cefepime	Ceftazidime
Outcome Measures	(n=164)	(n=153)
Primary episode resolved with no treatment modification, no new febrile episodes or infection, and oral antibiotics allowed for completion of treatment	51	55
Primary episode resolved with no treatment modification, no new febrile episodes or infection and no post-treatment oral antibiotics	34	39
Survival, any treatment modification allowed	93	97
Primary episode resolved with no treatment modification and oral antibiotics allowed for completion of treatment	62	67
Primary episode resolved with no treatment modification and no post-treatment oral antibiotics	46	51

Insufficient data exist to support the efficacy of cefepime monotherapy 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). No data are available in patients with septic shock.

Complicated Intra-Abdominal Infections:

Patients hospitalized with complicated intra-abdominal infections participated in a randomized, double-blind, multicenter trial comparing the combination of cefepime (2 g every 12 hours) plus intravenous metronidazole (500 mg every 6 hours) versus imipenem/cilastatin (500 mg every 6 hours) for a maximum duration of 14 days of therapy. The study was designed to demonstrate equivalence of the two therapies. The primary analyses were conducted on the population consisting of those with a surgically confirmed complicated infection, at least one pathogen isolated pretreatment, at least 5 days of treatment, and a 4 to 6 week follow-up assessment for cured patients. Subjects in the imipenem/cilastatin arm had higher APACHE II scores at baseline. The treatment groups were otherwise generally comparable with regard to their pretreatment characteristics. The overall clinical cure rate among the primary analysis patients was 81% (51 cured/63 evaluable patients) in the cefepime plus metronidazole group and 66% (62/94) in the imipenem/cilastatin group. The observed differences in efficacy may have been due to a greater proportion of patients with high APACHE II scores in the imipenem/cilastatin group.

5.3Preclinical safety data

Animal Toxicological

The dose- and time-dependent retinal toxicity of cefepime, a third generation cephalosporin, and using electroretinography was evaluated in pigmented rabbit eyes. Toxicity was evaluated following intravitreal doses ranging from 0.5 to 20mg/0.1ml (N=18). Electroretinographic patterns at one and two weeks indicated a toxic response to 20 mg of cefepime. B-waves were normal at one and two weeks for rabbits receiving doses of 0.5 to 10mg. Pharmacokinetic analysis after single intravitreal injection of 1 mg of cefepime (N = 3 rabbits/dose) disclosed the following vitreous fluid levels (µg/ml): 645 at 0h, 431 at 8h, 235 at 24h and 23 at 72h. Peak aqueous humor levels (56 µg/ml) were observed at 8h after injection. At 72h, µg/ml was detected in the aqueous fluid.

Teratogenic effects—Pregnancy Category B

Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/ day (4 times the recommended maximum human dose calculated on a mg/m2 basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/m2 basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m2 basis). 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal carcinogenicity studies have been conducted with cefepime. A battery of in vivo and in vitro genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests

indicated no definitive evidence of genotoxic potential. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m2 basis. Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with cefepime hydrochloride 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.

Animal Pharmacodynamics

Serum concentrations of cefepime were determined for four dosing regimes, 10 mg/kg or 20 mg/kg, given as single subcutaneous (SC) or intramuscular injections (IM) to dogs. Serial serum samples were analyzed for the presence of cefepime by high-performance liquid chromatography. In experiment 1, the overall mean (± SEM) serum concentration (for a 12-hour period) after a dose of 20 mg/kg for SC and IM routes (4.9 ± 0.74 micrograms/ml and 5.5 ± 0.63 micrograms/ml, respectively) was twice that for the 10 mg/kg dose given either SC or IM (2.2 ± 0.31 micrograms/ml and 2.8 ± 0.47 micrograms/ml, respectively). There was no significant difference (p greater than 0.05) in mean serum concentrations for SC and IM routes of administration at the same dosage. In subsequent experiments, 5 doses of cefepime (20 mg/kg) were administered IM at 12-hour (experiment 2) or 24-hour (experiment 3) intervals. The mean (± SEM) peak serum concentration was 12.1 ± 1.59 micrograms/ml, 2 hours after the 2nd injection in experiment 2. In experiment 3, the mean (± SEM) peak serum concentration was 10.9 ± 1.34 micrograms/ml, 4 hours after the 1st injection. Mean trough concentrations in experiment 2 were greater than or equal to 0.5 microgram/ml and less than or equal to 0.5 in experiment 3. Multiple IM doses produced transient edema at the injection site and mild lameness in all dogs. Cefepime was highly active against single canine isolates of Staphylococcus intermedius, Pseudomonas aeruginosa and Escherichia coli, with minimum inhibitory concentrations of 0.125 microgram/ml, 1 microgram/ml and 0.3 microgram/ml, respectively.

The efficacy of cefepime, a new broad-spectrum cephalosporin, was compared with those of cefpirome, ceftazidime, vancomycin, imipenem-cilastatin and penicillin G in a rat model of endocarditis caused by a methicillin-susceptible strain of Staphylococcus aureus. Rats were infected intravenously with approximately 10(5) cfu of a penicillin-resistant strain of S. aureus 24 h after placement of a catheter into the left ventricle of the heart via the carotid artery. Efficacy was evaluated by comparing bacterial counts in the cardiac vegetations of treated rats with those of untreated controls. Rats treated with cefepime, cefpirome, ceftazidime, imipenem-cilastatin and vancomycin showed a reduction in the number of bacteria recovered from cardiac vegetations compared with infected control animals; penicillin G was ineffective in this respect. Serum concentrations of the study antimicrobials were determined at selected times following the administration of a single subcutaneous dose. The pharmacokinetic parameters of the cephalosporins were similar in these animals. This study suggested that cefepime may be of value in the treatment of staphylococcal endocarditis.

Cefepime is a new parenteral cephalosporin antibiotic with excellent activity against a broad-spectrum of clinically important pathogens resistant to other new cephalosporins. A single bolus dose of 10, 20 or 40 mg/kg cefepime was given i.v. to male and female Sprague-Dawley rats from which blood and urine samples were collected. For statistical reasons, pharmacokinetic parameters (AUC, Kel) were derived by fitting an exponential curve to the plasma concentrations; subsequently, contrasts were made between the different doses for AUC and Kel and, in addition, plasma

concentrations observed after the first sampling time (Cmax). Cmax and AUC appeared to be linearly related to the administered dose in both males and females. The dose increased in the ratio 1:2:4 and mean Cmax in male and female rats increased in the ratio 1:2.3:4.1 and 1:2.3:4.4 respectively; similarly, AUC increased in the ratio 1:2.2:4.3 and 1:2.0:4.2 respectively. Deviations from linearity and proportionality were not significant (P0.05). The systemic clearance of cefepime in rats was 2.3 ml/min. The volume of distribution was about 60 ml and cefepime appears to be selectively distributed into the extracellular water. Plasma concentrations declined monoexponentially with a mean half-life of 15-20 min, which did not significantly change with increasing doses. The renal clearance of cefepime was 1.8 ml/min and approximately 80% of the dose was excreted in the urine unchanged; renal excretion of cefepime is the major route of elimination in rats. The elimination and distribution characteristics of cefepime in rats were similar to those observed in Man.

The pharmacokinetics of 14C-cefepime dihydrochloride (14C-CFPM) was studied in dogs after single intravenous administration at a dose of 20 mg/kg. Protein binding was also investigated both in vitro and in vivo. Blood level of radioactivity was 83.53 microns eq./ml at 5 minutes after single intravenous administration and declined biexponentially thereafter. The values of AUC and T1/2 were 229 microns eq.(.)hr/ml and 90 hours, respectively. Urinary and fecal excretion rates were 95.1% and 2.7%, respectively. The in vitro protein binding at 1 to 100 microns/ml of drug concentration was 7.9 to 12.7% in rat, 12.4 to 18.6% in human, and 12.5 to 14.5% in dog. In vivo protein binding, which increased with time after administration, was 10.8 to 92.9% in rat and 17.5 to 64.9% in dog at 5 minutes to 6 hours in influence of induced fever on the pharmacokinetics of intramuscularly administered cefepime in rabbits.

The effect of experimentally endotoxin induced fever on the pharmacokinetics of cefepime (75 mg/kg BW) administered intramuscularly to six rabbits was evaluated. The study was carried out in two consecutive phases separated by a two-week washout period. An infection was induced by an intravenous inoculation of 5 × 108 colony-forming units of Escherichia coli 24 h before the pharmacokinetic investigation. A quantitative microbiological assay was employed to measure the plasma cefepime concentrations using an agar-gel diffusion method with Bacillus subtilis ATCC 6633 as the test organism. Twenty-four hour after the injection, the rectal temperature in the infected animals increased by 1oC. There was a significant reduction in the elimination halflife by 21.8% in the febrile rabbits compared to healthy animals. In addition, the infection significantly increased the peak plasma concentrations by 11.9%, the mean residence time by 19.9%, the area under the plasma concentration- time curve by 53.6% and the area under the moment curve by 62.3%. In conclusion, the endotoxin-induced febrile state produced significant changes in the plasma levels as well as some of the pharmacokinetic variables of cefepime in rabbits.

6.Pharmaceutical particulars

6.1 List of excipients

Not applicable

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4Special precautions for storage

Store below 25°C. Protect from Light. Keep all medicines out of reach of children.

6.5Nature and contents of container

Ceficad 1000 is supplied in 20 ml, flint USP type III glass vials with 20 mm grey butyl rubber stopper & 20 mm aluminium flip off seals. Each vial is further packed in cartons.

6.6Special precautions for disposal and other handling

Use of freshly prepared solution is recommended.
Single Use vial.

7.Marketing authorisation holder

Cadila Pharmaceuticals Limited
Plot No. 1389, Trasad Road,
City: Dholka- 382 225, District: Ahmedabad,
Gujarat State, India

8.Marketing authorisation number(s)

04719/07030/REN/2019

9.Date of first authorisation/renewal of the authorization

07/05/2019

10.Date of revision of the text

July 2023