





7.2 Aminoglycosides

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

7.3 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no cases of cefepime exposure during pregnancy reported from postmarketing experience or from clinical trials. Available data from published observational studies and case reports over several decades with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes (*see Data*). Cefepime was not associated with adverse developmental outcomes in rats, mice, or rabbits when administered parenterally during organogenesis. The doses used in these studies were 1.6 (rats), approximately equal to (mice), and 0.3 times (rabbits) the recommended maximum human dose (*see Data*). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from case-control studies and case reports over several decades have not identified an association with cephalosporin use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Cefepime was not embryocidal and did not cause fetal malformations when administered parenterally during the period of organogenesis to rats at doses up to 1000 mg/kg/day, to mice at doses up to 1200 mg/kg/day, or to rabbits at doses up to 100 mg/kg/day. These doses are 1.6 times (rats), approximately equal to (mice), and 0.3 times (rabbits) the maximum recommended clinical dose based on body surface area.

8.2 Lactation

Risk Summary

Cefepime is present in human breast milk at low concentrations (approximately 0.5 mcg/mL) following a single intravenous dose of 1000 mg. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day (*see Data*). There is no information regarding the effects of cefepime on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cefepime and any potential adverse effects on the breastfed child from cefepime or from the underlying maternal condition.

Data

A pharmacokinetic study was conducted in 9 healthy lactating women to evaluate the concentrations of cefepime in plasma and breast milk following a single intravenous dose of 1000 mg. The mean breast milk concentrations of cefepime during the first 8 hours post-dose were approximately 0.5 mcg/mL and then declined and became undetectable between 12- and 24-hours post-dose. The mean cumulative breast milk excretion of cefepime over 24 hours was 0.01% of the administered dose. The pharmacokinetics of cefepime are similar between lactating and non-lactating women.

8.4 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 for injection 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 (*see Clinical Pharmacology (12.3)*). 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 for injection 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 meningial 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.

8.5 Geriatric Use

Of the more than 6,400 adults treated with cefepime for injection 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 (*see Warnings and Precautions (5.2), Adverse Reactions (6.2)*). 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 (12.3), Warnings and Precautions (5.2), Dosage and Administration 2.3*).

8.6 Renal Impairment

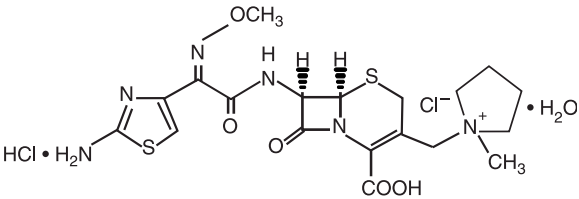
Adjust the dose of cefepime for injection in patients with creatinine clearance less than or equal to 60 mL/min to compensate for the slower rate of renal elimination (*see Dosage Adjustments in Patients with Renal Impairment (2.3)*).

10 OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability, and nonconvulsive status epilepticus (*see Warnings and Precautions (5.2), Adverse Reactions (6.2), Dosage and Administration (2.3)*).

11 DESCRIPTION

Cefepime for Injection, USP is a semi-synthetic, cephalosporin antibacterial for parenteral administration. The chemical name is 1-[[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride,7<sup>-</sup>-(Z)-(O-methyloxime), monohydrochloride, monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride is a white to pale yellow powder. Cefepime hydrochloride contains the equivalent of not less than 825 mcg and not more than 911 mcg of cefepime (C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>S) per mg, calculated on an anhydrous basis. It is highly soluble in water. Cefepime for Injection, USP is supplied for intramuscular or intravenous administration in strengths equivalent to 1 g, and 2 g of cefepime. Cefepime for Injection, USP is a sterile, dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of 707 mg/g of cefepime, is added to control the pH of the constituted solution at 4 to 6. Freshly constituted solutions of Cefepime for Injection, USP will range in color from pale yellow to amber.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cefepime is a cephalosporin antibacterial drug (*see Microbiology (12.4)*).

12.2 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.

12.3 Pharmacokinetics

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 Table 7. 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.

Table 7: Mean Pharmacokinetic Parameters for Cefepime (±SD), Intravenous Administration

Cefepime for Injection			
Parameter	500 mg IV	1 g IV	2 g IV
C <sub>max</sub> , 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 Table 8. 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 8: Mean Pharmacokinetic Parameters for Cefepime (±SD), Intramuscular Administration

Cefepime for Injection			
Parameter	500 mg IM	1 g IM	2 g IM
C <sub>max</sub> , mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T <sub>max</sub> , 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. Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 9.

Table 9: Mean Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)

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	3,120 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 (*see Dosage and Administration (2.3)*).

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 (*see Dosage and Administration (2.3)*).

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 (*see Dosage and Administration (2.3)*).

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 C<sub>max</sub>, AUC, and t<sub>1/2</sub> 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.

12.4 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, both *in vitro* and in clinical infections as described in the Indications and Usage section (1).

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*

*Haflnia 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 Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY

13.1 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 1,000 mg/kg/day (1.6 times the recommended maximum human dose based on body surface area).

14 CLINICAL STUDIES

14.1 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. Table 10 describes the characteristics of the evaluable patient population.

Table 10: 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 antibacterial drugs	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

Table 11 describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

Table 11: Pooled Response Rates for Empiric Therapy of Febrile Neutropenic Patients

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

14.2 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.

15 REFERENCES

- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31-41.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Cefepime for Injection, USP is supplied as follows:

Cefepime for Injection, USP in the dry state, is a white to pale yellow powder. Constituted solution of Cefepime for Injection, USP can range in color from pale yellow to amber.

Product Code	Unit of Sale	Strength	Each
320620	NDC 63323-326-20 Unit of 10	1 gram* per vial	NDC 63323-326-21
324020	NDC 63323-340-20 Unit of 10	2 grams* per vial	NDC 63323-340-21

\*Based on cefepime activity.

Storage and Handling

Cefepime for Injection, USP in the dry state should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use. Discard unused portion.

17 PATIENT COUNSELING INFORMATION

- Counsel patients that antibacterial drugs including cefepime for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefepime for injection 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 cefepime for injection or other antibacterial drugs in the future.
- Diarrhea is a common problem caused by antibacterial drugs, which usually ends when the antibacterial drug is discontinued. Inform patient that they may develop watery and bloody stools (with or without stomach cramps and fever) during treatment and as late as two or more months after having taken the last dose of the antibacterial drug. Inform patients that they should contact their physician as soon as possible if this occurs.
- Advise patients of neurological adverse events that could occur with cefepime for injection use. Instruct patients or their caregivers to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), aphasia (disturbance of speaking and understanding spoken and written language), myoclonus, seizures and nonconvulsive status epilepticus, for immediate treatment, dosage adjustment, or discontinuation of cefepime for injection.

The brand names mentioned in this document are the trademarks of their respective owners.

Manufactured for:



**FRESENIUS  
KABI**

Lake Zurich, IL 60047

Made in Brazil

[www.fresenius-kabi.com/us](http://www.fresenius-kabi.com/us)

4511280

BU06975