

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 1 of 24

Y36-002-807 LD-107-2

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Cefepime for Injection USP and Dextrose Injection USP safely and effectively. See full prescribing information for Cefepime for Injection USP and Dextrose Injection USP.

CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP IN DUPLEX® CONTAINER, for intravenous use

Initial U.S. Approval: 1996

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

INDICATIONS AND USAGE

Cefepime for Injection USP and Dextrose Injection USP is a cephalosporin antibacterial indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms: Moderate to severe pneumonia (1.1); empiric therapy for febrile neutropenic patients (1.2); uncomplicated and complicated urinary tract infections (1.3); moderate to severe uncomplicated skin and skin structure infections (1.4); and complicated intra-abdominal infections (used in combination with metronidazole) (1.5).

DOSAGE AND ADMINISTRATION

For intravenous use only over approximately 30 minutes. (2)

Use this formulation of cefepime only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)

Recommended Dosing Schedule in Adult Patients with CrCL >60 mL/min (2.1) [†]			
Site and Type of Infection	Dose	Frequency	Duration
Moderate to severe pneumonia	1 or 2 g IV	Every 12 hours	10 days
Empiric therapy for febrile neutropenic patients	2 g IV	Every 8 hours	7 days [‡]
Mild to moderate uncomplicated or complicated urinary tract infections	0.5 or 1 g IV	Every 12 hours	7-10 days
Severe uncomplicated or complicated urinary tract infections	2 g IV	Every 12 hours	10 days
Moderate to severe uncomplicated skin and skin structure infections	2 g IV	Every 12 hours	10 days
Complicated intra-abdominal infections (used in combination with metronidazole)	2 g IV	Every 12 hours	7-10 days

[†] Adjust dose in patients with CrCL less than or equal to 60 mL/min. (2.2)

[‡] Or until resolution of neutropenia. (2.1)

Pediatric Patients (2 months to 16 years)

- 50 mg per kg per dose every 12 hours (every 8 hours for febrile neutropenia). (2.1)
- Use this formulation of cefepime only in pediatric patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)

DOSAGE FORMS AND STRENGTHS

- 1 g in 50 mL and 2 g in 50 mL (3)

CONTRAINDICATIONS

- Hypersensitivity to cefepime or other cephalosporin class antibiotics, penicillins, or other beta-lactam antibiotics (4.1)
- Hypersensitivity to corn products (4.2)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Include anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug. (5.1)
- Use in patients with renal impairment: Dosage adjustment required for patients with CrCL ≤ 60 mL/min. (5.2)

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 2 of 24

- Neurotoxicity: May occur in patients receiving inappropriate dosage adjustment(s) for renal impairment. Discontinue cefepime or make appropriate dosage adjustments in patients with renal impairment in the event of neurotoxicity. (5.3)
- *Clostridium difficile*-associated diarrhea: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.4)

ADVERSE REACTIONS

- Most common adverse reactions (incidence >1%): Local reactions (including phlebitis, pain and/or inflammation) and rash. (6.1)
- At the highest dose (2 g every 8 hours), incidence of adverse reactions was $\geq 1\%$ for rash, diarrhea, nausea, vomiting, pruritis, fever, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Aminoglycosides: Increased potential of nephrotoxicity and ototoxicity. (7.1)
- Diuretics: Nephrotoxicity has been reported with concomitant administration of cephalosporins with potent diuretics such as furosemide. (7.2)

USE IN SPECIFIC POPULATIONS

- Geriatric use: Serious adverse reactions have occurred in geriatric patients with renal impairment given unadjusted doses of cefepime (5.2, 8.5)
- Pediatric use: Safety and efficacy not established in patients less than 2 months of age or for use in any pediatric patients with complicated intra-abdominal infections. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2012

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 3 of 24

FULL PRESCRIBING INFORMATION: CONTENTS*		5.10	Patients with Overt or Known Subclinical Diabetes Mellitus or Carbohydrate Intolerance
1	INDICATIONS AND USAGE	6	ADVERSE REACTIONS
1.1	Pneumonia	6.1	Clinical Trials Experience
1.2	Empiric Therapy for Febrile Neutropenic Patients	6.2	Postmarketing Experience
1.3	Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis)	6.3	Cephalosporin-class Adverse Reactions
1.4	Uncomplicated Skin and Skin Structure Infections	7	DRUG INTERACTIONS
1.5	Complicated Intra-abdominal infections	7.1	Aminoglycosides
2	DOSAGE AND ADMINISTRATION	7.2	Diuretics
2.1	Adult and Pediatric Population	8	USE IN SPECIFIC POPULATIONS
2.2	Patients with Renal Impairment	8.1	Pregnancy
2.3	Preparation for Use of Cefepime for Injection USP and Dextrose Injection USP in DUPLEX® Container	8.2	Labor and Delivery
3	DOSAGE FORMS AND STRENGTHS	8.3	Nursing Mothers
4	CONTRAINDICATIONS	8.4	Pediatric Use
4.1	Hypersensitivity to Cefepime or the Cephalosporin Class of Antibiotics, Penicillins, or Other Beta-lactam Antibiotics	8.5	Geriatric Use
4.2	Hypersensitivity to Corn Products	10	OVERDOSAGE
5	WARNINGS AND PRECAUTIONS	11	DESCRIPTION
5.1	Hypersensitivity Reactions to Cefepime, Cephalosporins, Penicillins, or Other Drugs	12	CLINICAL PHARMACOLOGY
5.2	Use in Patients with Renal Impairment	12.1	Mechanism of Action
5.3	Neurotoxicity	12.2	Pharmacodynamics
5.4	<i>Clostridium difficile</i> -associated Diarrhea	12.3	Pharmacokinetics
5.5	Risk of Development of Drug resistant Bacteria	12.4	Microbiology
5.6	Patients with Meningeal Seeding/Meningitis	13	NONCLINICAL TOXICOLOGY
5.7	Drug/Laboratory Test Interactions	13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
5.8	Patients with a History of Gastrointestinal Disease	14	CLINICAL STUDIES
5.9	Possible Effects of Arginine on Glucose Metabolism	14.1	Febrile Neutropenic Patients
		14.2	Complicated Intra-abdominal Infection
		15	REFERENCES
		16	HOW SUPPLIED/STORAGE AND HANDLING
		17	PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 4 of 24

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Pneumonia

Cefepime for Injection USP and Dextrose Injection USP is indicated for pneumonia (moderate to severe) caused by *Streptococcus pneumoniae* (including cases associated with concurrent bacteremia), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.

1.2 Empiric Therapy for Febrile Neutropenic Patients

Cefepime for Injection USP and Dextrose Injection USP 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 [see *Clinical Studies (14.1)*].

1.3 Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis)

Cefepime for Injection USP and Dextrose Injection USP is indicated for 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.

1.4 Uncomplicated Skin and Skin Structure Infections

Cefepime for Injection USP and Dextrose Injection USP is indicated for moderate to severe uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

1.5 Complicated Intra-abdominal Infections

Cefepime for Injection USP and Dextrose Injection USP is indicated for 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* [see *Clinical Studies (14.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Adult and Pediatric Population

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container should be used only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. The recommended adult and pediatric dosages and routes of administration are outlined in Table 1. Cefepime for Injection USP and Dextrose Injection USP should be administered intravenously (IV) over approximately 30 minutes.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
 CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Table 1: Recommended Dosing Schedule for Cefepime for Injection USP and Dextrose Injection USP in Patients with CrCL Greater Than 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration (days)
Adults			
Moderate to Severe Pneumonia due to <i>S. pneumoniae</i> *, <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , or <i>Enterobacter</i> species	1 or 2 g IV	Every 12 hours	10
Empiric therapy for febrile neutropenic patients [see <i>Indications and Usage (1)</i> and <i>Clinical Studies (14)</i>]	2 g IV	Every 8 hours	7**
Mild to moderate uncomplicated or complicated urinary tract infections, including pyelonephritis, due to <i>E. coli</i> , <i>K. pneumoniae</i> , or <i>P. mirabilis</i> *	0.5 or 1 g IV	Every 12 hours	7-10
Severe uncomplicated or complicated urinary tract infections, including pyelonephritis, due to <i>E. coli</i> or <i>K. pneumoniae</i> *	2 g IV	Every 12 hours	10
Moderate to severe uncomplicated skin and skin structure infections due to <i>S. aureus</i> or <i>S. pyogenes</i>	2 g IV	Every 12 hours	10
Complicated intra-abdominal infections (used in combination with metronidazole) caused by <i>E. coli</i> , viridans group streptococci, <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>Enterobacter</i> species, or <i>B. fragilis</i> . [see <i>Clinical Studies (14)</i>]	2 g IV	Every 12 hours	7-10

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.

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container is designed to deliver a 1 g or 2 g dose of cefepime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefepime.

* 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.

2.2 Patients with Renal Impairment

In patients with creatinine clearance less than or equal to 60 mL/min, the dose of Cefepime for Injection USP and Dextrose Injection USP should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of Cefepime for Injection USP and Dextrose Injection USP should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended maintenance doses of Cefepime for Injection USP and Dextrose Injection USP in patients with renal impairment are presented in Table 2. Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container should be used only in patients who require the entire 1 or 2 gram dose and not any fraction thereof.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
 CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)¹ may be used to estimate creatinine clearance [see *References (15)*]. The serum creatinine should represent a steady state of renal function:

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

Females: 0.85 x above value

Table 2: Recommended Dosing Schedule for Cefepime for Injection USP and Dextrose Injection USP 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
30-60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11-29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours
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 for Injection USP and Dextrose Injection USP should be administered following hemodialysis. Whenever possible, Cefepime for Injection USP and Dextrose Injection USP should be administered at the same time each day.

In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime for Injection USP and Dextrose Injection USP may be administered at normally 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 Injection USP and Dextrose Injection USP 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 for Injection USP and Dextrose Injection USP should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see Table 2).

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 7 of 24

2.3 Preparation for Use of Cefepime for Injection USP and Dextrose Injection USP in DUPLEX® Container

This reconstituted solution is for intravenous use only.

Do not use plastic containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

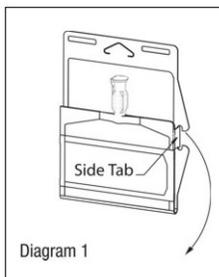
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use only if solution is clear and container and seals are intact.

DUPLEX® Drug Delivery System Storage

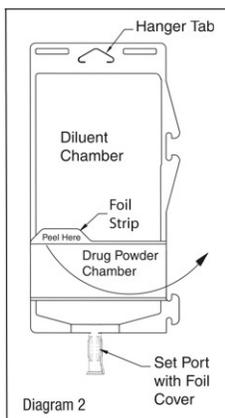
- To avoid inadvertent activation, the DUPLEX® Container should remain in the folded position until activation is intended.

Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. Use care to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX® Container (see *Diagram 1*).



- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber (see *Diagram 2*).



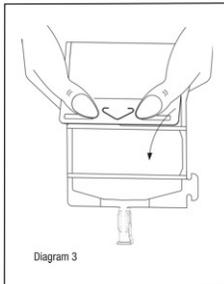
1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 8 of 24

- Protect from light after removal of foil strip.

Note: If foil strip is removed, the container should be re-folded and the side tab latched until ready to activate. The product must then be used within 7 days, but not beyond the labeled expiration date.

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX® container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber (see *Diagram 3*).

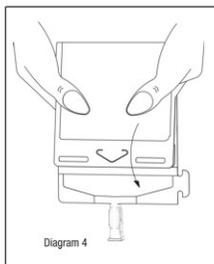


- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

Note: Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 5 days if stored under refrigeration.

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX® Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port (see *Diagram 4*).

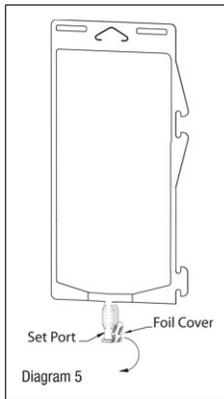


- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be compromised.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 9 of 24

- Using aseptic technique, peel foil cover from the set port and attach sterile administration set (see *Diagram 5*).



- Refer to directions for use accompanying the administration set.

Important Administration Instructions

- Do not use in series connections.
- Do not introduce additives into the DUPLEX® Container.
- Administer Cefepime for Injection USP and Dextrose Injection USP intravenously over approximately 30 minutes.
- Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of Cefepime for Injection USP and Dextrose Injection USP, it is advisable to discontinue the other solution.
- Solutions of cefepime 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 cefepime is indicated, each of these antibiotics can be administered separately.

3 DOSAGE FORMS AND STRENGTHS

Dual-chamber, single-use container:

- 1 g cefepime for injection USP and 50 mL of 5% dextrose injection USP
- 2 g cefepime for injection USP and 50 mL of 5% dextrose injection USP

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Cefepime or the Cephalosporin Class of Antibiotics, Penicillins, or Other Beta-lactam Antibiotics

Cefepime for Injection USP and Dextrose Injection USP is contraindicated in patients who have a history of immediate hypersensitivity reactions (e.g., anaphylaxis, serious skin reactions) to cefepime or the cephalosporin class of antibiotics, penicillins, or other beta-lactam antibiotics [see *Warnings and Precautions (5.1)*].

4.2 Hypersensitivity to Corn Products

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions to Cefepime, Cephalosporins, Penicillins, or Other Drugs

Before therapy with Cefepime for Injection USP and Dextrose Injection USP 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 Cefepime for Injection USP and Dextrose Injection USP 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.

5.2 Use in Patients with Renal Impairment

In patients with creatinine clearance less than or equal to 60 mL/min, the dose of Cefepime Injection should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged cefepime concentrations can occur from usual dosages in patients with renal impairment or other conditions that may compromise renal function, the maintenance dosage should be reduced when Cefepime Injection is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. Refer to specific recommendations for dosing adjustment [see *Dosage and Administration (2.2)*].

5.3 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 (6.2)*]. 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.

5.4 *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*.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 11 of 24

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.

5.5 Risk of Development of Drug-resistant Bacteria

Prescribing Cefepime for Injection USP and Dextrose Injection USP in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of Cefepime for Injection USP and Dextrose Injection USP 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.

5.6 Patients with Meningeal Seeding/Meningitis

In those patients in whom meningeal seeding from a distant infection site or in whom meningitis is suspected or documented, an alternate drug with demonstrated clinical efficacy in this setting should be used.

5.7 Drug/Laboratory Test Interactions

Urinary Glucose

The administration of cefepime may result in a false-positive reaction with glucose in the urine when using CLINITEST® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (e.g., CLINISTIX®) be used.

Coombs' Test

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.

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.

5.8 Patients with a History of Gastrointestinal Disease

Cefepime for Injection USP and Dextrose Injection USP should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

5.9 Possible Effects of Arginine on Glucose Metabolism

Cefepime for Injection USP and Dextrose Injection USP contains arginine. 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.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 12 of 24

5.10 Patients with Overt or Known Subclinical Diabetes Mellitus or Carbohydrate Intolerance

As with other dextrose-containing solutions, Cefepime for Injection USP and Dextrose Injection USP should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- Renal Impairment [see *Warnings and Precautions (5.2)*]
- Neurotoxicity [see *Warnings and Precautions (5.3)*]
- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 intravenously 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 thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these sixty-four 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 2.0%, respectively).

However, the incidence of discontinuation due to rash increased with the higher recommended doses.

The following adverse reactions were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n=3125 cefepime-treated patients).

Table 3: Adverse Clinical Reactions Cefepime Multiple-dose Dosing Regimens Clinical Trials – North America

Incidence equal to or greater than 1%	Local reactions* (3.0%), 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, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

* Local reactions, irrespective of relationship to cefepime in those patients who received intravenous infusion (n=3048).

At the higher dose of 2 g every 8 hours, the incidence of probably-related adverse reactions was higher among the 795 patients who received this dose of cefepime. Reactions included rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%).

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 13 of 24

The following adverse laboratory changes, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

Table 4: Adverse Laboratory Changes Cefepime Multiple-dose Dosing Regimens Clinical Trials – North America

Incidence equal to or greater than 1%	Positive Coombs' Test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%); eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
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.

6.2 Postmarketing Experience

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

Anaphylaxis (including anaphylactic shock, transient leukopenia, neutropenia, agranulocytosis and thrombocytopenia) has been reported.

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.

6.3 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 impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

7 DRUG INTERACTIONS

7.1 Aminoglycosides

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with Cefepime for Injection USP and Dextrose Injection USP because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

7.2 Diuretics

Nephrotoxicity has been reported following concomitant administration of cephalosporins with potent diuretics such as furosemide.

8 USE IN SPECIFIC POPULATIONS

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 14 of 24

8.1 Pregnancy

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 (1.6 times the recommended maximum human dose calculated on a mg/m² basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m² basis) or to rabbits at a dose level of 100 mg/kg (0.3 times 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.

8.2 Labor and Delivery

Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.

8.3 Nursing Mothers

Cefepime is excreted in human breast milk in very low concentrations (0.5 mcg/mL) [see *Clinical Pharmacology* (12.3)]. Caution should be exercised when cefepime is administered to a nursing woman.

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 USP and Dextrose Injection USP 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 efficacy in pediatric patients for the treatment of complicated intra-abdominal infections have not been established.

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 USP and Dextrose Injection USP 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.

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container should be used only in pediatric patients who require the entire 1 or 2 gram dose and not any fraction thereof.

8.5 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 nongeriatric adult patients.

Serious adverse reactions have occurred in geriatric patients with renal impairment given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, seizures, and nonconvulsive status epilepticus [see *Adverse Reactions* (6.2)].

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 15 of 24

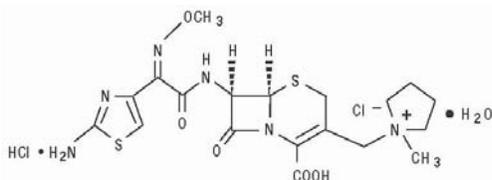
Cefepime is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.2), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Carefully observe patients who receive an overdose of cefepime, and give supportive treatment as appropriate. In the presence of renal impairment, 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, nonconvulsive status epilepticus, and neuromuscular excitability [see *Warnings and Precautions* (5.2)].

11 DESCRIPTION

Cefepime hydrochloride, USP is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[[(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(*Z*)-(O-methyloxime), monohydrochloride, monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular formula of C₁₉H₂₅ClN₆O₅S₂•HCl•H₂O.

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 (C₁₉H₂₄N₆O₅S₂) per mg, calculated on an anhydrous basis. It is highly soluble in water.

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® dual chamber container is supplied for intravenous administration in strengths equivalent to 1 g and 2 g of cefepime. Cefepime for Injection USP and Dextrose Injection USP is supplied as a sterile, nonpyrogenic, single-use packaged combination of cefepime hydrochloride with L-arginine (drug chamber) and 50 mL of 5% dextrose injection (diluent) in the DUPLEX® sterile container.

The powder chamber of the DUPLEX® container contains a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of cefepime (C₁₉H₂₄N₆O₅S₂). The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the reconstituted solution at 4.0 - 6.0.

The DUPLEX® container is a flexible dual chamber container. After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is hyperosmotic and is intended for single intravenous use. Each 50 mL contains cefepime hydrochloride equivalent to either 1 gram or 2 grams of cefepime. Reconstituted solutions of Cefepime for Injection USP and Dextrose Injection USP range in color from colorless to amber.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 16 of 24

The DUPLEX® Container is Latex-free, PVC-free, and Di(2-ethylhexyl)phthalate (DEHP)-free.

The DUPLEX® dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cefepime is an antibacterial drug [see *Clinical Pharmacology* (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/pharmacodynamic relationship for cefepime has not been evaluated in patients.

12.3 Pharmacokinetics

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n=9) at various times following single 30-minute IV infusions of cefepime 500 mg, 1 g, and 2 g are summarized in Table 5. Elimination of cefepime is principally via renal excretion with an average (\pm SD) half-life of 2 (\pm 0.3) hours and total body clearance of 120 (\pm 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 5: Average Plasma Concentrations (in mcg/mL) of Cefepime and Derived Pharmacokinetic Parameters (\pm SD), Intravenous Administration

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

Distribution

The average steady-state volume of distribution of cefepime is 18.0 (\pm 2.0) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
 CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

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 *Use in Specific Populations (8.3)*].

Concentrations of cefepime achieved in specific tissues and body fluids are listed in Table 6.

Table 6: Average Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)

Tissue or Fluid	Dose/Route	# of Patients	Average Time of Sample Post-Dose (h)	Average 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	0-4	292 mcg/mL
	1 g IV	12	0-4	926 mcg/mL
	2 g IV	12	0-4	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 are 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 (2.2)*].

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 (±2.0) 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 (2.2)*].

Patients with Hepatic Impairment

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 18 of 24

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 74.0 (\pm 15.0) 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* (2.2)].

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 (\pm 1.0) mL/min/kg and 0.3 (\pm 0.1) L/kg, respectively. The urinary recovery of unchanged cefepime was 60.4 (\pm 30.4) % of the administered dose, and the average renal clearance was 2.0 (\pm 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_{max} , AUC, and $t_{1/2}$ 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.

12.4 Microbiology

Antibacterial 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. 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* (1) section.

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

The following *in vitro* data are available, but their clinical significance is unknown. Cefepime has been shown to have *in vitro* activity against most isolates of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 19 of 24

- Gram-Negative Bacteria:
 - Acinetobacter calcoaceticus* subsp. *lwoffii*
 - Citrobacter diversus*
 - Citrobacter freundii*
 - Enterobacter agglomerans*
 - Haemophilus influenzae* (including beta-lactamase producing isolates)
 - Hafnia alvei*
 - Klebsiella oxytoca*
 - Moraxella catarrhalis* (including beta-lactamase producing isolates)
 - Morganella morganii*
 - Proteus vulgaris*
 - Providencia rettgeri*
 - Providencia stuartii*
 - Serratia marcescens*Cefepime is inactive against many isolates of *Stenotrophomonas* (formerly *Xanthomonas maltophilia* and *Pseudomonas maltophilia*).
- Gram-Positive Bacteria:
 - Staphylococcus epidermidis* (methicillin-susceptible isolates only)
 - Staphylococcus saprophyticus*
 - Streptococcus agalactiae* (Lancefield's Group B streptococci)Most isolates of enterococci (e.g., *Enterococcus faecalis* and methicillin-resistant staphylococci) are resistant to cefepime.
- Anaerobic Microorganisms:
 - Cefepime is inactive against most isolates of *Clostridium difficile*.

Susceptibility Test Methods

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)² [see *References (15)*]. The MIC values should be interpreted according to criteria provided in Table 7.

Diffusion Technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method³ [see *References (15)*]. This procedure uses paper disks impregnated with 30 mcg cefepime to test the susceptibility of microorganisms to cefepime. The disk diffusion interpretive criteria are provided in Table 7.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
 CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion (Zone diameters in mm)		
	S	I	R		I	R
Bacteria other than <i>S. pneumoniae</i> *	≤8	16	≥32		15-17	≤14
<i>S. pneumoniae</i> *	≤0.5	1	≥2	-	-	-

* Isolates from these species should be tested for susceptibility using specialized dilution testing methods² [see *References (15)*]

A report of “susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” 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 high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; 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^{2,3} [see *References (15)*]. Standard cefepime powder should provide the following MIC values noted in Table 8. For the diffusion technique using the 30 mcg disk, the criteria in Table 8 should be achieved.

QC Strain	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion Range (Zone diameters in mm)
<i>Escherichia coli</i> ATCC® 25922	0.016 - 0.12	29-35
<i>Staphylococcus aureus</i> ATCC® 29213	1-4	-
<i>Staphylococcus aureus</i> ATCC® 25923	-	23-29
<i>Pseudomonas aeruginosa</i> ATCC® 27853	1-4	24-30
<i>Streptococcus pneumoniae</i> ATCC® 49619	0.06-0.25	-

1.14.1.2 ANNOTATED DRAFT LABELING TEXT CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP

Page 21 of 24

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 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a mg/m² basis).

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 9 describes the characteristics of the evaluable patient population.

Table 9: Demographics of Evaluable Patients (First Episodes Only)

	Cefepime n=164	Ceftazidime n=153
Total		
Median age (yr)	56.0 (range, 18-82)	55.0 (range, 16-84)
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, 0-500)	20 (range, 0-500)
Median duration of neutropenia (days)	6 (range, 0-39)	6 (range, 0-32)
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

Table 10 describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
 CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
 Page 22 of 24

Table 10: Pooled Response Rates for Empiric Therapy of Febrile Neutropenic Patients

Outcome Measures	% Response	
	Cefepime (n=164)	Ceftazidime (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.

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 protocol-valid population, which consisted 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 protocol-valid 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

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31–41.
2. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* – 8th Edition. Approved CLSI Standard. Document M07-A8, CLSI, Wayne, PA, 2009.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests* – 10th Edition. Approved CLSI Standard Document M02- A10, CLSI, Wayne, PA, 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Drug Delivery System is a flexible dual chamber container supplied in two strengths, 1 and 2 g cefepime. The diluent chamber contains approximately 50 mL of 5% Dextrose Injection.

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 23 of 24

Cefepime for Injection USP and Dextrose Injection USP is supplied sterile and nonpyrogenic in the DUPLEX® Drug Delivery System containers packaged 24 units per case.

<u>NDC</u>	<u>REF</u>	<u>Dose</u>	<u>Volume</u>
0264-3193-11	3193-11	1 g	50 mL
0264-3195-11	3195-11	2 g	50 mL

Store the unactivated unit at 20–25°C (68–77°F). Excursions permitted to 15–30°C (59–86°F). [See USP Controlled Room Temperature.] Do not freeze.

As with other cephalosporins, reconstituted Cefepime for Injection USP and Dextrose Injection USP tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.

Use only if prepared solution is clear and free from particulate matter.

17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment and discontinuation of cefepime. Patients should report to their health care provider any previous allergic reactions to cefepime, cephalosporins, penicillins, or other similar antibiotics.

Advise patients of neurological adverse reactions that could occur with Cefepime for Injection USP and Dextrose Injection USP use. Instruct patients to inform a healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures, for immediate treatment, dosage adjustment, or discontinuation of Cefepime for Injection USP and Dextrose Injection USP.

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 a physician as soon as possible.

Patients should be counseled that antibacterial drugs, including Cefepime for Injection USP and Dextrose Injection USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefepime for Injection USP and Dextrose Injection USP 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 USP and Dextrose Injection USP or other antibacterial drugs in the future.

Rx only

1.14.1.2 ANNOTATED DRAFT LABELING TEXT
CEFEPIME FOR INJECTION USP AND DEXTROSE INJECTION USP
Page 24 of 24

DUPLEX is a registered trademark of B. Braun Medical Inc.
ATCC is a registered trademark of the American Type Culture Collection
Clinitest is a registered trademark of Siemens Healthcare Diagnostics Inc.
Clinistix is a registered trademark of Bayer HealthCare LLC.
Apache is a registered trademark of Cerner Innovation, Inc.

U.S. Patent Nos. 5,944,709, 6,165,161, 6,203,535, 6,846,305, and 6,996,951.

B. Braun Medical Inc.

Irvine, CA 92614-5895 USA
1-800-227-2862
www.bbraun.com
Made in USA.