MAXIPIME™

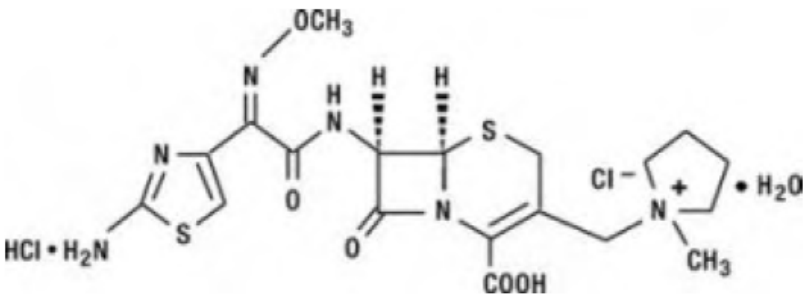
(Cefepime Hydrochloride, USP) for Injection

For Intravenous or Intramuscular Use

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

DESCRIPTION

MAXIPIME (cefepime hydrochloride, USP) is a semi-synthetic, broad spectrum, cephalosporin antibiotic 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,7^2-(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 ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on an anhydrous basis. It is highly soluble in water.

MAXIPIME for Injection is supplied for intramuscular or intravenous administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. (See **DOSAGE AND ADMINISTRATION**.) MAXIPIME is a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90 percent and not more than 115 percent of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$). 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 MAXIPIME will range in color from pale yellow to amber.

CLINICAL PHARMACOLOGY

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

Pharmacokinetics

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n=9) at various times following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in Table 1. 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.

Absorption

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

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

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

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single intramuscular injection are summarized in Table 2. 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 2: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (±SD), Intramuscular Administration

	MAXIPIME		
Parameter	**500 mg IM**	**1 g IM**	**2 g IM**
0.5 h	8.2	14.8	36.1
1 h	12.5	25.9	49.9
2 h	12	26.3	51.3
4 h	6.9	16	31.5
8 h	1.9	4.5	8.7
12 h	0.7	1.4	2.3
C_{max}, mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T_{max}, h	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, h•mcg/mL	60 (8)	137 (11)	262 (23)
Number of subjects (male)	6	6	12

Distribution

The average steady-state volume of distribution of cefepime is 18 (±2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

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

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

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

Tissue or Fluid	Dose/Route	# 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 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. (See **DOSAGE AND ADMINISTRATION**.)

Specific Populations

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**.)

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**.)

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_{max}, AUC, and $t_{½}$ were increased about 15% at steady state after 50 mg per kg every 8 hours. The exposure to cefepime following a 50 mg per kg intravenous dose in a pediatric patient is comparable to that in an adult treated with a 2 g intravenous dose. The absolute bioavailability of cefepime after an intramuscular dose of 50 mg per kg was 82.3 (±15)% in eight patients.

Microbiology

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of Gram-positive and Gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into Gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

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

Aerobic Gram-Negative Microorganisms:

Enterobacter

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Aerobic Gram-Positive Microorganisms:

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.

Aerobic Gram-Positive Microorganisms:

Staphylococcus epidermidis (methicillin-susceptible isolates only)

Staphylococcus saprophyticus

Streptococcus agalactiae (Lancefield's Group B streptococci)

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

Aerobic Gram-Negative Microorganisms:

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

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

Anaerobic Microorganisms:

NOTE: Cefepime is inactive against most isolates of *Clostridium difficile*.

Susceptibility Tests

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 procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefepime powder. The MIC values should be interpreted according to the following criteria:

Table 4

	MIC (mcg/mL)		
Microorganism	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Microorganisms other than *Haemophilus* spp.* and *Streptococcus pneumoniae**	≤8	16	≥32
Haemophilus spp.*	≤2	—*	—*
*S. pneumoniae**	≤0.5	1	≥2

*NOTE: Isolates from these species should be tested for susceptibility using specialized dilution testing methods.[1] Also, isolates of *Haemophilus* spp. with MICs greater than 2 mcg/mL should be considered equivocal and should be further evaluated.

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.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. Standard cefepime powder should provide the following MIC values (Table 5) when tested against the designated quality control strains:

Table 5

Microorganism	ATCC	MIC (mcg/mL)
Escherichia coli	25922	0.016 to 0.12
Staphylococcus aureus	29213	1 to 4
Pseudomonas aeruginosa	27853	1 to 4
Haemophilus influenzae	49247	0.5 to 2
Streptococcus pneumoniae	49619	0.06 to 0.25

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of cefepime to test the susceptibility of microorganisms to cefepime. Interpretation is identical to that stated above for results using dilution techniques.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefepime disk should be interpreted according to the following criteria:

Table 6

	Zone Diameter (mm)		
Microorganism	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Microorganisms other than *Haemophilus* spp.* and *S. pneumoniae**	≥18	15 to 17	≤14
Haemophilus spp.*	≥26	—*	—*

*NOTE: Isolates from these species should be tested for susceptibility using specialized diffusion testing methods.[2] Isolates of *Haemophilus* spp. with zones smaller than 26 mm should be considered equivocal and should be further evaluated. Isolates of *S. pneumoniae* should be tested against a 1-mcg oxacillin disk; isolates with oxacillin zone sizes larger than or equal to 20 mm may be considered susceptible to cefepime.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. For the diffusion technique, the 30 mcg cefepime disk should provide the following zone diameters in these laboratory test quality control strains (Table 7):

Table 7

Microorganism	ATCC	Zone Size Range (mm)
Escherichia coli	25922	29 to 35
Staphylococcus aureus	25923	23 to 29
Pseudomonas aeruginosa	27853	24 to 30
Haemophilus influenzae	49247	25 to 31

INDICATIONS AND USAGE

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

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

Empiric Therapy for Febrile Neutropenic Patients. Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients. (See **CLINICAL STUDIES**.)

Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.

Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides fragilis*. (See **CLINICAL STUDIES**.)

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

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. Table 8 describes the characteristics of the evaluable patient population.

Table 8: 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

Table 9 describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

Table 9: 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 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.

CONTRAINDICATIONS

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

WARNINGS

Hypersensitivity Reactions to Cefepime, Cephalosporins, Penicillins, or Other Drugs
Before therapy with MAXIPIME 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 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 MAXIPIME occurs, discontinue the drug.

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

Neurotoxicity
During postmarketing surveillance, serious adverse reactions have been reported including life-threatening or fatal occurrences of the following: encephalopathy

(disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and nonconvulsive status epilepticus (see **ADVERSE REACTIONS**: **Postmarketing Experience**). Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving a dosage adjustment appropriate for their degree of renal impairment. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with cefepime therapy occurs, consider discontinuing cefepime or making appropriate dosage adjustments in patients with renal impairment.

***Clostridium difficile* Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MAXIPIME, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

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

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

PRECAUTIONS

General

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

As with other antimicrobials, prolonged use of MAXIPIME may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs' tests have been reported during treatment with MAXIPIME. 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.

MAXIPIME (cefepime hydrochloride) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of MAXIPIME. The effect of lower doses is not presently known.

Information for Patients

Before therapy with MAXIPIME 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 MAXIPIME occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency 15 measures including oxygen, corticosteroids, intravenous fluids, intravenous antihistamines, pressor amines, and airway management, as clinically indicated.

Patients should be counseled that antibacterial drugs including MAXIPIME should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When MAXIPIME 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 MAXIPIME or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be advised of neurological adverse events that could occur with MAXIPIME use. Patients should be instructed to inform their healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus,

seizures, and nonconvulsive status epilepticus for immediate treatment, dosage adjustment, or discontinuation of MAXIPIME.

Drug Interactions

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with MAXIPIME 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.

Drug/Laboratory Test Interactions

The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest™ tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™) be used.

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/m^2 basis).

Pregnancy

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 (1.6 times the recommended maximum human dose calculated on a mg/m^2 basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m^2 basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum human dose calculated on a mg/m^2 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.

Nursing Mothers

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

Labor and Delivery

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

Pediatric Use

The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of MAXIPIME 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**).

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 MAXIPIME in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b.

IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED.

Geriatric Use

Of the more than 6400 adults treated with MAXIPIME 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 events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. (See **WARNINGS** and **ADVERSE REACTIONS**.)

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See **CLINICAL**

PHARMACOLOGY: Specific Populations, **WARNINGS**, and **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

Clinical Trials

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 events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. 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 events was very 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 events 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 10: Adverse Reactions Cefepime Multiple-Dose Dosing Regimens Clinical Trials—North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local 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

* 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 events 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, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

Table 11: 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.

A similar safety profile was seen in clinical trials of pediatric patients (see **PRECAUTIONS: Pediatric Use**).

Postmarketing Experience

In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience.

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

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

Cephalosporin-Class Adverse Reactions

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

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

OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular excitability and non-convulsive status epilepticus (See **WARNINGS**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION**.)

DOSAGE AND ADMINISTRATION

The recommended adult and pediatric dosages and routes of administration are outlined in the following table. MAXIPIME should be administered intravenously over approximately 30 minutes.

Table 12: Recommended Dosage Schedule for MAXIPIME 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 *S. pneumoniae**, *P. aeruginosa*, *K. pneumoniae*, or *Enterobacter* species	1 to 2 g IV	Every 12 hours	10
Empiric therapy for febrile neutropenic patients (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**.)	2 g IV	Every 8 hours	7**
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli*, *K. pneumoniae*, or *P. mirabilis**	0.5 to 1 g IV/IM***	Every 12 hours	7 to 10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli* or *K. pneumoniae**	2 g IV	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections due to *S. aureus* or *S. pyogenes*	2 g IV	Every 12 hours	10
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *E. coli*, viridans group streptococci, *P. aeruginosa*, *K. pneumoniae*, *Enterobacter* species, or *B. fragilis*. (See **CLINICAL STUDIES**.)	2 g IV	Every 12 hours	7 to 10
Pediatric Patients (2 months up to 16 years) The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg per kg per dose, administered every 12 hours (50 mg per kg per dose, every 8 hours for febrile neutropenic patients), for durations as given above.			

*including cases associated with concurrent bacteremia

**or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.

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

Patients with Hepatic Impairment

No adjustment is necessary for patients with hepatic impairment.

Patients with Renal Impairment

In patients with creatinine clearance less than or equal to 60 mL/min, the dose of MAXIPIME should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of MAXIPIME should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended doses of MAXIPIME in patients with renal impairment are presented in Table 13.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)[3] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

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

Females: 0.85 × above value

Table 13: Recommended Dosing Schedule for MAXIPIME in Adult Patients (Normal Renal Function, Renal Impairment, and Hemodialysis)

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule			
Greater than 60 Normal recommended dosing schedule	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30 to 60	500 mg every 24 hours	1 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
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, MAXIPIME may be administered at normally recommended doses at a dosage interval of every 48 hours (see Table 13).

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 MAXIPIME 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.

MAXIPIME should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see Table 13).

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients (see **CLINICAL PHARMACOLOGY**), changes in the dosing regimen proportional to those in adults (see Tables 12 and 13) are recommended for pediatric patients.

Administration

For Intravenous Infusion, Dilute with a suitable parenteral vehicle prior to intravenous infusion. Constitute the 500 mg, 1 g, or 2 g vial, and add an appropriate quantity of the resulting solution to an intravenous container with one of the compatible intravenous fluids listed in the **Compatibility and Stability** subsection. **THE RESULTING SOLUTION SHOULD BE ADMINISTERED OVER APPROXIMATELY 30 MINUTES.**

Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing cefepime, it is desirable to discontinue the other solution.

ADD-Vantage™ vials are to be constituted only with 50 mL or 100 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection in ADD-Vantage flexible diluent containers. (See ADD-Vantage Vial Instructions for Use.)

Intramuscular Administration: For intramuscular administration, MAXIPIME (cefepime hydrochloride) should be constituted with one of the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride, 5% Dextrose Injection, 0.5% or 1 % Lidocaine Hydrochloride, or Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol (refer to Table 14).

Preparation of MAXIPIME solutions is summarized in Table 14.

Table 14: Preparation of Solutions of MAXIPIME

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

Compatibility and Stability

Intravenous: MAXIPIME is compatible at concentrations between 1 mg per mL and 40 mg per mL with the following intravenous infusion fluids: 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, M/6 Sodium Lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection, Normosol™-R, and Normosol™-M in 5% Dextrose Injection. These solutions may be stored up to 24 hours at controlled room temperature 20°C to 25°C (68°F to 77°F) or 7 days in a refrigerator 2°C to 8°C (36°F to 46°F). MAXIPIME in ADD-Vantage vials is stable at concentrations of 10 to 40 mg per mL in 5% Dextrose Injection or 0.9% Sodium Chloride Injection for 24 hours at controlled room temperature 20°C to 25°C or 7 days in a refrigerator 2°C to 8°C.

MAXIPIME admixture compatibility information is summarized in Table 15.

Table 15: Cefepime Admixture Stability

			Stability Time for	
MAXIPIME Concentration	**Admixture and Concentration**	**IV Infusion Solutions**	**RT/L (20° to 25°C)**	**Refrigeration (2° to 8°C)**
40 mg/mL	Amikacin 6 mg/mL	NS or D5W	24 hours	7 days
40 mg/mL	Ampicillin 1 mg/mL	D5W	8 hours	8 hours
40 mg/mL	Ampicillin 10 mg/mL	D5W	2 hours	8 hours
40 mg/mL	Ampicillin 1 mg/mL	NS	24 hours	48 hours
40 mg/mL	Ampicillin 10 mg/mL	NS	8 hours	48 hours
4 mg/mL	Ampicillin 40 mg/mL	NS	8 hours	8 hours

4 to 40 mg/mL	Clindamycin Phosphate 0.25 to 6 mg/mL	NS or D5W	24 hours	7 days
4 mg/mL	Heparin 10 to 50 units/mL	NS or D5W	24 hours	7 days
4 mg/mL	Potassium Chloride 10 to 40 mEq/L	NS or D5W	24 hours	7 days
4 mg/mL	Theophylline 0.8 mg/mL	D5W	24 hours	7 days
1 to 4 mg/mL	na	Aminosyn™ II 4.25% with electrolytes and calcium	8 hours	3 days
0.125 to 0.25 mg/mL	na	Inpersol™ with 4.25% dextrose	24 hours	7 days

NS = 0.9% Sodium Chloride Injection
D5W = 5% Dextrose Injection
na = not applicable
RT/L = Ambient room temperature and light

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

Intramuscular: MAXIPIME (cefepime hydrochloride) constituted as directed is stable for 24 hours at controlled room temperature 20°C to 25°C (68°F to 77°F) or for 7 days in a refrigerator 2°C to 8°C (36°F to 46°F) with the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine Hydrochloride.

NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER BEFORE ADMINISTRATION. IF PARTICULATE MATTER IS EVIDENT IN RECONSTITUTED FLUIDS, THE DRUG SOLUTION SHOULD BE DISCARDED.

As with other cephalosporins, the color of MAXIPIME powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

INSTRUCTIONS FOR USE

These instructions for use should be made available to the individuals who perform the reconstitution steps.

To Open:

Peel overwrap at corner and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container:

(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (SEE FIGURE 1.), then pull straight up to remove the cap. (SEE FIGURE 2.)

NOTE: Once the breakaway cap has been removed, do not access vial with syringe.

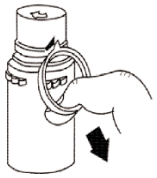


Fig. 1

Fig. 2

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.

NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

4. Label appropriately.

Fig. 3

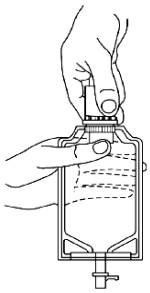


Fig. 4

To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)

3**. Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.**

4. Mix container contents thoroughly and use within the specified time.

5. Look through the bottom of the vial to verify that the stopper has been removed and complete mixing has occurred. (SEE FIGURE 7.)

If the rubber stopper is not removed from the vial and medication is not released on the first attempt, the inner cap may be manipulated back into the rubber stopper without removing the drug vial from the diluent container. Repeat steps 3 through 5.

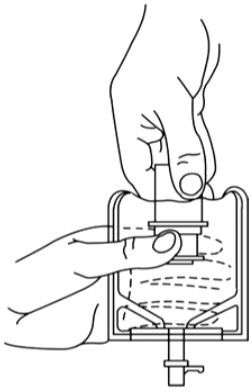


Fig. 5

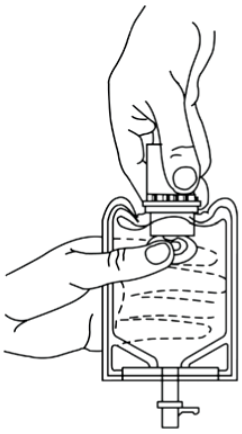


Fig. 6

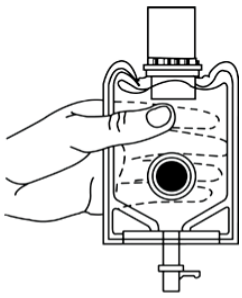


Fig. 7

Preparation for Administration:

(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.

2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

3. Close flow control clamp of administration set.

4. Remove cover from outlet port at bottom of container.

5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.

6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.

7. Squeeze and release drip chamber to establish proper fluid level in chamber.

8. Open flow control clamp and clear air from set. Close clamp.

9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.

10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

MAXIPIME (cefepime hydrochloride, USP) for Injection is supplied as follows: MAXIPIME (cefepime hydrochloride, USP) for Injection in the dry state, is a white to pale yellow powder. Constituted solution of MAXIPIME can range in color from pale yellow to amber.

500 mg*	(carton of 10)	NDC 0409-0221-01
1 g*	(carton of 10)	NDC 0409-0219-01
2 g*	(carton of 10)	NDC 0409-0220-01
1 g*	ADD-Vantage (carton of 25)	NDC 0409-0217-01
2 g*	ADD-Vantage (carton of 25)	NDC 0409-0218-01

*Based on cefepime activity

Storage

IN THE DRY STATE STORE AT 20 TO 25°C (68 TO 77°F) [SEE USP CONTROLLED ROOM TEMPERATURE.] PROTECT FROM LIGHT.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*—Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests*—Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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

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