

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-817**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**Cefepime Injection in GALAXY Container for intravenous use**  
Initial U.S. Approval: 1996

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

**INDICATIONS AND USAGE**

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

**DOSAGE AND ADMINISTRATION**

Recommended Dosage Schedule in Patients with CrCL Greater Than 60 mL/min (2.1) †			
Site and Type of Infection (Adults)	Dose (IV)	Frequency	Duration (Days)
Moderate to Severe Pneumonia	1-2 g	Every 12 hours	10
Empiric therapy for febrile neutropenic patients	2 g	Every 8 hours	7 ‡
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections	0.5-1 g	Every 12 hours	7-10
Severe Uncomplicated or Complicated Urinary Tract Infections	2 g	Every 12 hours	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections	2 g	Every 12 hours	10
Complicated Intra-abdominal Infections (used in combination with metronidazole)	2 g	Every 12 hours	7-10

† The dose should be adjusted in patients with CrCL less than or equal to 60 mL/min. (2.3)

‡ Or until resolution of neutropenia. (2.1)

- Pediatric Patients (2 months to 16 years) – The recommended dose is 50 mg per kg per dose every 12 hours (every 8 hours for febrile neutropenia). Cefepime Injection in GALAXY Container should be used only in pediatric patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)
- Administer intravenously over approximately 30 minutes. (2.1)
- Do not force thaw frozen container by immersion in water baths or by microwave irradiation. (2.4)

**DOSAGE FORMS AND STRENGTHS**

- Intravenous Injection: 1 g in 50 mL and 2 g in 100 mL. (3)

**CONTRAINDICATIONS**

- Prior immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins, and other beta-lactam antibiotics. (4)

**WARNINGS and PRECAUTIONS**

- Cross-hypersensitivity among beta-lactam antibiotics may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefepime Injection occurs, discontinue the drug. (5.1)
- Patients with CrCL less than or equal to 60 mL/min: Dose should be adjusted or serious adverse reactions, including life-threatening or fatal occurrences of encephalopathy, myoclonus, and seizures may occur. (5.2)
- *Clostridium difficile* associated diarrhea (ranging from mild diarrhea to fatal colitis): Evaluate if diarrhea occurs (5.3)

**ADVERSE REACTIONS**

- The most common adverse reactions (incidence  $\geq 1\%$ ) were local reactions (including phlebitis), pain and/or inflammation, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter at 1-866-888-2472 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Aminoglycosides -- increased potential of nephrotoxicity and ototoxicity. (7.1)
- Diuretics -- nephrotoxicity has been reported with concomitant administration of other 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)

See 17 for Patient Counseling Information.

Revised: 12/2007

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## 1 FULL PRESCRIBING INFORMATION

### 2 1 INDICATIONS AND USAGE

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

#### 10 1.1 Pneumonia

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

#### 14 1.2 Empiric Therapy for Febrile Neutropenic Patients

15 Cefepime Injection as monotherapy is indicated for empiric treatment of febrile  
16 neutropenic patients. In patients at high risk for severe infection (including patients with a  
17 history of recent bone marrow transplantation, with hypotension at presentation, with an  
18 underlying hematologic malignancy, or with severe or prolonged neutropenia),  
19 antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the  
20 efficacy of cefepime monotherapy in such patients [see *Clinical Studies (14)*].

#### 21 1.3 Uncomplicated and Complicated Urinary Tract Infections (including 22 pyelonephritis)

23 Cefepime Injection is indicated for uncomplicated and complicated urinary tract  
24 infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella*  
25 *pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella*  
26 *pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including  
27 cases associated with concurrent bacteremia with these microorganisms.

28 **1.4 Uncomplicated Skin and Skin Structure Infections**

29 Cefepime Injection is indicated for uncomplicated skin and skin structure infections  
30 caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus*  
31 *pyogenes*.

32 **1.5 Complicated Intra-abdominal Infections**

33 Cefepime Injection is indicated for complicated intra-abdominal infections (used in  
34 combination with metronidazole) caused by *Escherichia coli*, viridans group streptococci,  
35 *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides*  
36 *fragilis* [see *Clinical Studies (14)*].

37 **2 DOSAGE AND ADMINISTRATION**

38 **2.1 Adults and Pediatric Population**

39 The recommended adult and pediatric dosages and routes of administration are outlined  
40 in Table 1. Cefepime Injection should be administered intravenously over  
41 approximately 30 minutes.

**Table 1: Recommended Dosage Schedule for Cefepime Injection in Patients with CrCL Greater Than 60 mL/min**

Site and Type of Infection	Dose	Frequency	Duration (days)
<b>Adults</b>			
Moderate to Severe Pneumonia due to <i>S. pneumoniae</i> *, <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , or <i>Enterobacter</i> species	1-2 g IV	Every 12 hours	10
Empiric therapy for febrile neutropenic patients [see <i>Indications and Usage (1) and 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> *	0.5-1 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 Injection in GALAXY Container should be used only in pediatric patients who require the entire 1 or 2 g dose and not any fraction thereof.

- 42 \* including cases associated with concurrent bacteremia  
 43 \*\* or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for  
 44 more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.

**45 2.2 Patients with Hepatic Impairment**

46 No adjustment is necessary for patients with impaired hepatic function.

47 **2.3 Patients with Renal Impairment**

48 In patients with creatinine clearance less than or equal to 60 mL/min, the dose of  
 49 Cefepime Injection should be adjusted to compensate for the slower rate of renal  
 50 elimination. The recommended initial dose of Cefepime Injection should be the same as  
 51 in patients with normal renal function except in patients undergoing hemodialysis. The  
 52 recommended doses of Cefepime Injection in patients with renal impairment are  
 53 presented in Table 2.

54 When only serum creatinine is available, the following formula (Cockcroft and Gault  
 55 equation)<sup>1</sup> may be used to estimate creatinine clearance. The serum creatinine should  
 56 represent a steady state of renal function:

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

59 Females: 0.85 x above value

**Table 2: Recommended Dosing Schedule for Cefepime Injection 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 Injection should be administered following hemodialysis. Whenever possible, Cefepime Injection should be administered at the same time each day.

60 In patients undergoing continuous ambulatory peritoneal dialysis, Cefepime Injection  
61 may be administered at normally recommended doses at a dosage interval of every 48  
62 hours (see Table 2).

63 In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime  
64 present in the body at the start of dialysis will be removed during a 3-hour dialysis  
65 period. The dosage of Cefepime Injection for hemodialysis patients is 1 g on Day 1  
66 followed by 500 mg every 24 hours for the treatment of all infections except febrile  
67 neutropenia, which is 1 g every 24 hours. Cefepime Injection should be administered at  
68 the same time each day following the completion of hemodialysis on hemodialysis days  
69 (see Table 2).

70 Data in pediatric patients with impaired renal function are not available; however, since  
71 cefepime pharmacokinetics are similar in adults and pediatric patients [*see Clinical*  
72 *Pharmacology (12)*], changes in the dosing regimen proportional to those in adults (see  
73 Table 1 and Table 2) are recommended for pediatric patients.

#### 74 **2.4 Directions for Use of Cefepime Injection in GALAXY Container**

75 Cefepime Injection in GALAXY Container (PL 2040 Plastic) is for intravenous  
76 administration using sterile equipment after thawing to room temperature.

##### 77 *Thawing of Plastic Container*

78 Thaw frozen container at room temperature 25°C (77°F) or under refrigeration 5°C  
79 (41°F). Do not force thaw by immersion in water baths or by microwave irradiation. [*See*  
80 *How Supplied/Storage and Handling (16).*]

81 Check for minute leaks by squeezing container firmly. If leaks are detected, discard  
82 solution as sterility may be impaired.

83 Do not add supplementary medication.

84 Parenteral drug products should be inspected visually for particulate matter and  
85 discoloration prior to administration, whenever solution and container permit.

86 Components of the solution may precipitate in the frozen state and will dissolve upon  
87 reaching room temperature with little or no agitation. Potency is not affected. Agitate  
88 after solution has reached room temperature. If after visual inspection the solution  
89 remains cloudy or if an insoluble precipitate is noted or if any seals or the outlet port are  
90 not intact, the container should be discarded.

91 **Caution: Do not use plastic containers in series connections.** Such use could result in  
92 air embolism due to residual air being drawn from the primary container before  
93 administration of the fluid from the secondary container is complete.

94 *Preparation for intravenous administration.*

- 95 1. Suspend container from eyelet support.
- 96 2. Remove protector from outlet port at bottom of container.
- 97 3. Attach administration set. Refer to complete directions accompanying set.

98 Cefepime Injection should be administered intravenously over approximately 30 minutes.

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

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

### 107 **3 DOSAGE FORMS AND STRENGTHS**

108 Intravenous Injection:

- 109 • 1 g in 50 mL (contains 1 g of cefepime as Cefepime Hydrochloride, USP)
- 110 • 2 g in 100 mL (contains 2 g of cefepime as Cefepime Hydrochloride, USP)

### 111 **4 CONTRAINDICATIONS**

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

115 Solutions containing dextrose may be contraindicated in patients with known allergy to  
116 corn or corn products.

## 117 5 WARNINGS AND PRECAUTIONS

### 118 5.1 Hypersensitivity

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

### 129 5.2 Renal Impairment

130 In patients with creatinine clearance less than or equal to 60 mL/min, the dose of  
131 Cefepime Injection should be adjusted to compensate for the slower rate of renal  
132 elimination. Because high and prolonged serum antibiotic concentrations can occur from  
133 usual dosages in patients with renal impairment or other conditions that may compromise  
134 renal function, the maintenance dosage should be reduced when Cefepime Injection is  
135 administered to such patients. Continued dosage should be determined by degree of renal  
136 impairment, severity of infection, and susceptibility of the causative organisms. Refer to  
137 specific recommendations for dosing adjustment [*See Dosage and Administration (2)*].  
138 During postmarketing surveillance, serious adverse events have been reported including  
139 life-threatening or fatal occurrences of the following: encephalopathy (disturbance of  
140 consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and  
141 seizures [*see Adverse Reactions (6.2)*]. Most cases occurred in patients with renal  
142 impairment who received doses of cefepime that exceeded the recommended dosage  
143 schedules. However, some cases of encephalopathy occurred in patients receiving a  
144 dosage adjustment for their renal function. In the majority of cases, symptoms of  
145 neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after  
146 hemodialysis.

### 147 5.3 *Clostridium difficile* Associated Diarrhea

148 *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all  
149 antibacterial agents, including Cefepime Injection, and may range in severity from mild  
150 diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the

151 colon leading to overgrowth of *C. difficile*.  
152 *C. difficile* produces toxins A and B which contribute to the development of CDAD.  
153 Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as  
154 these infections can be refractory to antimicrobial therapy and may require colectomy.  
155 CDAD must be considered in all patients who present with diarrhea following antibiotic  
156 use. Careful medical history is necessary since CDAD has been reported to occur over  
157 two months after the administration of antibacterial agents.  
158 If CDAD is suspected or confirmed, ongoing antibiotic use not directed against  
159 *difficile* may need to be discontinued. Appropriate fluid and electrolyte management,  
160 protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation  
161 should be instituted as clinically indicated.

#### 162 **5.4 Risk of Development of Drug-Resistant Bacteria**

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

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

#### 170 **5.5 Patients with Meningeal Seeding/Meningitis**

171  
172 In those patients in whom meningeal seeding from a distant infection site or in whom  
173 meningitis is suspected or documented, an alternate agent with demonstrated clinical  
174 efficacy in this setting should be used.

#### 175 **5.6 Drug/Laboratory Test Interactions**

##### 176 Urinary Glucose

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

##### 180 Coombs' Test

181 Positive direct Coombs' tests have been reported during treatment with cefepime. In  
182 hematologic studies or in transfusion cross-matching procedures when antiglobulin

183 tests are performed on the minor side or in Coombs' testing of newborns whose  
184 mothers have received cephalosporin antibiotics before parturition, it should be  
185 recognized that a positive Coombs' test may be due to the drug.

#### 186 Prothrombin Time

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

### 192 **5.7 Patients with a History of Gastrointestinal Disease**

193 Cefepime Injection should be prescribed with caution in individuals with a history of  
194 gastrointestinal disease, particularly colitis.

### 195 **5.8 Possible Effects of Arginine on Glucose Metabolism**

196 Cefepime Injection contains arginine to adjust pH [*see Description (11)*]. Arginine has  
197 been shown to alter glucose metabolism and elevate serum potassium transiently when  
198 administered at 33 times the amount provided by the maximum recommended human  
199 dose of cefepime. The effect of lower doses is not presently known.

## 200 **6 ADVERSE REACTIONS**

### 201 **6.1 Clinical Trials Experience**

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

205 In clinical trials using multiple doses of cefepime, 4137 patients were treated with the  
206 recommended dosages of cefepime (500 mg to 2 g intravenously every 12 hours).  
207 Sixty-four (1.5%) patients discontinued medication due to adverse events thought by  
208 the investigators to be possibly, probably, or almost certainly related to drug toxicity.  
209 Thirty-three (51%) of these 64 patients who discontinued therapy did so because of  
210 rash. The percentage of cefepime-treated patients who discontinued study drug because  
211 of drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g  
212 every 12 hours (0.8%, 1.1%, and 2.0%, respectively). However, the incidence of  
213 discontinuation due to rash increased with the higher recommended doses.

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

**Table 3: 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, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

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

219 At the higher dose of 2 g every 8 hours, the incidence of probably-related adverse  
 220 events was higher among the 795 patients who received this dose of cefepime. They  
 221 consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever  
 222 (1%), and headache (1%).

223 The following adverse laboratory changes, irrespective of relationship to therapy with  
 224 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

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

227 A similar safety profile was seen in clinical trials of pediatric patients [*see Use in Specific*  
 228 *Populations (8.4)*].

229

## 230 **6.2 Postmarketing Experience**

231 In addition to the events reported during North American clinical trials with cefepime,  
232 the following adverse experiences have been reported during worldwide postmarketing  
233 experience. Because these reactions are reported voluntarily from a population of  
234 uncertain size, it is not always possible to reliably estimate their frequency or establish a  
235 causal relationship to drug exposure.

236 As with some other drugs in this class, encephalopathy (disturbance of consciousness  
237 including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have  
238 been reported. Although most cases occurred in patients with renal impairment who  
239 received doses of cefepime that exceeded the recommended dosage schedules, some  
240 cases of encephalopathy occurred in patients receiving a dosage adjustment for their  
241 renal function [*see Warnings and Precautions (5)*]. If seizures associated with drug  
242 therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if  
243 clinically indicated. Precautions should be taken to adjust daily dosage in patients with  
244 renal impairment or other conditions that may compromise renal function to reduce  
245 antibiotic concentrations that can lead or contribute to these and other serious adverse  
246 events, including renal failure.

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

## 249 **6.3 Cephalosporin-class Adverse Reactions**

250 In addition to the adverse reactions listed above that have been observed in patients  
251 treated with cefepime, the following adverse reactions have been reported for  
252 cephalosporin-class antibiotics:

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

## 256 **7 DRUG INTERACTIONS**

### 257 **7.1 Aminoglycosides**

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

261 **7.2 Diuretics**

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

264 **8 USE IN SPECIFIC POPULATIONS**

265 **8.1 Pregnancy**

266 Pregnancy Category B. Cefepime was not teratogenic or embryocidal when  
267 administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day  
268 (1.6 times the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis) or to  
269 mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum  
270 human dose calculated on a mg/m<sup>2</sup> basis) or to rabbits at a dose level of 100 mg/kg (0.3  
271 times the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis).

272 There are, however, no adequate and well-controlled studies of cefepime use in  
273 pregnant women. Because animal reproduction studies are not always predictive of  
274 human response, this drug should be used during pregnancy only if clearly needed.

275 **8.2 Labor and Delivery**

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

278 **8.3 Nursing Mothers**

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

282 **8.4 Pediatric Use**

283 The safety and effectiveness of cefepime in the treatment of uncomplicated and  
284 complicated urinary tract infections (including pyelonephritis), uncomplicated skin and  
285 skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic  
286 patients have been established in the age groups 2 months up to 16 years. Use of  
287 Cefepime Injection in these age groups is supported by evidence from adequate and  
288 well-controlled studies of cefepime in adults with additional pharmacokinetic and  
289 safety data from pediatric trials [see *Clinical Pharmacology (12)*].

290 Safety and effectiveness in pediatric patients below the age of 2 months have not been  
291 established. There are insufficient clinical data to support the use of Cefepime Injection  
292 in pediatric patients under 2 months of age or for the treatment of serious infections in  
293 the pediatric population where the suspected or proven pathogen is *Haemophilus*  
294 *influenzae* type b.

295 Cefepime Injection in GALAXY Container should be used only in pediatric patients who  
296 require the entire 1 or 2 g dose and not any fraction thereof.

### 297 **8.5 Geriatric Use**

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

302 Serious adverse events have occurred in geriatric patients with renal impairment given  
303 unadjusted doses of cefepime, including life-threatening or fatal occurrences of the  
304 following: encephalopathy, myoclonus, and seizures [*see Warnings and Precautions (5)*  
305 *and Adverse Reactions (6)*].

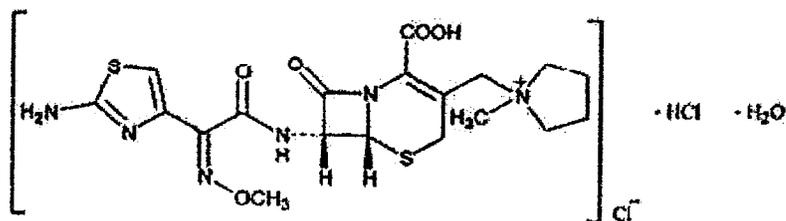
306 This drug is known to be substantially excreted by the kidney, and the risk of toxic  
307 reactions to this drug may be greater in patients with impaired renal function. Because  
308 elderly patients are more likely to have decreased renal function, care should be taken in  
309 dose selection, and renal function should be monitored [*see Clinical Pharmacology (12)*,  
310 *Warnings and Precautions (5)*, and *Dosage and Administration (2)*].

## 311 **10 OVERDOSAGE**

312 Patients who receive an overdose should be carefully observed and given supportive  
313 treatment. In the presence of renal impairment, hemodialysis, not peritoneal dialysis, is  
314 recommended to aid in the removal of cefepime from the body. Accidental overdosing  
315 has occurred when large doses were given to patients with impaired renal function.  
316 Symptoms of overdose include encephalopathy (disturbance of consciousness including  
317 confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular  
318 excitability [*see Warnings and Precautions (5)*, *Adverse Reactions (6)*, and *Dosage and*  
319 *Administration (2)*].

320 **11 DESCRIPTION**

321 Cefepime Injection in GALAXY Containers (PL 2040 Plastic) is a sterile, injectable  
 322 product consisting of Cefepime Hydrochloride, USP, a semi-synthetic, broad spectrum,  
 323 cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[[(6R,7R)-  
 324 7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]  
 325 oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7<sup>2</sup>-(Z)-(O-methyloxime),  
 326 monohydrochloride, monohydrate, which corresponds to the following structural  
 327 formula:



328  
 329  
 330

331 Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular  
 332 formula of  $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ .

333

334 Cefepime Injection in GALAXY Container (PL 2040 Plastic) is a frozen, iso-osmotic,  
 335 sterile, non-pyrogenic premixed solution supplied for intravenous administration in  
 336 strengths equivalent to 1 g and 2 g of cefepime [see *Dosage and Administration (2)*]. It  
 337 contains the equivalent of not less than 90 percent and not more than 115 percent of the  
 338 labeled amount of cefepime ( $C_{19}H_{24}N_6O_5S_2$ ).

339 The solution is intended for intravenous use after thawing to room temperature. The  
 340 components and dosage formulations are given in the table below:

**Table 5: Cefepime Injection in GALAXY Containers (PL 2040 Plastic) Premixed Frozen Solution**

Component*	Function	Dosage Formulations	
		1 g in 50 mL	2 g in 100 mL
Cefepime	active ingredient	1 g	2 g
Dextrose Hydrus, USP	osmolality adjuster	1.03 g	2.06 g
L-Arginine, USP**	pH adjuster	725 mg	1.45 g
Hydrochloric Acid**	pH adjuster	As needed	As needed
Water for Injection, USP	vehicle	q.s.*** 50 mL	q.s.*** 100 mL

341 \* Cefepime is present in the formulation as Cefepime Hydrochloride, USP. The amounts of Dextrose  
342 Hydrous, USP and L-Arginine, USP are approximate.  
343 \*\* The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is  
344 4.0 – 6.0.

345 \*\*\* This is an abbreviation for sufficient quantity.

346 Cefepime Injection will range in color from colorless to amber.

347 The plastic container is fabricated from a specially designed multilayer plastic (PL 2040).  
348 Solutions are in contact with the polyethylene layer of this container and can leach out  
349 certain chemical components of the plastic in very small amounts within the expiration  
350 period. The suitability of the plastic has been confirmed in tests in animals according to  
351 the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

## 352 12 CLINICAL PHARMACOLOGY

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

### 356 12.1 Mechanism of Action

357 Cefepime is an antibacterial drug. [See *Clinical Pharmacology* (12.4)]

### 358 12.2 Pharmacodynamics

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

### 364 12.3 Pharmacokinetics

365 The average plasma concentrations of cefepime observed in healthy adult male  
366 volunteers (n=9) at various times following single 30-minute intravenous infusions of  
367 cefepime 500 mg, 1 g, and 2 g are summarized in Table 6. Elimination of cefepime is  
368 principally via renal excretion with an average ( $\pm$ SD) half-life of 2 ( $\pm$ 0.3) hours and total  
369 body clearance of 120 ( $\pm$ 8) mL/min in healthy volunteers. Cefepime pharmacokinetics  
370 are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy  
371 adult male volunteers (n=7) receiving clinically relevant doses for a period of 9 days.

**Table 6: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters ( $\pm$ SD), Intravenous Administration**

Parameter	CEFEPIME		
	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

372

373 *Distribution*

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

377 Cefepime is excreted in human milk. A nursing infant consuming approximately  
 378 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per  
 379 day [see *Use in Specific Populations (8.3)*].

380 Concentrations of cefepime achieved in specific tissues and body fluids are listed in  
 381 Table 7.

**Table 7: 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
Gall Bladder	2 g IV	38	8.9	11.9 mcg/g
Prostate	2 g IV	5	1	31.5 mcg/g

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

384 *Metabolism and Excretion*

385 Cefepime is metabolized to N-methylpyrrolidine (NMP), which is rapidly converted to  
 386 the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for  
 387 approximately 85% of the administered dose. Less than 1% of the administered dose is  
 388 recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of  
 389 cefepime. Because renal excretion is a significant pathway of elimination, patients with  
 390 renal dysfunction and patients undergoing hemodialysis require dosage adjustment [*see*  
 391 *Dosage and Administration (2)*].

392 *Specific Populations*

393 Patients with Renal Impairment

394 Cefepime pharmacokinetics have been investigated in patients with various degrees of  
 395 renal impairment (n=30). The average half-life in patients requiring hemodialysis was 13.5  
 396 ( $\pm 2.7$ ) hours and in patients requiring continuous peritoneal dialysis was 19 ( $\pm 2.0$ ) hours.  
 397 Cefepime total body clearance decreased proportionally with creatinine clearance in  
 398 patients with abnormal renal function, which serves as the basis for dosage adjustment  
 399 recommendations in this group of patients [*see Dosage and Administration (2)*].

400 Patients with Hepatic Impairment

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

403 Geriatric Patients

404 Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older)  
405 men (n=12) and women (n=12) whose mean (SD) creatinine clearance was 74.0 (±15.0)  
406 mL/min. There appeared to be a decrease in cefepime total body clearance as a function  
407 of creatinine clearance. Therefore, dosage administration of cefepime in the elderly  
408 should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or  
409 less [see *Dosage and Administration (2)*].

410 Pediatric Patients

411 Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to  
412 11 years of age following single and multiple doses on every 8 hours (n=29) and every 12  
413 hours (n=13) schedules. Following a single intravenous dose, total body clearance and the  
414 steady-state volume of distribution averaged 3.3 (±1.0) mL/min/kg and 0.3 (±0.1) L/kg,  
415 respectively. The urinary recovery of unchanged cefepime was 60.4 (±30.4) % of the  
416 administered dose, and the average renal clearance was 2.0 (±1.1) mL/min/kg. There  
417 were no significant effects of age or gender (25 male vs. 17 female) on total body  
418 clearance or volume of distribution, corrected for body weight. No accumulation was  
419 seen when cefepime was given at 50 mg per kg every 12 hours (n=13), while  $C_{max}$ , AUC,  
420 and  $t_{1/2}$  were increased about 15% at steady state after 50 mg per kg every 8 hours. The  
421 exposure to cefepime following a 50 mg per kg intravenous dose in a pediatric patient is  
422 comparable to that in an adult treated with a 2 g intravenous dose.

423 **12.4 Microbiology**

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

431 Cefepime has been shown to be active against most isolates of the following  
432 microorganisms, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

433 • **Aerobic Gram-Negative Microorganisms:**

434 *Enterobacter*  
435 *Escherichia coli*  
436 *Klebsiella pneumoniae*  
437 *Proteus mirabilis*  
438 *Pseudomonas aeruginosa*

439 • **Aerobic Gram-Positive Microorganisms:**

440 *Staphylococcus aureus* (methicillin-susceptible isolates only)  
441 *Streptococcus pneumoniae*  
442 *Streptococcus pyogenes* (Lancefield's Group A streptococci)  
443 Viridans group streptococci

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

449 • **Aerobic Gram-Positive Microorganisms:**

450 *Staphylococcus epidermidis* (methicillin-susceptible isolates only)  
451 *Staphylococcus saprophyticus*  
452 *Streptococcus agalactiae* (Lancefield's Group B streptococci)

453 NOTE: Most isolates of enterococci, e.g., *Enterococcus faecalis*, and methicillin-resistant  
454 staphylococci are resistant to cefepime.

455 • **Aerobic Gram-Negative Microorganisms:**

456 *Acinetobacter calcoaceticus* subsp. *lwoffii*  
457 *Citrobacter diversus*  
458 *Citrobacter freundii*  
459 *Enterobacter agglomerans*  
460 *Haemophilus influenzae* (including beta-lactamase producing isolates)  
461 *Hafnia alvei*  
462 *Klebsiella oxytoca*

- 463 *Moraxella catarrhalis* (including beta-lactamase producing isolates)  
 464 *Morganella morganii*  
 465 *Proteus vulgaris*  
 466 *Providencia rettgeri*  
 467 *Providencia stuartii*  
 468 *Serratia marcescens*

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

471 • **Anaerobic Microorganisms:**

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

473 **Susceptibility Tests**

474 Dilution Techniques

475 Quantitative methods are used to determine antimicrobial minimum inhibitory  
 476 concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to  
 477 antimicrobial compounds. The MICs should be determined using a standardized  
 478 procedure. Standardized procedures are based on a dilution method<sup>2</sup> (broth or agar) or  
 479 equivalent with standardized inoculum concentrations and standardized concentrations of  
 480 cefepime powder. The MIC values should be interpreted according to the following  
 481 criteria:

**Table 8**

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

482 \* NOTE: Isolates from these species should be tested for susceptibility using specialized dilution testing  
 483 methods.<sup>2</sup> Also, strains of *Haemophilus* spp. with MICs greater than 2 mcg/mL should be considered  
 484 equivocal and should be further evaluated.

485 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the  
 486 antimicrobial compound in the blood reaches the concentrations usually achievable. A

487 report of "Intermediate" indicates that the result should be considered equivocal, and, if  
488 the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test  
489 should be repeated. This category implies possible clinical applicability in body sites  
490 where the drug is physiologically concentrated or in situations where high dosage of drug  
491 can be used. This category also provides a buffer zone which prevents small uncontrolled  
492 technical factors from causing major discrepancies in interpretation. A report of  
493 "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial  
494 compound in the blood reaches the concentrations usually achievable; other therapy  
495 should be selected.

496           Standardized susceptibility test procedures require the use of laboratory control  
497 microorganisms to control the technical aspects of the laboratory procedures. Laboratory  
498 control microorganisms are specific strains of microbiological assay organisms with  
499 intrinsic biological properties relating to resistance mechanisms and their genetic  
500 expression within bacteria; the specific strains are not clinically significant in their  
501 current microbiological status. Standard cefepime powder should provide the following  
502 MIC values (Table 9) when tested against the designated quality control strains:

Table 9

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

## 503 Diffusion Techniques

504 Quantitative methods that require measurement of zone diameters also provide  
 505 reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One  
 506 such standardized procedure<sup>3</sup> requires the use of standardized inoculum concentrations.  
 507 This procedure uses paper disks impregnated with 30 mcg of cefepime to test the  
 508 susceptibility of microorganisms to cefepime. Interpretation is identical to that stated  
 509 above for results using dilution techniques.

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

Table 10

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

513 \*NOTE: Isolates from these species should be tested for susceptibility using specialized diffusion testing  
 514 methods.<sup>3</sup> Isolates of *Haemophilus* spp. with zones smaller than 26 mm should be considered equivocal  
 515 and should be further evaluated. Isolates of *S. pneumoniae* should be tested against a 1-mcg oxacillin disk;  
 516 isolates with oxacillin zone sizes larger than or equal to 20 mm may be considered susceptible to cefepime.

517 As with standardized dilution techniques, diffusion methods require the use of laboratory  
 518 control microorganisms to control the technical aspects of the laboratory procedures.  
 519 Laboratory control microorganisms are specific strains of microbiological assay organisms  
 520 with intrinsic biological properties relating to resistance mechanisms and their genetic  
 521 expression within bacteria; the specific strains are not clinically significant in their  
 522 current microbiological status. For the diffusion technique, the 30-mcg cefepime disk

523 should provide the following zone diameters in these laboratory test quality control  
524 strains (Table 11):

**Table 11**

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

525 **13 NONCLINICAL TOXICOLOGY**

526 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

527 No long-term animal carcinogenicity studies have been conducted with cefepime. A  
528 battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella  
529 reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay,  
530 chromosomal aberration and sister chromatid exchange assays in human lymphocytes,  
531 CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice  
532 were conducted. The overall conclusion of these tests indicated no definitive evidence  
533 of genotoxic potential. No untoward effects on fertility were observed in rats when  
534 cefepime was administered subcutaneously at doses up to 1000 mg/kg/day (1.6 times  
535 the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis).

536 **14 CLINICAL STUDIES**

537 **14.1 Febrile Neutropenic Patients**

538 The safety and efficacy of empiric cefepime monotherapy of febrile neutropenic patients  
539 have been assessed in two multicenter, randomized trials, comparing cefepime  
540 monotherapy (at a dose of 2 g intravenously every 8 hours) to ceftazidime monotherapy (at  
541 a dose of 2 g intravenously every 8 hours). These studies comprised 317 evaluable  
542 patients. Table 12 describes the characteristics of the evaluable patient population.

543

544

**Table 12: Demographics of Evaluable Patients (First Episodes Only)**

Total	Cefepime	Ceftazidime
	164	153
Median age (yr)	56 (range, 18-82)	55 (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 per 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%)

545           ANC = absolute neutrophil count; SBP = systolic blood pressure.

546   Table 13 describes the clinical response rates observed. For all outcome measures,  
547   cefepime was therapeutically equivalent to ceftazidime.

**Table 13: 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

548 Insufficient data exist to support the efficacy of cefepime monotherapy in patients at high  
 549 risk for severe infection (including patients with a history of recent bone marrow  
 550 transplantation, with hypotension at presentation, with an underlying hematologic  
 551 malignancy, or with severe or prolonged neutropenia). No data are available in patients  
 552 with septic shock.

#### 553 **14.2 Complicated Intra-abdominal Infections**

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

567 efficacy may have been due to a greater proportion of patients with high APACHE II  
568 scores in the imipenem/cilastatin group.

## 569 15 REFERENCES

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577 *for Antimicrobial Disk Susceptibility Tests*—Fifth Edition. Approved Standard NCCLS  
578 Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

## 579 16 HOW SUPPLIED/STORAGE AND HANDLING

580 Cefepime Injection is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in  
581 50 mL and 100 mL single-dose GALAXY containers (PL 2040 Plastic) as follows:

582	2G3578	NDC 0338-1301-41	1 g* in 50 mL	Supplied 24/box
583	2G3579	NDC 0338-1301-48	2 g* in 100 mL	Supplied 12/box

584

585 \* Based on cefepime activity

586 Store at or below  $-20^{\circ}\text{C}$  ( $-4^{\circ}\text{F}$ ).

587 Thaw frozen container at room temperature  $25^{\circ}\text{C}$  ( $77^{\circ}\text{F}$ ) or under refrigeration  $5^{\circ}\text{C}$   
588 ( $41^{\circ}\text{F}$ ). Do not force thaw by immersion in water baths or by microwave irradiation.

589 The thawed solution remains stable for 7 days under refrigeration  $5^{\circ}\text{C}$  ( $41^{\circ}\text{F}$ ) or 24 hours  
590 at room temperature  $25^{\circ}\text{C}$  ( $77^{\circ}\text{F}$ ). Do not refreeze.

591 [See *Dosage and Administration* (2.4)].

## 592 17 PATIENT COUNSELING INFORMATION

593 • Patients should be counseled that antibacterial drugs including Cefepime Injection  
594 should only be used to treat bacterial infections. They do not treat viral infections

595 (e.g., the common cold). When Cefepime Injection is prescribed to treat a  
596 bacterial infection, patients should be told that although it is common to feel  
597 better early in the course of therapy, the medication should be taken exactly as  
598 directed. Skipping doses or not completing the full course of therapy may (1)  
599 decrease the effectiveness of the immediate treatment and (2) increase the  
600 likelihood that bacteria will develop resistance and will not be treatable by  
601 Cefepime Injection or other antibacterial drugs in the future.

602 • Patients should be advised of neurological adverse events that could occur with  
603 Cefepime Injection use. Patients should be instructed to inform their healthcare  
604 provider at once of any neurological signs and symptoms including  
605 encephalopathy (disturbance of consciousness including confusion,  
606 hallucinations, stupor, and coma), myoclonus and seizures for immediate  
607 treatment, dosage adjustment, or discontinuation of Cefepime Injection.

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

614

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616 Baxter Healthcare Corporation

617 Deerfield, IL 60015

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Colors: Black

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Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION. Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Do not refreeze.  
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07-94-50-712  
PL 2040 Plastic  
Made in USA

**Baxter**  
**Cefepime Injection** 1g  
Rx Only

12 - 50 mL Single-Dose Containers Iso-osmotic.  
Store at or below -20°C/-4°F. Do not refreeze.  
NDC 0838-1301-41  
C016 263578  
\*BAR CODE POSITION ONLY  
(01) 20303381301419

**GALAXY Container**  
12 - 50 mL Containers: Cefepime Hydrochloride, USP equivalent to 1 g of cefepime with approx. 1.03 g of Deoxos Hydrate, USP added to adjust osmolality. NDC 0838-1301-41. Contains 1.03 g of cefepime to adjust the pH. The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is 4.0 - 6.0.  
Caution: Intentionally as directed by a physician. See insert.  
Check for minute leaks and solution clarity. Check for minute leaks by squeezing toward bag firmly. If leaks are found, discard bag, as sterility may be impaired. Do not use unless solution is clear.

Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION. Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Do not refreeze.  
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07-94-50-712  
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**Baxter**  
**Cefepime Injection** 1g  
Rx Only

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NDC 0838-1301-41  
C016 263578  
\*BAR CODE POSITION ONLY  
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\*This artwork requires that the supplier insert a UCC/EAN 128 bar code master in the position indicated. Bar code must match human readable on art and on spec. Do not alter human readable information on art. Bar code must conform to all applicable Baxter specifications.

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Document No.: F7-04-50-713

Change No.: CP0195419

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P1 12/21/2007  
Colors: Black,            red

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**b(4)**

Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Do not refreeze.

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**Baxter**  
**Cefepime Injection** Rx Only

**2g**

6.105 mL Single-Dose Containers, Iso-osmotic.  
Store at or below -20°C/-4°F. Do not refreeze.

MDC 0338-1391-48  
C008 203579

\*BAR CODE POSITION ONLY

(01) 203033813017488

Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Do not refreeze.

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07-04-50-713  
07-04-50-713  
PL 2040 Plastic  
Made in USA

**Baxter**  
**Cefepime Injection** Rx Only

**2g**

6.105 mL Single-Dose Containers, Iso-osmotic.  
Store at or below -20°C/-4°F. Do not refreeze.

MDC 0338-1391-48  
C008 203579

\*BAR CODE POSITION ONLY

(01) 203033813017488

**GALAXY Container**  
Sterile Nonpyrogenic  
Each 100 mL Single-Dose Container, Iso-osmotic.  
of Cefepime Hydrochloride, USP equivalent to 2 g of cefepime with 2.06 g of Dextrose Hydroxide, USP added to adjust osmolality. Aminoacids, USP added to adjust pH. The pH is 4.0-6.0.  
Cefepime Hydrochloride, USP is a cephalosporin antibiotic. It is indicated for the treatment of infections caused by susceptible organisms. See insert for complete prescribing information. Do not use unless solution is clear. Check for minute leaks and solution clarity. Check for minute leaks by squeezing thawed bag firmly. If leaks are found, discard bag as sterility may be impaired. Do not use unless solution is clear.

**GALAXY Container**  
Sterile Nonpyrogenic  
Each 100 mL Single-Dose Container, Iso-osmotic.  
of Cefepime Hydrochloride, USP equivalent to 2 g of cefepime with 2.06 g of Dextrose Hydroxide, USP added to adjust osmolality. Aminoacids, USP added to adjust pH. The pH is 4.0-6.0.  
Cefepime Hydrochloride, USP is a cephalosporin antibiotic. It is indicated for the treatment of infections caused by susceptible organisms. See insert for complete prescribing information. Do not use unless solution is clear. Check for minute leaks and solution clarity. Check for minute leaks by squeezing thawed bag firmly. If leaks are found, discard bag as sterility may be impaired. Do not use unless solution is clear.

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Document No.: F7-34-50-710

Change No.: CP0190601

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P2 10/31/2007 ia

P3 11/05/2007 ia

Colors: Black, White

Black White

**PROOFREADING INSPECTION / RELEASED ARTWORK**

Proofreading Approval	Print Name	Signature	Date
Proofreading Approval	Print Name	Signature	Date

**Baxter** **1g**

**Cefepime Injection**

**GALAXY** **50 mL** **NDC 0338-1301-41**  
 Single-Dose **iso-osmotic** **Code 2G3578**  
 Container **Sterile Nonpyrogenic**

Each 50 mL contains: Cefepime Hydrochloride, USP equivalent to 1 g of cefepime with approx. 1.03 g of Dextrose Hydrated, USP added to adjust osmolality. Approx. 725 mg of L-Arginine, USP added per g of cefepime to adjust the pH. The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is 4.0 - 6.0.

Dosage: Intravenously as directed by a physician. See insert.

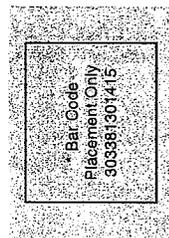
Cautions: Do not add supplementary medication. Must not be used in series connections. Check for minute leaks and solution clarity.

Store at or below -20°C/-4°F. Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). Do not refreeze.

**Rx Only**

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P2 10/31/2007 ia  
P3 11/05/2007 ia  
Colors: Black, White, Red

Black White Red

Prereading Approval	Print Name	Signature	Date
Prereading Approval	Print Name	Signature	Date

**Baxter** **2g**

## Cefepime Injection

**GALAXY** **100 mL** **NDC 0338-1301-48**  
Single-Dose **iso-osmotic** **Code 2G3579**  
Container **Sterile Nonpyrogenic**

Each 100 mL contains: Cefepime Hydrochloride, USP equivalent to 2 g of cefepime with approx. 2.06 g of Dextrose Hydrated, USP added to adjust osmolality. Approx. 725 mg of L-Arginine, USP added per g of cefepime to adjust the pH. The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is 4.0 - 6.0.

Dosage: Intravenously as directed by a physician. See insert.  
Cautions: Do not add supplementary medication. Must not be used in series connections. Check for minute leaks and solution clarity.

Store at or below -20°C/-4°F. Thaw at room temperature (25°C/77°F) or under refrigeration (5°C/41°F). **DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.** Thawed solution remains stable for 7 days under refrigeration (5°C/41°F) or 24 hours at room temperature (25°C/77°F). **Do not refreeze.**

**Rx Only**

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Bar Code  
Placement Only  
303381301484

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