

**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.

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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 hepatic impairment.

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) =  $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$   
 58

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 per 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.

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

174 **5.6 Drug/Laboratory Test Interactions**

175 Urinary Glucose

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

179 Coombs' Test

180 Positive direct Coombs' tests have been reported during treatment with cefepime. In  
181 hematologic studies or in transfusion cross-matching procedures when antiglobulin  
182 tests are performed on the minor side or in Coombs' testing of newborns whose  
183 mothers have received cephalosporin antibiotics before parturition, it should be  
184 recognized that a positive Coombs' test may be due to the drug.

185 Prothrombin Time

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

191 **5.7 Patients with a History of Gastrointestinal Disease**

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

194 **5.8 Possible Effects of Arginine on Glucose Metabolism**

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

199 **6 ADVERSE REACTIONS**

200 **6.1 Clinical Trials Experience**

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

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

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

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

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

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

**Table 4: Adverse Laboratory Changes  
Cefepime Multiple-Dose Dosing Regimens  
Clinical Trials—North America**

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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

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

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

## 228 6.2 Postmarketing Experience

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

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

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

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247 **6.3 Cephalosporin-class Adverse Reactions**

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

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

254 **7 DRUG INTERACTIONS**

255 **7.1 Aminoglycosides**

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

259 **7.2 Diuretics**

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

262 **8 USE IN SPECIFIC POPULATIONS**

263 **8.1 Pregnancy**

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

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

273 **8.2 Labor and Delivery**

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

276 **8.3 Nursing Mothers**

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

280 **8.4 Pediatric Use**

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

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

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

295 **8.5 Geriatric Use**

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

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

304 This drug is known to be substantially excreted by the kidney, and the risk of toxic  
305 reactions to this drug may be greater in patients with impaired renal function. Because  
306 elderly patients are more likely to have decreased renal function, care should be taken in

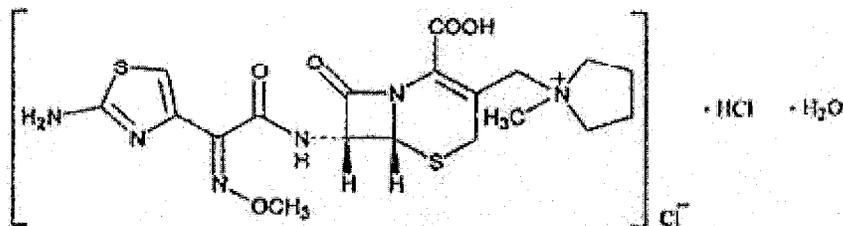
307 dose selection, and renal function should be monitored [see *Clinical Pharmacology (12)*,  
308 *Warnings and Precautions (5)*, and *Dosage and Administration (2)*].

## 309 10 OVERDOSAGE

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

## 318 11 DESCRIPTION

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



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

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

334 The solution is intended for intravenous use after thawing to room temperature. The  
 335 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 Hydrous, 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

336 \* Cefepime is present in the formulation as Cefepime Hydrochloride, USP. The amounts of Dextrose  
 337 Hydrous, USP and L-Arginine, USP are approximate.

338 † The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is  
 339 4.0 – 6.0.

340 ‡ This is an abbreviation for sufficient quantity.

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

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

347 **12 CLINICAL PHARMACOLOGY**

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

351 **12.1 Mechanism of Action**

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

353 **12.2 Pharmacodynamics**

354 Similar to other beta-lactam antimicrobial agents, the time that the unbound plasma  
 355 concentration of cefepime exceeds the MIC of the infecting organism has been shown to  
 356 best correlate with efficacy in animal models of infection. However, the

357 pharmacokinetic/pharmacodynamic relationship for cefepime has not been evaluated in  
 358 patients.

359 **12.3 Pharmacokinetics**

360 The average plasma concentrations of cefepime observed in healthy adult male  
 361 volunteers (n=9) at various times following single 30-minute intravenous infusions of  
 362 cefepime 500 mg, 1 g, and 2 g are summarized in Table 6. Elimination of cefepime is  
 363 principally via renal excretion with an average ( $\pm$ SD) half-life of 2 ( $\pm$ 0.3) hours and total  
 364 body clearance of 120 ( $\pm$ 8) mL/min in healthy volunteers. Cefepime pharmacokinetics  
 365 are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy  
 366 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 <sub>max</sub> , mcg/mL	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, h•mcg/mL	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

367 *Distribution*

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

371 Cefepime is excreted in human milk. A nursing infant consuming approximately  
 372 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per  
 373 day [see *Use in Specific Populations (8.3)*].

374 Concentrations of cefepime achieved in specific tissues and body fluids are listed in  
 375 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

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

378 *Metabolism and Excretion*

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

386 *Specific Populations*

387 Patients with Renal Impairment

388 Cefepime pharmacokinetics have been investigated in patients with various degrees of  
 389 renal impairment (n=30). The average half-life in patients requiring hemodialysis was 13.5  
 390 ( $\pm 2.7$ ) hours and in patients requiring continuous peritoneal dialysis was 19 ( $\pm 2.0$ ) hours.

391 Cefepime total body clearance decreased proportionally with creatinine clearance in  
392 patients with abnormal renal function, which serves as the basis for dosage adjustment  
393 recommendations in this group of patients [see *Dosage and Administration (2)*].

#### 394 Patients with Hepatic Impairment

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

#### 397 Geriatric Patients

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

#### 404 Pediatric Patients

405 Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to  
406 11 years of age following single and multiple doses on every 8 hours (n=29) and every 12  
407 hours (n=13) schedules. Following a single intravenous dose, total body clearance and the  
408 steady-state volume of distribution averaged 3.3 ( $\pm$ 1.0) mL/min/kg and 0.3 ( $\pm$ 0.1) L/kg,  
409 respectively. The urinary recovery of unchanged cefepime was 60.4 ( $\pm$ 30.4)% of the  
410 administered dose, and the average renal clearance was 2.0 ( $\pm$ 1.1) mL/min/kg. There  
411 were no significant effects of age or gender (25 male vs. 17 female) on total body  
412 clearance or volume of distribution, corrected for body weight. No accumulation was  
413 seen when cefepime was given at 50 mg per kg every 12 hours (n=13), while  $C_{max}$ , AUC,  
414 and  $t_{1/2}$  were increased about 15% at steady state after 50 mg per kg every 8 hours. The  
415 exposure to cefepime following a 50 mg per kg intravenous dose in a pediatric patient is  
416 comparable to that in an adult treated with a 2 g intravenous dose.

### 417 **12.4 Microbiology**

418 Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.  
419 Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of  
420 Gram-positive and Gram-negative bacteria. Cefepime has a low affinity for  
421 chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by  
422 most beta-lactamases and exhibits rapid penetration into Gram-negative bacterial cells.

423 Within bacterial cells, the molecular targets of cefepime are the penicillin binding  
424 proteins (PBP).

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

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

428 *Enterobacter*

429 *Escherichia coli*

430 *Klebsiella pneumoniae*

431 *Proteus mirabilis*

432 *Pseudomonas aeruginosa*

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

434 *Staphylococcus aureus* (methicillin-susceptible isolates only)

435 *Streptococcus pneumoniae*

436 *Streptococcus pyogenes* (Lancefield's Group A streptococci)

437 Viridans group streptococci

438 The following *in vitro* data are available, **but their clinical significance is unknown.**

439 Cefepime has been shown to have *in vitro* activity against most isolates of the following  
440 microorganisms; however, the safety and effectiveness of cefepime in treating clinical  
441 infections due to these microorganisms have not been established in adequate and well-  
442 controlled trials.

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

444 *Staphylococcus epidermidis* (methicillin-susceptible isolates only)

445 *Staphylococcus saprophyticus*

446 *Streptococcus agalactiae* (Lancefield's Group B streptococci)

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

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

450 *Acinetobacter calcoaceticus* subsp. *lwoffii*

451 *Citrobacter diversus*

452 *Citrobacter freundii*

453 *Enterobacter agglomerans*

454 *Haemophilus influenzae* (including beta-lactamase producing isolates)

- 455 *Hafnia alvei*
- 456 *Klebsiella oxytoca*
- 457 *Moraxella catarrhalis* (including beta-lactamase producing isolates)
- 458 *Morganella morganii*
- 459 *Proteus vulgaris*
- 460 *Providencia rettgeri*
- 461 *Providencia stuartii*
- 462 *Serratia marcescens*

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

465 • **Anaerobic Microorganisms:**

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

467 **Susceptibility Tests**

468 Dilution Techniques

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

**Table 8**

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

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

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

490 Standardized susceptibility test procedures require the use of laboratory control  
491 microorganisms to control the technical aspects of the laboratory procedures. Laboratory  
492 control microorganisms are specific strains of microbiological assay organisms with  
493 intrinsic biological properties relating to resistance mechanisms and their genetic  
494 expression within bacteria; the specific strains are not clinically significant in their  
495 current microbiological status. Standard cefepime powder should provide the following  
496 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

497 Diffusion Techniques

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

504 Reports from the laboratory providing results of the standard single-disk susceptibility  
 505 test with a 30-mcg cefepime disk should be interpreted according to the following  
 506 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	—*	—*

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

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

517 should provide the following zone diameters in these laboratory test quality control  
 518 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

519 **13 NONCLINICAL TOXICOLOGY**

520 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

521 No animal carcinogenicity studies have been conducted with cefepime. In  
 522 chromosomal aberration studies, cefepime was positive for clastogenicity in primary  
 523 human lymphocytes, but negative in Chinese hamster ovary cells. In other *in vitro*  
 524 assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes,  
 525 and sister chromatid exchange in human lymphocytes), cefepime was negative for  
 526 genotoxic effects. Moreover, *in vivo* assessments of cefepime in mice (2 chromosomal  
 527 aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward  
 528 effects on fertility were observed in rats when cefepime was administered  
 529 subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum  
 530 human dose calculated on a mg/m<sup>2</sup> basis).

531 **14 CLINICAL STUDIES**

532 **14.1 Febrile Neutropenic Patients**

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

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

	Cefepime	Ceftazidime
<b>Total</b>	<b>164</b>	<b>153</b>

---

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%)

---

538           ANC = absolute neutrophil count; SBP = systolic blood pressure

539   Table 13 describes the clinical response rates observed. For all outcome measures,  
540   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

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

546 **14.2 Complicated Intra-abdominal Infections**

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

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

## 562 **15 REFERENCES**

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564 creatinine. *Nephron*. 1976; 16:31-41.

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566 *Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*—Third Edition.  
567 Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA,  
568 December 1993.

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

## 572 **16 HOW SUPPLIED/STORAGE AND HANDLING**

573 Cefepime Injection is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in  
574 50 mL and 100 mL single-dose GALAXY containers (PL 2040 Plastic) as follows:

575	2G3578	NDC 0338-1301-41	1 g* in 50 mL	Supplied 24/box
576	2G3579	NDC 0338-1301-48	2 g* in 100 mL	Supplied 12/box

577

578 \* Based on cefepime activity

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

580 Thaw frozen container at room temperature  $25^{\circ}\text{C}$  ( $77^{\circ}\text{F}$ ) or under refrigeration  $5^{\circ}\text{C}$   
581 ( $41^{\circ}\text{F}$ ). Do not force thaw by immersion in water baths or by microwave irradiation.

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

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

## 585 **17 PATIENT COUNSELING INFORMATION**

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

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

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

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

607 Manufactured by:

608 Baxter Healthcare Corporation

609 Deerfield, IL 60015

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