

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)
- Use in patients with renal impairment: dosage adjustment required for patients with CrCL ≤ 60 mL/min. (5.2)
- Neurotoxicity: May occur in patients receiving inappropriate dosage adjustment(s) for renal impairment. Discontinue cefepime or make appropriate dosage adjustments in patients with renal impairment in the event of neurotoxicity. (5.3)
- *Clostridium difficile* associated diarrhea: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs (5.4)

ADVERSE REACTIONS

- The most common adverse reactions (incidence ≥ 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.

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)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Pneumonia
- 1.2 Empiric Therapy for Febrile Neutropenic Patients
- 1.3 Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis)
- 1.4 Uncomplicated Skin and Skin Structure Infections
- 1.5 Complicated Intra-abdominal Infections

2 DOSAGE AND ADMINISTRATION

- 2.1 Adults and Pediatric Population
- 2.2 Patients with Hepatic Impairment
- 2.3 Patients with Renal Impairment
- 2.4 Directions for Use of Cefepime Injection in GALAXY Container

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity
- 5.2 Renal Impairment
- 5.3 Neurotoxicity
- 5.4 *Clostridium difficile* Associated Diarrhea
- 5.5 Risk of Development of Drug-Resistant Bacteria
- 5.6 Patients with Meningeal Seeding/Meningitis
- 5.7 Drug/Laboratory Test Interactions
- 5.8 Patients with a History of Gastrointestinal Disease
- 5.9 Possible Effects of Arginine on Glucose Metabolism

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience
- 6.3 Cephalosporin-class Adverse Reactions

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

See 17 for Patient Counseling Information.

Revised: 09/2012

7 DRUG INTERACTIONS

- 7.1 Aminoglycosides
- 7.2 Diuretics

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Febrile Neutropenic Patients
- 14.2 Complicated Intra-abdominal Infections

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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) |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------------|-----------------|
| Adults | | | |
| Moderate to Severe Pneumonia due to <i>S. pneumoniae</i> *, <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , or <i>Enterobacter</i> species | 1-2 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)¹ 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.

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 cefepime concentrations can occur from usual
133 dosages in patients with renal impairment or other conditions that may compromise renal
134 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 **5.3 Neurotoxicity**

139 During postmarketing surveillance, serious adverse reactions have been reported
140 including life-threatening or fatal occurrences of the following: encephalopathy
141 (disturbance of consciousness including confusion, hallucinations, stupor, and coma),
142 myoclonus, seizures, and nonconvulsive status epilepticus [*see Adverse Reactions (6.2)*].
143 Most cases occurred in patients with renal impairment who did not receive appropriate
144 dosage adjustment. However, some cases of neurotoxicity occurred in patients receiving
145 a dosage adjustment appropriate for their degree of renal impairment.

146 In the majority of cases, symptoms of neurotoxicity were reversible and resolved after
147 discontinuation of cefepime and/or after hemodialysis. If neurotoxicity associated with
148 cefepime therapy occurs, consider discontinuing cefepime or making appropriate dosage
149 adjustments in patients with renal impairment.

150 **5.4 Clostridium difficile Associated Diarrhea**

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

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

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

165 **5.5 Risk of Development of Drug-Resistant Bacteria**

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

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

173 **5.6 Patients with Meningeal Seeding/Meningitis**

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

177 **5.7 Drug/Laboratory Test Interactions**

178 Urinary Glucose

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

182 Coombs' Test

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

188 Prothrombin Time

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

194 **5.8 Patients with a History of Gastrointestinal Disease**

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

197 **5.9 Possible Effects of Arginine on Glucose Metabolism**

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

202 **6 ADVERSE REACTIONS**

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

- 204
- 205 • Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
 - 206 • Renal Impairment [see *Warnings and Precautions (5.2)*]
 - 207 • Neurotoxicity [see *Warnings and Precautions (5.3)*]
 - *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.4)*]

208 **6.1 Clinical Trials Experience**

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

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

221 The following adverse events were thought to be probably related to cefepime during
222 evaluation of the drug in clinical trials conducted in North America (n=3125 cefepime-
223 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 |

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

226 At the higher dose of 2 g every 8 hours, the incidence of probably-related adverse
227 events was higher among the 795 patients who received this dose of cefepime. They
228 consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever
229 (1%), and headache (1%).

230 The following adverse laboratory changes, irrespective of relationship to therapy with
231 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 |

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

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

236 6.2 Postmarketing Experience

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

242 Encephalopathy (disturbance of consciousness including confusion, hallucinations,
243 stupor, and coma), myoclonus, seizures, and nonconvulsive status epilepticus have been
244 reported. Although most cases occurred in patients with renal impairment who received
245 doses of cefepime that exceeded the recommended dosage schedules, some cases of
246 neurotoxicity occurred in patients receiving an appropriate dosage adjustment for their
247 degree of renal impairment. If neurotoxicity associated with cefepime therapy occurs,
248 consider discontinuing cefepime or making appropriate dosage adjustments in patients
249 with renal impairment.

250
251 As with other cephalosporins, anaphylaxis including anaphylactic shock, transient
252 leukopenia, neutropenia, agranulocytosis, and thrombocytopenia have been reported.

253 6.3 Cephalosporin-class Adverse Reactions

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

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

260 **7 DRUG INTERACTIONS**

261 **7.1 Aminoglycosides**

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

265 **7.2 Diuretics**

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

268 **8 USE IN SPECIFIC POPULATIONS**

269 **8.1 Pregnancy**

270 Pregnancy Category B. Cefepime was not teratogenic or embryocidal when
271 administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day
272 (1.6 times the recommended maximum human dose calculated on a mg/m² basis) or to
273 mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum
274 human dose calculated on a mg/m² basis) or to rabbits at a dose level of 100 mg/kg (0.3
275 times the recommended maximum human dose calculated on a mg/m² basis).

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

279 **8.2 Labor and Delivery**

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

282 **8.3 Nursing Mothers**

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

286 **8.4 Pediatric Use**

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

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

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

301 **8.5 Geriatric Use**

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

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

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

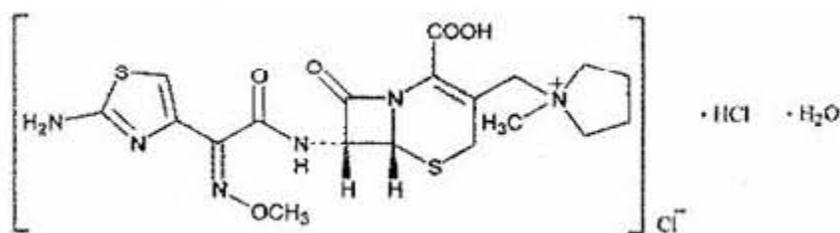
315 **10 OVERDOSAGE**

316 Patients who receive an overdose should be carefully observed and given supportive
317 treatment. In the presence of renal impairment, hemodialysis, not peritoneal dialysis, is

318 recommended to aid in the removal of cefepime from the body. Accidental overdosing
 319 has occurred when large doses were given to patients with impaired renal function.
 320 Symptoms of overdose include encephalopathy (disturbance of consciousness including
 321 confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular
 322 excitability [see Warnings and Precautions (5), Adverse Reactions (6), and Dosage and
 323 Administration (2)].

324 **11 DESCRIPTION**

325 Cefepime Injection in GALAXY Containers (PL 2040 Plastic) is a sterile, injectable
 326 product consisting of Cefepime Hydrochloride, USP, a semi-synthetic, broad spectrum,
 327 cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[[(6R,7R)-
 328 7-[2-(2-Amino-4-thiazolyl) glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]
 329 oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(Z)-(O-methyloxime),
 330 monohydrochloride, monohydrate, which corresponds to the following structural
 331 formula:



332
 333 Cefepime hydrochloride (monohydrate) has a molecular mass of 571.50 and a molecular
 334 formula of C₁₉H₂₅ClN₆O₅S₂·HCl·H₂O.

335 Cefepime Injection in GALAXY Container (PL 2040 Plastic) is a frozen, iso-osmotic,
 336 sterile, non-pyrogenic premixed solution supplied for intravenous administration in
 337 strengths equivalent to 1 g and 2 g of cefepime [see Dosage and Administration (2)]. It
 338 contains the equivalent of not less than 90 percent and not more than 115 percent of the
 339 labeled amount of cefepime (C₁₉H₂₄N₆O₅S₂).

340 The solution is intended for intravenous use after thawing to room temperature. The
 341 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 |

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

344 † The pH may have been adjusted with hydrochloric acid and/or additional L-Arginine, USP. The pH is
 345 4.0 – 6.0.

346 ‡ This is an abbreviation for sufficient quantity.

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

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

353 12 CLINICAL PHARMACOLOGY

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

357 12.1 Mechanism of Action

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

359 12.2 Pharmacodynamics

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

365 12.3 Pharmacokinetics

366 The average plasma concentrations of cefepime observed in healthy adult male
 367 volunteers (n=9) at various times following single 30-minute intravenous infusions of
 368 cefepime 500 mg, 1 g, and 2 g are summarized in Table 6. Elimination of cefepime is

369 principally via renal excretion with an average (\pm SD) half-life of 2 (\pm 0.3) hours and total
 370 body clearance of 120 (\pm 8) mL/min in healthy volunteers. Cefepime pharmacokinetics
 371 are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy
 372 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 |

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.

382

383

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 |

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

386 *Metabolism and Excretion*

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

394 *Specific Populations*

395 Patients with Renal Impairment

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

402 Patients with Hepatic Impairment

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

405 Geriatric Patients

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

412 Pediatric Patients

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

425 **12.4 Microbiology**

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

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

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

436 *Enterobacter*
437 *Escherichia coli*
438 *Klebsiella pneumoniae*
439 *Proteus mirabilis*
440 *Pseudomonas aeruginosa*

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

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

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

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

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

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

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

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

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

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

473 • **Anaerobic Microorganisms:**

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

475 **Susceptibility Tests**

476 Dilution Techniques

477 Quantitative methods are used to determine antimicrobial minimum inhibitory
 478 concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to
 479 antimicrobial compounds. The MICs should be determined using a standardized
 480 procedure. Standardized procedures are based on a dilution method² (broth or agar) or
 481 equivalent with standardized inoculum concentrations and standardized concentrations of
 482 cefepime powder. The MIC values should be interpreted according to the following
 483 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 |

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

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

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

498 Standardized susceptibility test procedures require the use of laboratory control
499 microorganisms to control the technical aspects of the laboratory procedures. Laboratory
500 control microorganisms are specific strains of microbiological assay organisms with
501 intrinsic biological properties relating to resistance mechanisms and their genetic
502 expression within bacteria; the specific strains are not clinically significant in their
503 current microbiological status. Standard cefepime powder should provide the following
504 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 |

505 Diffusion Techniques

506 Quantitative methods that require measurement of zone diameters also provide
 507 reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One
 508 such standardized procedure³ requires the use of standardized inoculum concentrations.
 509 This procedure uses paper disks impregnated with 30 mcg of cefepime to test the
 510 susceptibility of microorganisms to cefepime. Interpretation is identical to that stated
 511 above for results using dilution techniques.

512 Reports from the laboratory providing results of the standard single-disk susceptibility
 513 test with a 30-mcg cefepime disk should be interpreted according to the following
 514 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 | —* | —* |

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

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

525 should provide the following zone diameters in these laboratory test quality control
526 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 |

527 **13 NONCLINICAL TOXICOLOGY**

528 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

529 No animal carcinogenicity studies have been conducted with cefepime. In
530 chromosomal aberration studies, cefepime was positive for clastogenicity in primary
531 human lymphocytes, but negative in Chinese hamster ovary cells. In other *in vitro*
532 assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes,
533 and sister chromatid exchange in human lymphocytes), cefepime was negative for
534 genotoxic effects. Moreover, *in vivo* assessments of cefepime in mice (2 chromosomal
535 aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward
536 effects on fertility were observed in rats when cefepime was administered
537 subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum
538 human dose calculated on a mg/m² basis).

539 **14 CLINICAL STUDIES**

540 **14.1 Febrile Neutropenic Patients**

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

546

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%) |

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

548 Table 13 describes the clinical response rates observed. For all outcome measures,
 549 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 |

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

555 **14.2 Complicated Intra-abdominal Infections**

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

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

571 **15 REFERENCES**

572 (1) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum
573 creatinine. *Nephron*. 1976; 16:31-41.

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

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

581 **16 HOW SUPPLIED/STORAGE AND HANDLING**

582 Cefepime Injection is supplied as a frozen, iso-osmotic, sterile, nonpyrogenic solution in
583 50 mL and 100 mL single-dose GALAXY containers (PL 2040 Plastic) as follows:

| | | | | |
|-----|--------|------------------|----------------|-----------------|
| 584 | 2G3578 | NDC 0338-1301-41 | 1 g* in 50 mL | Supplied 24/box |
| 585 | 2G3579 | NDC 0338-1301-48 | 2 g* in 100 mL | Supplied 12/box |

586

587 * Based on cefepime activity

588 Store at or below -20°C (-4°F).

589 Handle frozen product containers with care. Product containers may be fragile in the
590 frozen state.

591 Thaw frozen container at room temperature 25°C (77°F) or under refrigeration 5°C
592 (41°F). Do not force thaw by immersion in water baths or by microwave irradiation.

593 The thawed solution remains stable for 7 days under refrigeration 5°C (41°F) or 24 hours
594 at room temperature 25°C (77°F). Do not refreeze.

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

596

597 **17 PATIENT COUNSELING INFORMATION**

- 598 • Patients should be counseled that antibacterial drugs including Cefepime Injection
599 should only be used to treat bacterial infections. They do not treat viral infections
600 (e.g., the common cold). When Cefepime Injection is prescribed to treat a
601 bacterial infection, patients should be told that although it is common to feel
602 better early in the course of therapy, the medication should be taken exactly as
603 directed. Skipping doses or not completing the full course of therapy may (1)
604 decrease the effectiveness of the immediate treatment and (2) increase the
605 likelihood that bacteria will develop resistance and will not be treatable by
606 Cefepime Injection or other antibacterial drugs in the future.
- 607 • Diarrhea is a common problem caused by antibiotics, which usually ends when
608 the antibiotic is discontinued. Sometimes after starting treatment with antibiotics,
609 patients can develop watery and bloody stools (with or without stomach cramps
610 and fever) even as late as two or more months after having taken the last dose of
611 the antibiotic. If this occurs, patients should be instructed to contact their
612 physician as soon as possible.
- 613 • Patients should be advised of neurological adverse events that could occur with
614 Cefepime Injection use. Patients should be instructed to inform their healthcare
615 provider at once of any neurological signs and symptoms including
616 encephalopathy (disturbance of consciousness including confusion,
617 hallucinations, stupor, and coma), myoclonus and seizures for immediate
618 treatment, dosage adjustment, or discontinuation of Cefepime Injection.

619 Manufactured by:

620 Baxter Healthcare Corporation

621 Deerfield, IL 60015

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623 Clinitest is a registered trademark of Siemens Healthcare Diagnostics Inc.

624 Clinistix is a registered trademark of Bayer Healthcare LLC.

625 F7-19-69-226