

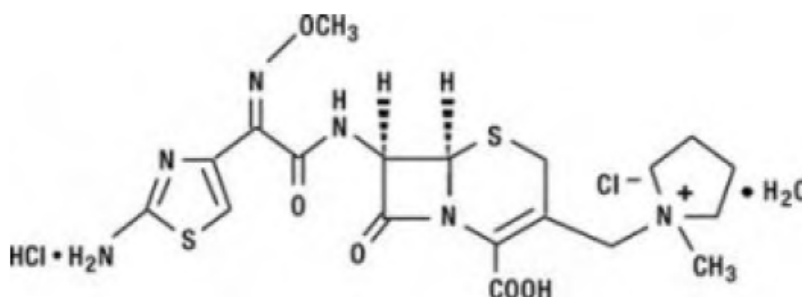
1 **MAXIPIME™**
2
3 **(Cefepime Hydrochloride, USP) for Injection**

4
5 **For Intravenous or Intramuscular Use**

6
7 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
8 MAXIPIME and other antibacterial drugs, MAXIPIME should be used only to treat or
9 prevent infections that are proven or strongly suspected to be caused by bacteria.

10
11 **DESCRIPTION**

12
13 MAXIPIME (cefepime hydrochloride, USP) is a semi-synthetic, broad spectrum,
14 cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[[(6R,7R)-
15 7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]
16 oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(Z)-(O-methyloxime),
17 monohydrochloride, monohydrate, which corresponds to the following structural
18 formula:



34 Cefepime hydrochloride is a white to pale yellow powder. Cefepime hydrochloride
35 contains the equivalent of not less than 825 mcg and not more than 911 mcg of cefepime
36 ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on an anhydrous basis. It is highly soluble in water.

37 MAXIPIME for Injection is supplied for intramuscular or intravenous administration in
38 strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. (See **DOSAGE AND**
39 **ADMINISTRATION**.) MAXIPIME is a sterile, dry mixture of cefepime hydrochloride
40 and L-arginine. It contains the equivalent of not less than 90 percent and not more than
41 115 percent of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$). The L-arginine, at an
42 approximate concentration of 707 mg/g of cefepime, is added to control the pH of the
43 constituted solution at 4 to 6. Freshly constituted solutions of MAXIPIME will range in
44 color from pale yellow to amber.

45
46
47
48

43 **CLINICAL PHARMACOLOGY**

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

49 **Pharmacokinetics**

50

51 The average plasma concentrations of cefepime observed in healthy adult male
52 volunteers (n=9) at various times following single 30-minute infusions (IV) of cefepime
53 500 mg, 1 g, and 2 g are summarized in Table 1. Elimination of cefepime is principally
54 via renal excretion with an average (\pm SD) half-life of 2 (\pm 0.3) hours and total body
55 clearance of 120 (\pm 8) mL/min in healthy volunteers. Cefepime pharmacokinetics are
56 linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy
57 adult male volunteers (n=7) receiving clinically relevant doses for a period of 9 days.

58

59 **Absorption**

60

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

63

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

Parameter	MAXIPIME		
	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

66

67 Following intramuscular (IM) administration, cefepime is completely absorbed. The
68 average plasma concentrations of cefepime at various times following a single
69 intramuscular injection are summarized in Table 2. The pharmacokinetics of cefepime are
70 linear over the range of 500 mg to 2 g intramuscularly and do not vary with respect to
71 treatment duration.

72

73 Table 2: Average Plasma Concentrations in mcg/mL of Cefepime and Derived
74 Pharmacokinetic Parameters (\pm SD), Intramuscular Administration

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

75

76 **Distribution**

77
78 The average steady-state volume of distribution of cefepime is 18 (\pm 2) L. The serum
79 protein binding of cefepime is approximately 20% and is independent of its concentration
80 in serum.

81
82 Cefepime is excreted in human milk. A nursing infant consuming approximately
83 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per
84 day. (See **PRECAUTIONS: Nursing Mothers**.)

85
86 Concentrations of cefepime achieved in specific tissues and body fluids are listed in
87 Table 3.

88
89 Table 3: Average Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or
90 Tissues (mcg/g)

Tissue or Fluid	Dose/Route	# of Patients	Average Time of Sample Post-Dose (h)	Average Concentration
Blister Fluid	2 g IV	6	1.5	81.4 mcg/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 mcg/g
Sputum	2 g IV	5	4	7.4 mcg/mL
Urine	500 mg IV	8	0 to 4	292 mcg/mL
	1 g IV	12	0 to 4	926 mcg/mL
	2 g IV	12	0 to 4	3120 mcg/mL
Bile	2 g IV	26	9.4	17.8 mcg/mL
Peritoneal Fluid	2 g IV	19	4.4	18.3 mcg/mL
Appendix	2 g IV	31	5.7	5.2 mcg/g
Gallbladder	2 g IV	38	8.9	11.9 mcg/g
Prostate	2 g IV	5	1	31.5 mcg/g

91
92 Data suggest that cefepime does cross the inflamed blood-brain barrier. **The clinical**
93 **relevance of these data is uncertain at this time.**

94
95 **Metabolism and Excretion**

96
97 Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the
98 N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for
99 approximately 85% of the administered dose. Less than 1% of the administered dose is
100 recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of
101 cefepime. Because renal excretion is a significant pathway of elimination, patients with
102 renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See
103 **DOSAGE AND ADMINISTRATION**.)

104
105 **Specific Populations**

106
107 *Renal impairment:* Cefepime pharmacokinetics have been investigated in patients with
108 various degrees of renal impairment (n=30). The average half-life in patients requiring
109 hemodialysis was 13.5 (\pm 2.7) hours and in patients requiring continuous peritoneal
110 dialysis was 19 (\pm 2) hours. Cefepime total body clearance decreased proportionally with

111 creatinine clearance in patients with abnormal renal function, which serves as the basis
112 for dosage adjustment recommendations in this group of patients. (See **DOSAGE AND**
113 **ADMINISTRATION.**)

114
115 *Hepatic impairment:* The pharmacokinetics of cefepime were unaltered in patients with
116 hepatic impairment who received a single 1 g dose (n=11).

117
118 *Geriatric patients:* Cefepime pharmacokinetics have been investigated in elderly
119 (65 years of age and older) men (n=12) and women (n=12) whose mean (SD) creatinine
120 clearance was 74 (\pm 15) mL/min. There appeared to be a decrease in cefepime total body
121 clearance as a function of creatinine clearance. Therefore, dosage administration of
122 cefepime in the elderly should be adjusted as appropriate if the patient's creatinine
123 clearance is 60 mL/min or less. (See **DOSAGE AND ADMINISTRATION.**)

124
125 *Pediatric patients:* Cefepime pharmacokinetics have been evaluated in pediatric patients
126 from 2 months to 11 years of age following single and multiple doses on every 8 hours
127 (n=29) and every 12 hours (n=13) schedules. Following a single intravenous dose, total
128 body clearance and the steady-state volume of distribution averaged 3.3 (\pm 1) mL/min/kg
129 and 0.3 (\pm 0.1) L/kg, respectively. The urinary recovery of unchanged cefepime was 60.4
130 (\pm 30.4)% of the administered dose, and the average renal clearance was 2 (\pm 1.1)
131 mL/min/kg. There were no significant effects of age or gender (25 male vs 17 female) on
132 total body clearance or volume of distribution, corrected for body weight. No
133 accumulation was seen when cefepime was given at 50 mg per kg every 12 hours (n=13),
134 while C_{max} , AUC, and $t_{1/2}$ were increased about 15% at steady state after 50 mg per kg
135 every 8 hours. The exposure to cefepime following a 50 mg per kg intravenous dose in a
136 pediatric patient is comparable to that in an adult treated with a 2 g intravenous dose. The
137 absolute bioavailability of cefepime after an intramuscular dose of 50 mg per kg was 82.3
138 (\pm 15)% in eight patients.

139 140 **Microbiology**

141
142 Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.
143 Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of
144 Gram-positive and Gram-negative bacteria. Cefepime has a low affinity for
145 chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by
146 most beta-lactamases and exhibits rapid penetration into Gram-negative bacterial cells.
147 Within bacterial cells, the molecular targets of cefepime are the penicillin binding
148 proteins (PBP).

149
150 Cefepime has been shown to be active against most isolates of the following
151 microorganisms, both *in vitro* and in clinical infections as described in the
152 **INDICATIONS AND USAGE** section.

153
154 Aerobic Gram-Negative Microorganisms:

- 155 *Enterobacter*
- 156 *Escherichia coli*
- 157 *Klebsiella pneumoniae*

158 *Proteus mirabilis*

159 *Pseudomonas aeruginosa*

160 Aerobic Gram-Positive Microorganisms:

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

162 *Streptococcus pneumoniae*

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

164 Viridans group streptococci

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

171 Aerobic Gram-Positive Microorganisms:

172
173 *Staphylococcus epidermidis* (methicillin-susceptible isolates only)

174 *Staphylococcus saprophyticus*

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

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

178
179 Aerobic Gram-Negative Microorganisms:

180
181 *Acinetobacter calcoaceticus* subsp. *lwoffii*

182 *Citrobacter diversus*

183 *Citrobacter freundii*

184 *Enterobacter agglomerans*

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

186 *Hafnia alvei*

187 *Klebsiella oxytoca*

188 *Moraxella catarrhalis* (including beta-lactamase producing isolates)

189 *Morganella morganii*

190 *Proteus vulgaris*

191 *Providencia rettgeri*

192 *Providencia stuartii*

193 *Serratia marcescens*

194 NOTE: Cefepime is inactive against many isolates of *Stenotrophomonas* (formerly
195 *Xanthomonas maltophilia* and *Pseudomonas maltophilia*).
196

197 Anaerobic Microorganisms:
198

199 NOTE: Cefepime is inactive against most isolates of *Clostridium difficile*.
200

201 **Susceptibility Tests**

202
203 **Dilution Techniques**

204
205 Quantitative methods are used to determine antimicrobial minimum inhibitory
206 concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to
207 antimicrobial compounds. The MICs should be determined using a standardized
208 procedure. Standardized procedures are based on a dilution method¹ (broth or agar) or
209 equivalent with standardized inoculum concentrations and standardized concentrations of
210 cefepime powder. The MIC values should be interpreted according to the following
211 criteria:
212

Table 4

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

213 *NOTE: Isolates from these species should be tested for susceptibility using specialized dilution testing
214 methods.¹ Also, isolates of *Haemophilus* spp. with MICs greater than 2 mcg/mL should be considered
215 equivocal and should be further evaluated.
216

217 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the
218 antimicrobial compound in the blood reaches the concentrations usually achievable. A
219 report of “Intermediate” indicates that the result should be considered equivocal, and, if
220 the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test
221 should be repeated. This category implies possible clinical applicability in body sites
222 where the drug is physiologically concentrated or in situations where high dosage of drug
223 can be used. This category also provides a buffer zone which prevents small uncontrolled
224 technical factors from causing major discrepancies in interpretation. A report of
225 “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial
226 compound in the blood reaches the concentrations usually achievable; other therapy
227 should be selected.
228

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

236

Table 5

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

237

238

239

Diffusion Techniques

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245

246

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of cefepime to test the susceptibility of microorganisms to cefepime. Interpretation is identical to that stated above for results using dilution techniques.

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251

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

Table 6

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

252

253

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257

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

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267

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

Table 7

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

268 **INDICATIONS AND USAGE**

269

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

273

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

277

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

285

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

291

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

294

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

299

300 To reduce the development of drug-resistant bacteria and maintain the effectiveness of
301 MAXIPIME and other antibacterial drugs, MAXIPIME should be used only to treat or
302 prevent infections that are proven or strongly suspected to be caused by susceptible
303 bacteria. When culture and susceptibility information are available, they should be
304 considered in selecting or modifying antibacterial therapy. In the absence of such data,
305 local epidemiology and susceptibility patterns may contribute to the empiric selection of
306 therapy.

307

308 **CLINICAL STUDIES**

309

310 **Febrile Neutropenic Patients**

311

312 The safety and efficacy of empiric cefepime monotherapy of febrile neutropenic patients
313 have been assessed in two multicenter, randomized trials comparing cefepime
314 monotherapy (at a dose of 2 g intravenously every 8 hours) to ceftazidime monotherapy

315 (at a dose of 2 g intravenously every 8 hours). These studies comprised 317 evaluable
316 patients. Table 8 describes the characteristics of the evaluable patient population.

317
318

Table 8: Demographics of Evaluable Patients (First Episodes Only)

Total	Cefepime	Ceftazidime
	164	153
Median age (yr)	56 (range, 18 to 82)	55 (range, 16 to 84)
Male	86 (52%)	85 (56%)
Female	78 (48%)	68 (44%)
Leukemia	65 (40%)	52 (34%)
Other hematologic malignancies	43 (26%)	36 (24%)
Solid tumor	54 (33%)	56 (37%)
Median ANC nadir (cells/microliter)	20 (range, 0 to 500)	20 (range, 0 to 500)
Median duration of neutropenia (days)	6 (range, 0 to 39)	6 (range, 0 to 32)
Indwelling venous catheter	97 (59%)	86 (56%)
Prophylactic antibiotics	62 (38%)	64 (42%)
Bone marrow graft	9 (5%)	7 (5%)
SBP less than 90 mm Hg at entry	7 (4%)	2 (1%)

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

320

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

323

324 Table 9: 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

325

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

331

332 **Complicated Intra-Abdominal Infections**

333

334 Patients hospitalized with complicated intra-abdominal infections participated in a
335 randomized, double-blind, multicenter trial comparing the combination of cefepime (2 g
336 every 12 hours) plus intravenous metronidazole (500 mg every 6 hours) versus
337 imipenem/cilastatin (500 mg every 6 hours) for a maximum duration of 14 days of
338 therapy. The study was designed to demonstrate equivalence of the two therapies. The
339 primary analyses were conducted on the protocol-valid population, which consisted of
340 those with a surgically confirmed complicated infection, at least one pathogen isolated
341 pretreatment, at least 5 days of treatment, and a 4 to 6 week follow-up assessment for
342 cured patients. Subjects in the imipenem/cilastatin arm had higher APACHE II scores at
343 baseline. The treatment groups were otherwise generally comparable with regard to their
344 pretreatment characteristics. The overall clinical cure rate among the protocol-valid
345 patients was 81% (51 cured/63 evaluable patients) in the cefepime plus metronidazole
346 group and 66% (62/94) in the imipenem/cilastatin group. The observed differences in
347 efficacy may have been due to a greater proportion of patients with high APACHE II
348 scores in the imipenem/cilastatin group.

349

350 **CONTRAINDICATIONS**

351

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

355

356 **WARNINGS**

357

358 **Hypersensitivity Reactions to Cefepime, Cephalosporins, Penicillins, or Other Drugs**

359 Before therapy with MAXIPIME for Injection is instituted, careful inquiry should be
360 made to determine whether the patient has had previous immediate hypersensitivity
361 reactions to cefepime, cephalosporins, penicillins, or other drugs. Exercise caution if this
362 product is to be given to penicillin-sensitive patients because cross-hypersensitivity
363 among beta-lactam antibiotics has been clearly documented and may occur in up to 10%
364 of patients with a history of penicillin allergy. If an allergic reaction to MAXIPIME
365 occurs, discontinue the drug.

366

367 **Use in Patients with Renal Impairment**

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

375

376 **Neurotoxicity**

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

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

388

389 ***Clostridium difficile* Associated Diarrhea**

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

394

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

401

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

406

407 **PRECAUTIONS**

408

409 **General**

410

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

414

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

419

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

425

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

431

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

434

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

439

440 **Information for Patients**

441

442 Before therapy with MAXIPIME is instituted, careful inquiry should be made to
443 determine whether the patient has had previous immediate hypersensitivity reactions to
444 cefepime, cephalosporins, penicillins, or other drugs. Exercise caution if this product is to
445 be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam
446 antibiotics has been clearly documented and may occur in up to 10% of patients with a
447 history of penicillin allergy. If an allergic reaction to MAXIPIME occurs, discontinue the
448 drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and
449 other emergency 15 measures including oxygen, corticosteroids, intravenous fluids,
450 intravenous antihistamines, pressor amines, and airway management, as clinically
451 indicated.

452

453 Patients should be counseled that antibacterial drugs including MAXIPIME should only
454 be used to treat bacterial infections. They do not treat viral infections (eg, the common
455 cold). When MAXIPIME is prescribed to treat a bacterial infection, patients should be
456 told that although it is common to feel better early in the course of therapy, the
457 medication should be taken exactly as directed. Skipping doses or not completing the full
458 course of therapy may (1) decrease the effectiveness of the immediate treatment and (2)
459 increase the likelihood that bacteria will develop resistance and will not be treatable by
460 MAXIPIME or other antibacterial drugs in the future.

461

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

467

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

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

474

475 **Drug Interactions**

476

477 Renal function should be monitored carefully if high doses of aminoglycosides are to be
478 administered with MAXIPIME because of the increased potential of nephrotoxicity and
479 ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following
480 concomitant administration of other cephalosporins with potent diuretics such as
481 furosemide.

482

483 **Drug/Laboratory Test Interactions**

484

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

488

489 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

490

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

501

502 **Pregnancy**

503

504 **Teratogenic Effects: Pregnancy Category B**

505

506 Cefepime was not teratogenic or embryocidal when administered during the period of
507 organogenesis to rats at doses up to 1000 mg/kg/day (1.6 times the recommended
508 maximum human dose calculated on a mg/m² basis) or to mice at doses up to 1200 mg/kg
509 (approximately equal to the recommended maximum human dose calculated on a mg/m²
510 basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum
511 human dose calculated on a mg/m² basis).

512

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

516

517

518

519 **Nursing Mothers**

520
521 Cefepime is excreted in human breast milk in very low concentrations (0.5 mcg/mL).
522 Caution should be exercised when cefepime is administered to a nursing woman.
523

524 **Labor and Delivery**

525
526 Cefepime has not been studied for use during labor and delivery. Treatment should only
527 be given if clearly indicated.
528

529 **Pediatric Use**

530
531 The safety and effectiveness of cefepime in the treatment of uncomplicated and
532 complicated urinary tract infections (including pyelonephritis), uncomplicated skin and
533 skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic
534 patients have been established in the age groups 2 months up to 16 years. Use of
535 MAXIPIME in these age groups is supported by evidence from adequate and well-
536 controlled studies of cefepime in adults with additional pharmacokinetic and safety data
537 from pediatric trials (see **CLINICAL PHARMACOLOGY**).
538

539 Safety and effectiveness in pediatric patients below the age of 2 months have not been
540 established. There are insufficient clinical data to support the use of MAXIPIME in
541 pediatric patients under 2 months of age or for the treatment of serious infections in the
542 pediatric population where the suspected or proven pathogen is *Haemophilus influenzae*
543 type b.
544

545 IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT
546 INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR
547 DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL
548 EFFICACY IN THIS SETTING SHOULD BE USED.
549

550 **Geriatric Use**

551
552 Of the more than 6400 adults treated with MAXIPIME in clinical studies, 35% were
553 65 years or older while 16% were 75 years or older. When geriatric patients received the
554 usual recommended adult dose, clinical efficacy and safety were comparable to clinical
555 efficacy and safety in nongeriatric adult patients.
556

557 Serious adverse events have occurred in geriatric patients with renal insufficiency given
558 unadjusted doses of cefepime, including life-threatening or fatal occurrences of the
559 following: encephalopathy, myoclonus, and seizures. (See **WARNINGS** and **ADVERSE**
560 **REACTIONS**.)
561

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

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

568
569 **ADVERSE REACTIONS**

570
571 **Clinical Trials**

572
573 Because clinical trials are conducted under widely varying conditions, adverse reaction
574 rates observed in clinical trials of a drug cannot be directly compared to rates in the
575 clinical trials of another drug and may not reflect the rates observed in practice.

576
577 In clinical trials using multiple doses of cefepime, 4137 patients were treated with the
578 recommended dosages of cefepime (500 mg to 2 g intravenous every 12 hours). There
579 were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four
580 (1.5%) patients discontinued medication due to adverse events thought by the
581 investigators to be possibly, probably, or almost certainly related to drug toxicity.
582 Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash.
583 The percentage of cefepime-treated patients who discontinued study drug because of
584 drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g every
585 12 hours (0.8%, 1.1%, and 2 %, respectively). However, the incidence of discontinuation
586 due to rash increased with the higher recommended doses.

587
588 The following adverse events were thought to be probably related to cefepime during
589 evaluation of the drug in clinical trials conducted in North America (n=3125
590 cefepime-treated patients).

591
592 **Table 10: Adverse Reactions Cefepime Multiple-Dose Dosing Regimens Clinical**
593 **Trials—North America**

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions (3 %), including phlebitis (1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, erythema, fever, headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting, anemia

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

596
597 At the higher dose of 2 g every 8 hours, the incidence of probably-related adverse events
598 was higher among the 795 patients who received this dose of cefepime. They consisted of
599 rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and
600 headache (1%).

601
602 The following adverse laboratory changes, irrespective of relationship to therapy with
603 cefepime, were seen during clinical trials conducted in North America.

607
608
609
610
611

Table 11: Adverse Laboratory Changes Cefepime Multiple-Dose Dosing Regimens
Clinical Trials—North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

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

614
615 A similar safety profile was seen in clinical trials of pediatric patients (see
616 **PRECAUTIONS: Pediatric Use**).

617
618 **Postmarketing Experience**

619
620 In addition to the events reported during North American clinical trials with cefepime, the
621 following adverse experiences have been reported during worldwide postmarketing
622 experience.

623
624 Encephalopathy (disturbance of consciousness including confusion, hallucinations,
625 stupor, and coma), myoclonus, seizures, and non-convulsive status epilepticus have been
626 reported. Although most cases occurred in patients with renal impairment who received
627 doses of cefepime that exceeded the recommended dosage schedules, some cases of
628 neurotoxicity occurred in patients receiving an appropriate dosage adjustment for their
629 degree of renal impairment. If neurotoxicity associated with cefepime therapy occurs,
630 consider discontinuing cefepime or making appropriate dosage adjustments in patients
631 with renal impairment. (See **WARNINGS**).

632
633 As with other cephalosporins, anaphylaxis including anaphylactic shock, transient
634 leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported.

635
636 **Cephalosporin-Class Adverse Reactions**

637
638 In addition to the adverse reactions listed above that have been observed in patients
639 treated with cefepime, the following adverse reactions and altered laboratory tests have
640 been reported for cephalosporin-class antibiotics:

641
642 Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal
643 dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic
644 dysfunction including cholestasis, and pancytopenia.

645
646

647 **OVERDOSAGE**

648
649 Patients who receive an overdose should be carefully observed and given supportive
650 treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is
651 recommended to aid in the removal of cefepime from the body. Accidental overdosing
652 has occurred when large doses were given to patients with impaired renal function.
653 Symptoms of overdose include encephalopathy (disturbance of consciousness including
654 confusion, hallucinations, stupor, and coma), myoclonus, seizures, neuromuscular
655 excitability and non-convulsive status epilepticus (See **WARNINGS, ADVERSE**
656 **REACTIONS, and DOSAGE AND ADMINISTRATION.**)

657
658 **DOSAGE AND ADMINISTRATION**

659
660 The recommended adult and pediatric dosages and routes of administration are outlined
661 in the following table. MAXIPIME should be administered intravenously over
662 approximately 30 minutes.

663
664 Table 12: Recommended Dosage Schedule for MAXIPIME in Patients with CrCL
665 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 to 2 g IV	Every 12 hours	10
Empiric therapy for febrile neutropenic patients (See INDICATIONS AND USAGE and CLINICAL STUDIES.)	2 g IV	Every 8 hours	7**
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to <i>E. coli</i> , <i>K. pneumoniae</i> , or <i>P. mirabilis</i> *	0.5 to 1 g IV/IM***	Every 12 hours	7 to 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 CLINICAL STUDIES.)	2 g IV	Every 12 hours	7 to 10

Pediatric Patients (2 months up to 16 years)

The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg per kg per dose, administered every 12 hours (50 mg per kg per dose, every 8 hours for febrile neutropenic patients), for durations as given above.

666 *including cases associated with concurrent bacteremia

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

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

672

673 **Patients with Hepatic Impairment**

674

675 No adjustment is necessary for patients with hepatic impairment.

676

677 **Patients with Renal Impairment**

678

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

684

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

688

$$689 \text{ Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

690

691 Females: 0.85 × above value

692

693
694 **Table 13: Recommended Dosing Schedule for MAXIPIME in Adult Patients**
695 **(Normal Renal Function, Renal Impairment, and Hemodialysis)**

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule			
Greater than 60 Normal recommended dosing schedule	500 mg every 12 hours	1 g every 12 hours	2 g every 12 hours	2 g every 8 hours
30 to 60	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours	2 g every 12 hours
11 to 29	500 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours	2 g every 24 hours
Less than 11	250 mg every 24 hours	250 mg every 24 hours	500 mg every 24 hours	1 g every 24 hours
CAPD	500 mg every 48 hours	1 g every 48 hours	2 g every 48 hours	2 g every 48 hours
Hemodialysis*	1 g on day 1, then 500 mg every 24 hours thereafter			1 g every 24 hours

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697

*On hemodialysis days, cefepime should be administered following hemodialysis. Whenever possible, cefepime should be administered at the same time each day.

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In patients undergoing continuous ambulatory peritoneal dialysis, MAXIPIME may be administered at normally recommended doses at a dosage interval of every 48 hours (see Table 13).

In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3-hour dialysis period. The dosage of MAXIPIME for hemodialysis patients is 1 g on Day 1 followed by 500 mg every 24 hours for the treatment of all infections except febrile neutropenia, which is 1 g every 24 hours.

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

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

Administration

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

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

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

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

Preparation of MAXIPIME solutions is summarized in Table 14.

745

Table 14: Preparation of Solutions of MAXIPIME

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

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Compatibility and Stability

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

760

MAXIPIME admixture compatibility information is summarized in Table 15.

761

762

Table 15: Cefepime Admixture Stability

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

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

763 NS = 0.9% Sodium Chloride Injection
764 D5W = 5% Dextrose Injection
765 na = not applicable
766 RT/L = Ambient room temperature and light
767

768 Solutions of MAXIPIME, like those of most beta-lactam antibiotics, should not be added
769 to solutions of ampicillin at a concentration greater than 40 mg per mL, and should not be
770 added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate, or
771 aminophylline because of potential interaction. However, if concurrent therapy with
772 MAXIPIME is indicated, each of these antibiotics can be administered separately.
773

774 **Intramuscular:** MAXIPIME (cefepime hydrochloride) constituted as directed is stable
775 for 24 hours at controlled room temperature 20°C to 25°C (68°F to 77°F) or for 7 days in
776 a refrigerator 2°C to 8°C (36°F to 46°F) with the following diluents: Sterile Water for
777 Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Sterile Bacteriostatic
778 Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine
779 Hydrochloride.
780

781 **NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR**
782 **PARTICULATE MATTER BEFORE ADMINISTRATION. IF PARTICULATE**
783 **MATTER IS EVIDENT IN RECONSTITUTED FLUIDS, THE DRUG SOLUTION**
784 **SHOULD BE DISCARDED.**
785

786 As with other cephalosporins, the color of MAXIPIME powder, as well as its solutions,
787 tend to darken depending on storage conditions; however, when stored as recommended,
788 the product potency is not adversely affected.
789

790 ***INSTRUCTIONS FOR USE***

791
792 **These instructions for use should be made available to the individuals who perform**
793 **the reconstitution steps.**
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To Open:

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

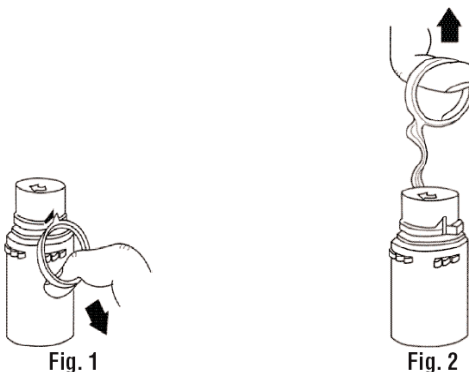
To Assemble Vial and Flexible Diluent Container:

(Use Aseptic Technique)

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

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

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



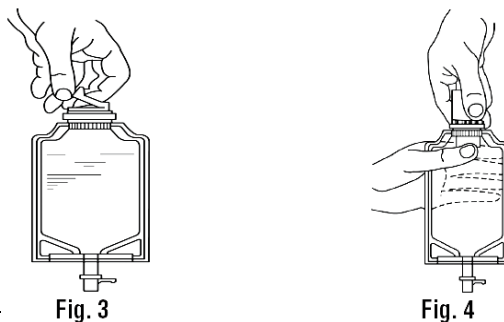
- b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)

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

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

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

4. Label appropriately.



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To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. **Pull the inner cap from the drug vial. (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.**
4. Mix container contents thoroughly and use within the specified time.
5. Look through the bottom of the vial to verify that the stopper has been removed and complete mixing has occurred. (SEE FIGURE 7.)

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

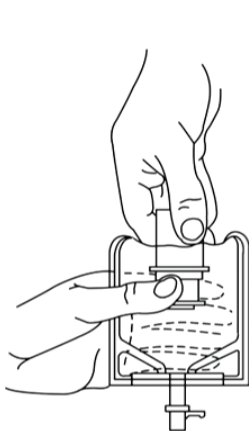


Fig. 5

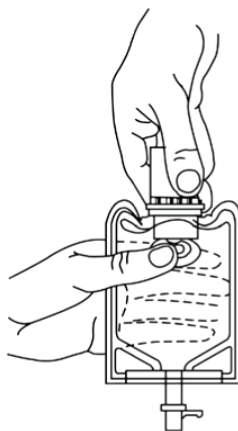


Fig. 6

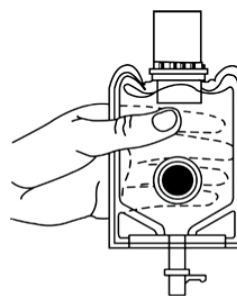


Fig. 7

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Preparation for Administration:

(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.

- 883 5. Insert piercing pin of administration set into port with a twisting motion until the pin is
884 firmly seated. NOTE: See full directions on administration set carton.
885
- 886 6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie
887 strings. Bend the loop outward to lock it in the upright position, then suspend container
888 from hanger.
889
- 890 7. Squeeze and release drip chamber to establish proper fluid level in chamber.
891
- 892 8. Open flow control clamp and clear air from set. Close clamp.
893
- 894 9. Attach set to venipuncture device. If device is not indwelling, prime and make
895 venipuncture.
896
- 897 10. Regulate rate of administration with flow control clamp.
898

899 **WARNING: Do not use flexible container in series connections.**
900

901 **HOW SUPPLIED**
902

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

907	500 mg* (carton of 10)	NDC 0409-0221-01
908	1 g* (carton of 10)	NDC 0409-0219-01
909	2 g* (carton of 10)	NDC 0409-0220-01
910	1 g* ADD-Vantage (carton of 25)	NDC 0409-0217-01
911	2 g* ADD-Vantage (carton of 25)	NDC 0409-0218-01

912
913 *Based on cefepime activity
914

915 **Storage**
916

917 **IN THE DRY STATE STORE AT 20 TO 25°C (68 TO 77°F) [SEE USP**
918 **CONTROLLED ROOM TEMPERATURE.] PROTECT FROM LIGHT.**
919

920 **REFERENCES**
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