

1 **PRODUCT INFORMATION**

2 **FORTAZ[®]**

3 **(ceftazidime for injection)**

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5 **FORTAZ[®]**

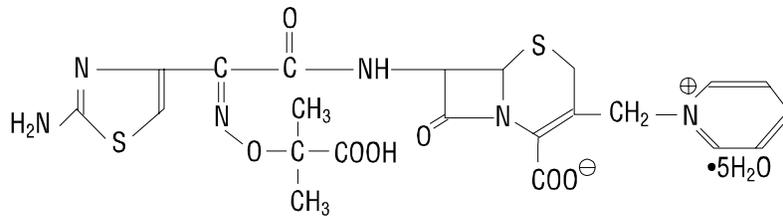
6 **(ceftazidime sodium injection)**

7

8 **For Intravenous or Intramuscular Use**

9

10 **DESCRIPTION:** Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for
11 parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[[(2-amino-4-thiazolyl)](1-
12 carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-
13 en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6 α ,7 β (Z)]]]. It has the following structure:



17 The empirical formula is C₂₂H₃₂N₆O₁₂S₂, representing a molecular weight of 636.6.

18 FORTAZ is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate.
19 The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to
20 facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g
21 of ceftazidime activity.

22 FORTAZ in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of
23 anhydrous ceftazidime and in ADD-Vantage[®] vials equivalent to 1 or 2 g of anhydrous
24 ceftazidime. Solutions of FORTAZ range in color from light yellow to amber, depending on the
25 diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8.

26 FORTAZ is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution with 1 or 2 g of

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27 ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of
28 dextrose hydrous, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is
29 used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH
30 may have been adjusted with hydrochloric acid. Solutions of premixed FORTAZ range in color
31 from light yellow to amber. The solution is intended for intravenous (IV) use after thawing to
32 room temperature. The osmolality of the solution is approximately 300 mOsmol/kg, and the pH of
33 thawed solutions ranges from 5 to 7.5.

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

39
40 **CLINICAL PHARMACOLOGY:** After IV administration of 500-mg and 1-g doses of
41 ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of
42 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500-mg, 1-g, and 2-g doses
43 of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum
44 concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum
45 concentrations following IV infusion of 500-mg, 1-g, and 2-g doses to these volunteers over an
46 8-hour interval are given in Table 1.

47
48 **Table 1: Average Serum Concentrations of Ceftazidime**

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 h	1 h	2 h	4 h	8 h
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

49
50 The absorption and elimination of ceftazidime were directly proportional to the size of the dose.
51 The half-life following IV administration was approximately 1.9 hours. Less than 10% of

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52 ceftazidime was protein bound. The degree of protein binding was independent of concentration.
53 There was no evidence of accumulation of ceftazidime in the serum in individuals with normal
54 renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

55 Following intramuscular (IM) administration of 500-mg and 1-g doses of ceftazidime to normal
56 adult volunteers, the mean peak serum concentrations were 17 and 39 mcg/mL, respectively, at
57 approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the
58 IM administration of 500-mg and 1-g doses, respectively. The half-life of ceftazidime in these
59 volunteers was approximately 2 hours.

60 The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in
61 individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage
62 adjustment from the normal recommended dosage is not required for patients with hepatic
63 dysfunction, provided renal function is not impaired.

64 Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the
65 kidneys over a 24-hour period. After the IV administration of single 500-mg or 1-g doses,
66 approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was
67 excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared
68 in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in
69 high therapeutic concentrations in the urine.

70 The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated
71 plasma clearance of approximately 115 mL/min indicated nearly complete elimination of
72 ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the
73 elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular
74 filtration and is not actively secreted by renal tubular mechanisms.

75 Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly
76 prolonged in patients with impaired renal function. Consequently, dosage adjustments in such
77 patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

78 Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.
79

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Table 2: Ceftazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0-2 h	2,100.0
	2 g IV	6	0-2 h	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 h	25.6
Peritoneal fluid	2 g IV	8	2 h	48.6
Sputum	1 g IV	8	1 h	9.0
Cerebrospinal fluid	2 g q8h IV	5	120 min	9.8
(inflamed meninges)	2 g q8h IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 h	11.0
Blister fluid	1 g IV	7	2-3 h	19.7
Lymphatic fluid	1 g IV	7	2-3 h	23.4
Bone	2 g IV	8	0.67 h	31.1
Heart muscle	2 g IV	35	30-280 min	12.7
Skin	2 g IV	22	30-180 min	6.6
Skeletal muscle	2 g IV	35	30-280 min	9.4
Myometrium	2 g IV	31	1-2 h	18.7

81

82 **Microbiology:** Ceftazidime is bactericidal in action, exerting its effect by inhibition of enzymes
83 responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to
84 ceftazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In
85 addition, ceftazidime has been shown to be active against gram-positive organisms. It is highly
86 stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced
87 by both gram-negative and gram-positive organisms and, consequently, is active against many
88 strains resistant to ampicillin and other cephalosporins.

89 Ceftazidime has been shown to be active against the following organisms both *in vitro* and in
90 clinical infections (see INDICATIONS AND USAGE).

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91 **Aerobes, Gram-negative:** *Citrobacter* spp., including *Citrobacter freundii* and *Citrobacter*
92 *diversus*; *Enterobacter* spp., including *Enterobacter cloacae* and *Enterobacter aerogenes*;
93 *Escherichia coli*; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp.
94 (including *Klebsiella pneumoniae*); *Neisseria meningitidis*; *Proteus mirabilis*; *Proteus vulgaris*;
95 *Pseudomonas* spp. (including *Pseudomonas aeruginosa*); and *Serratia* spp.

96 **Aerobes, Gram-positive:** *Staphylococcus aureus*, including penicillinase- and
97 non-penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci);
98 *Streptococcus pneumoniae*; and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

99 **Anaerobes:** *Bacteroides* spp. (NOTE: many strains of *Bacteroides fragilis* are resistant).

100 Ceftazidime has been shown to be active *in vitro* against most strains of the following
101 organisms; however, the clinical significance of these data is unknown: *Acinetobacter* spp.,
102 *Clostridium* spp. (not including *Clostridium difficile*), *Haemophilus parainfluenzae*, *Morganella*
103 *morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae*, *Peptococcus* spp.,
104 *Peptostreptococcus* spp., *Providencia* spp. (including *Providencia rettgeri*, formerly *Proteus*
105 *rettgeri*), *Salmonella* spp., *Shigella* spp., *Staphylococcus epidermidis*, and *Yersinia enterocolitica*.

106 Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against
107 *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also been
108 shown to be synergistic *in vitro* against *Pseudomonas aeruginosa*.

109 Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus*
110 *faecalis* and many other enterococci, *Listeria monocytogenes*, *Campylobacter* spp., or *Clostridium*
111 *difficile*.

112 **Susceptibility Tests: Diffusion Techniques:** Quantitative methods that require measurement of
113 zone diameters give an estimate of antibiotic susceptibility. One such procedure¹⁻³ has been
114 recommended for use with disks to test susceptibility to ceftazidime.

115 Reports from the laboratory giving results of the standard single-disk susceptibility test with a
116 30-mcg ceftazidime disk should be interpreted according to the following criteria:

117 Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism
118 is likely to respond to therapy.

119 Organisms that produce zones of 15 to 17 mm are expected to be susceptible if high dosage
120 is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic

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121 levels are attained.

122 Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be
123 selected.

124 Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by *in*
125 *vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used.

126 Standardized procedures require the use of laboratory control organisms. The 30-mcg
127 ceftazidime disk should give zone diameters between 25 and 32 mm for *Escherichia coli*
128 ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be between
129 22 and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be between
130 16 and 20 mm.

131 **Dilution Techniques:** In other susceptibility testing procedures, e.g., ICS agar dilution or the
132 equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory
133 concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are considered
134 resistant to ceftazidime if the MIC is ≥ 64 mcg/mL. Organisms having an MIC value of
135 < 64 mcg/mL but > 16 mcg/mL are expected to be susceptible if high dosage is used or if the
136 infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

137 As with standard diffusion methods, dilution procedures require the use of laboratory control
138 organisms. Standard ceftazidime powder should give MIC values in the range of 4 to 16 mcg/mL
139 for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range
140 should be between 0.125 and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC
141 range should be between 0.5 and 2 mcg/mL.

142

143 **INDICATIONS AND USAGE:** FORTAZ is indicated for the treatment of patients with
144 infections caused by susceptible strains of the designated organisms in the following diseases:

145 **1. Lower Respiratory Tract Infections**, including pneumonia, caused by *Pseudomonas*

146 *aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including

147 ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia*

148 *coli*; *Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae*; and *Staphylococcus aureus*

149 (methicillin-susceptible strains).

150 **2. Skin and Skin-Structure Infections** caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.;

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151 *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*;
152 *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and
153 *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

154 **3. Urinary Tract Infections**, both complicated and uncomplicated, caused by *Pseudomonas*
155 *aeruginosa*; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive
156 *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.

157 **4. Bacterial Septicemia** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Haemophilus*
158 *influenzae*, *Escherichia coli*, *Serratia* spp., *Streptococcus pneumoniae*, and *Staphylococcus*
159 *aureus* (methicillin-susceptible strains).

160 **5. Bone and Joint Infections** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacter*
161 spp., and *Staphylococcus aureus* (methicillin-susceptible strains).

162 **6. Gynecologic Infections**, including endometritis, pelvic cellulitis, and other infections of the
163 female genital tract caused by *Escherichia coli*.

164 **7. Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli*, *Klebsiella* spp.,
165 and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused
166 by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis*
167 are resistant).

168 **8. Central Nervous System Infections**, including meningitis, caused by *Haemophilus influenzae*
169 and *Neisseria meningitidis*. Cefazidime has also been used successfully in a limited number of
170 cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

171 Specimens for bacterial cultures should be obtained before therapy in order to isolate and
172 identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be
173 instituted before results of susceptibility studies are known; however, once these results become
174 available, the antibiotic treatment should be adjusted accordingly.

175 FORTAZ may be used alone in cases of confirmed or suspected sepsis. Cefazidime has been
176 used successfully in clinical trials as empiric therapy in cases where various concomitant therapies
177 with other antibiotics have been used.

178 FORTAZ may also be used concomitantly with other antibiotics, such as aminoglycosides,
179 vancomycin, and clindamycin; in severe and life-threatening infections; and in the
180 immunocompromised patient. When such concomitant treatment is appropriate, prescribing

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181 information in the labeling for the other antibiotics should be followed. The dose depends on the
182 severity of the infection and the patient's condition.

183

184 **CONTRAINDICATIONS:** FORTAZ is contraindicated in patients who have shown
185 hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

186

187 **WARNINGS:** BEFORE THERAPY WITH FORTAZ IS INSTITUTED, CAREFUL INQUIRY
188 SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS
189 HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS,
190 OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE
191 PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY
192 AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND
193 MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN
194 ALLERGY. IF AN ALLERGIC REACTION TO FORTAZ OCCURS, DISCONTINUE THE
195 DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE
196 TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING
197 OXYGEN, IV FLUIDS, IV ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES,
198 AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

199 **Pseudomembranous colitis has been reported with nearly all antibacterial agents,**
200 **including ceftazidime, and may range in severity from mild to life threatening. Therefore, it**
201 **is important to consider this diagnosis in patients who present with diarrhea subsequent to**
202 **the administration of antibacterial agents.**

203 Treatment with antibacterial agents alters the normal flora of the colon and may permit
204 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one
205 primary cause of "antibiotic-associated colitis."

206 After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic
207 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug
208 discontinuation alone. In moderate to severe cases, consideration should be given to management
209 with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug
210 clinically effective against *Clostridium difficile* colitis.

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211 Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures,
212 encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see
213 PRECAUTIONS).

214

215 **PRECAUTIONS:**

216 **General:** High and prolonged serum ceftazidime concentrations can occur from usual dosages in
217 patients with transient or persistent reduction of urinary output because of renal insufficiency. The
218 total daily dosage should be reduced when ceftazidime is administered to patients with renal
219 insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these
220 patients can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and
221 myoclonia. Continued dosage should be determined by degree of renal impairment, severity of
222 infection, and susceptibility of the causative organisms.

223 As with other antibiotics, prolonged use of FORTAZ may result in overgrowth of
224 nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If
225 superinfection occurs during therapy, appropriate measures should be taken.

226 Inducible type I beta-lactamase resistance has been noted with some organisms (e.g.,
227 *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum
228 beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some
229 cases. When treating infections caused by these organisms, periodic susceptibility testing should
230 be performed when clinically appropriate. If patients fail to respond to monotherapy, an
231 aminoglycoside or similar agent should be considered.

232 Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include
233 patients with renal and hepatic impairment, or poor nutritional state, as well as patients receiving a
234 protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at
235 risk and exogenous vitamin K administered as indicated.

236 FORTAZ should be prescribed with caution in individuals with a history of gastrointestinal
237 disease, particularly colitis.

238 Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

239 **Drug Interactions:** Nephrotoxicity has been reported following concomitant administration of
240 cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal

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241 function should be carefully monitored, especially if higher dosages of the aminoglycosides are to
242 be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity
243 of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime
244 was given alone in clinical trials.

245 Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including
246 ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due
247 to the possibility of antagonism *in vivo*, particularly when bactericidal activity is desired, this
248 drug combination should be avoided.

249 **Drug/Laboratory Test Interactions:** The administration of ceftazidime may result in a
250 false-positive reaction for glucose in the urine when using CLINITEST[®] tablets, Benedict's
251 solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose
252 oxidase reactions (such as CLINISTIX[®]) be used.

253 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not
254 been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an
255 Ames test were both negative for mutagenic effects.

256 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
257 performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence
258 of impaired fertility or harm to the fetus due to FORTAZ. There are, however, no adequate and
259 well-controlled studies in pregnant women. Because animal reproduction studies are not always
260 predictive of human response, this drug should be used during pregnancy only if clearly needed.

261 **Nursing Mothers:** Ceftazidime is excreted in human milk in low concentrations. Caution should
262 be exercised when FORTAZ is administered to a nursing woman.

263 **Pediatric Use:** (see DOSAGE AND ADMINISTRATION).
264

265 **ADVERSE REACTIONS:** Ceftazidime is generally well tolerated. The incidence of adverse
266 reactions associated with the administration of ceftazidime was low in clinical trials. The most
267 common were local reactions following IV injection and allergic and gastrointestinal reactions.
268 Other adverse reactions were encountered infrequently. No disulfiramlike reactions were reported.

269 The following adverse effects from clinical trials were considered to be either related to
270 ceftazidime therapy or were of uncertain etiology:

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271 **Local Effects**, reported in fewer than 2% of patients, were phlebitis and inflammation at the site of
272 injection (1 in 69 patients).

273 **Hypersensitivity Reactions**, reported in 2% of patients, were pruritus, rash, and fever. Immediate
274 reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Toxic
275 epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been
276 reported with cephalosporin antibiotics, including ceftazidime. Angioedema and anaphylaxis
277 (bronchospasm and/or hypotension) have been reported very rarely.

278 **Gastrointestinal Symptoms**, reported in fewer than 2% of patients, were diarrhea (1 in 78),
279 nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of
280 pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

281 **Central Nervous System Reactions** (fewer than 1%) included headache, dizziness, and
282 paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In
283 addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been
284 reported in renally impaired patients treated with unadjusted dosing regimens of ceftazidime (see
285 PRECAUTIONS: General).

286 **Less Frequent Adverse Events** (fewer than 1%) were candidiasis (including oral thrush) and
287 vaginitis.

288 **Hematologic:** Rare cases of hemolytic anemia have been reported.

289 **Laboratory Test Changes** noted during clinical trials with FORTAZ were transient and included:
290 eosinophilia (1 in 13), positive Coombs test without hemolysis (1 in 23), thrombocytosis (1 in 45),
291 and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST,
292 SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1 in 19),
293 and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient elevations of
294 blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient
295 leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very
296 rarely.

297

298 **POSTMARKETING EXPERIENCE WITH FORTAZ PRODUCTS:** In addition to the
299 adverse events reported during clinical trials, the following events have been observed during
300 clinical practice in patients treated with FORTAZ and were reported spontaneously. For some of

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301 these events, data are insufficient to allow an estimate of incidence or to establish causation. **General:** Anaphylax

302 **Hepatobiliary Tract:** Hyperbilirubinemia, jaundice.

303 **Renal and Genitourinary:** Renal impairment.

304 **Cephalosporin-Class Adverse Reactions:** In addition to the adverse reactions listed above that
305 have been observed in patients treated with ceftazidime, the following adverse reactions and
306 altered laboratory tests have been reported for cephalosporin-class antibiotics:

307 **Adverse Reactions:** Colitis, toxic nephropathy, hepatic dysfunction including cholestasis,
308 aplastic anemia, hemorrhage.

309 **Altered Laboratory Tests:** Prolonged prothrombin time, false-positive test for urinary
310 glucose, pancytopenia.

311
312 **OVERDOSAGE:** Ceftazidime overdosage has occurred in patients with renal failure. Reactions
313 have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma.
314 Patients who receive an acute overdosage should be carefully observed and given supportive
315 treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the
316 removal of ceftazidime from the body.

317

318 **DOSAGE AND ADMINISTRATION:**

319 **Dosage:** The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8
320 to 12 hours. The dosage and route should be determined by the susceptibility of the causative
321 organisms, the severity of infection, and the condition and renal function of the patient.

322 The guidelines for dosage of FORTAZ are listed in Table 3. The following dosage schedule is
323 recommended.

324

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Table 3: Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dosage	1 gram IV or IM	q8-12h
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 grams IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8-12h
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 gram IV or IM	q8h
Serious gynecologic and intra-abdominal infections	2 grams IV	q8h
Meningitis	2 grams IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8h
Lung infections caused by <i>Pseudomonas</i> spp. in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 grams per day	q8h
Neonates (0-4 weeks)	30 mg/kg IV	q12h
Infants and children (1 month-12 years)	30-50 mg/kg IV to a maximum of 6 grams per day [†]	q8h

326 *Although clinical improvement has been shown, bacteriologic cures cannot be expected in
 327 patients with chronic respiratory disease and cystic fibrosis.

328 † The higher dose should be reserved for immunocompromised pediatric patients or pediatric
 329 patients with cystic fibrosis or meningitis.

330

331 **Impaired Hepatic Function:** No adjustment in dosage is required for patients with hepatic
 332 dysfunction.

333 **Impaired Renal Function:** Ceftazidime is excreted by the kidneys, almost exclusively by
 334 glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate
 335 [GFR] <50 mL/min), it is recommended that the dosage of ceftazidime be reduced to compensate

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336 for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of
 337 1 gram of FORTAZ may be given. An estimate of GFR should be made to determine the
 338 appropriate maintenance dosage. The recommended dosage is presented in Table 4.

339
 340 **Table 4: Recommended Maintenance Dosages of FORTAZ in Renal Insufficiency**

341 **NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT**
 342 **RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN**
 343 **TABLE 4, THE LOWER DOSE SHOULD BE USED.**

Creatinine Clearance (mL/min)	Recommended Unit Dose of FORTAZ	Frequency of Dosing
50-31	1 gram	q12h
30-16	1 gram	q24h
15-6	500 mg	q24h
<5	500 mg	q48h

344
 345 When only serum creatinine is available, the following formula (Cockcroft's equation)⁴ may be
 346 used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal
 347 function:

348
 349 Males: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$
 350

351 Females: 0.85 x male value

352
 353 In patients with severe infections who would normally receive 6 grams of FORTAZ daily were
 354 it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the
 355 dosing frequency may be increased appropriately. Further dosing should be determined by
 356 therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

357 In pediatric patients as for adults, the creatinine clearance should be adjusted for body surface
 358 area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

359 In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by

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360 1 gram after each hemodialysis period.

361 FORTAZ can also be used in patients undergoing intraperitoneal dialysis and continuous
362 ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of FORTAZ may be
363 given, followed by 500 mg every 24 hours. In addition to IV use, FORTAZ can be incorporated in
364 the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

365 **Note:** Generally FORTAZ should be continued for 2 days after the signs and symptoms of
366 infection have disappeared, but in complicated infections longer therapy may be required.

367 **Administration:** FORTAZ may be given intravenously or by deep IM injection into a large
368 muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.
369 Intra-arterial administration should be avoided (see PRECAUTIONS).

370 ***Intramuscular Administration:*** For IM administration, FORTAZ should be constituted with
371 one of the following diluents: Sterile Water for Injection, Bacteriostatic Water for Injection, or
372 0.5% or 1% Lidocaine Hydrochloride Injection. Refer to Table 5.

373 ***Intravenous Administration:*** The IV route is preferable for patients with bacterial septicemia,
374 bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who
375 may be poor risks because of lowered resistance resulting from such debilitating conditions as
376 malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present
377 or pending.

378 ***For direct intermittent IV administration,*** constitute FORTAZ as directed in Table 5 with
379 Sterile Water for Injection. Slowly inject directly into the vein over a period of 3 to 5 minutes or
380 give through the tubing of an administration set while the patient is also receiving one of the
381 compatible IV fluids (see COMPATIBILITY AND STABILITY).

382 ***For IV infusion,*** constitute the 1- or 2-gram infusion pack with 100 mL of Sterile Water for
383 Injection or one of the compatible IV fluids listed under the COMPATIBILITY AND STABILITY
384 section. Alternatively, constitute the 500-mg, 1-gram, or 2-gram vial and add an appropriate
385 quantity of the resulting solution to an IV container with one of the compatible IV fluids.

386 ***Intermittent IV infusion with a Y-type administration set*** can be accomplished with
387 compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable
388 to discontinue the other solution.

389 ADD-Vantage vials are to be constituted only with 50 or 100 mL of 5% Dextrose Injection,

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390 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection in Abbott ADD-Vantage
391 flexible diluent containers (see Instructions for Constitution). ADD-Vantage vials that have been
392 joined to Abbott ADD-Vantage diluent containers and activated to dissolve the drug are stable for
393 24 hours at room temperature or for 7 days under refrigeration. Joined vials that have not been
394 activated may be used within a 14-day period; this period corresponds to that for use of Abbott
395 ADD-Vantage containers following removal of the outer packaging (overwrap).

396 Freezing solutions of FORTAZ in the ADD-Vantage system is not recommended.

397

398

Table 5: Preparation of Solutions of FORTAZ

Size	Amount of Diluent to be Added (mL)	Approximate Available Volume (mL)	Approximate Cefazidime Concentration (mg/mL)
Intramuscular			
500-mg vial	1.5	1.8	280
1-gram vial	3.0	3.6	280
Intravenous			
500-mg vial	5.0	5.3	100
1-gram vial	10.0	10.6	100
2-gram vial	10.0	11.5	170
Infusion pack			
1-gram vial	100*	100	10
2-gram vial	100*	100	20
Pharmacy bulk package			
6-gram vial	26	30	200

399 *Note: Addition should be in 2 stages (see Instructions for Constitution).

400

401 All vials of FORTAZ as supplied are under reduced pressure. When FORTAZ is dissolved,
402 carbon dioxide is released and a positive pressure develops. For ease of use please follow the

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403 recommended techniques of constitution described on the detachable Instructions for Constitution
404 section of this insert.

405 Solutions of FORTAZ, like those of most beta-lactam antibiotics, should not be added to
406 solutions of aminoglycoside antibiotics because of potential interaction.

407 However, if concurrent therapy with FORTAZ and an aminoglycoside is indicated, each of
408 these antibiotics can be administered separately to the same patient.

409 **Directions for Use of FORTAZ Frozen in GALAXY[®] Plastic Containers:** FORTAZ supplied
410 as a frozen, sterile, iso-osmotic, nonpyrogenic solution in plastic containers is to be administered
411 after thawing either as a continuous or intermittent IV infusion. The thawed solution is stable for
412 24 hours at room temperature or for 7 days if stored under refrigeration. **Do not refreeze.**

413 Thaw container at room temperature (25°C) or under refrigeration (5°C). Do not force thaw by
414 immersion in water baths or by microwave irradiation. Components of the solution may precipitate
415 in the frozen state and will dissolve upon reaching room temperature with little or no agitation.
416 Potency is not affected. Mix after solution has reached room temperature. Check for minute leaks
417 by squeezing bag firmly. Discard bag if leaks are found as sterility may be impaired. Do not add
418 supplementary medication. Do not use unless solution is clear and seal is intact.

419 Use sterile equipment.

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

423 ***Preparation for Administration:***

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

427

428 **COMPATIBILITY AND STABILITY:**

429 **Intramuscular:** FORTAZ, when constituted as directed with Sterile Water for Injection,
430 Bacteriostatic Water for Injection, or 0.5% or 1% Lidocaine Hydrochloride Injection, maintains
431 satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions
432 in Sterile Water for Injection that are frozen immediately after constitution in the original

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433 container are stable for 3 months when stored at -20°C. Once thawed, solutions should not be
434 refrozen. Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a
435 refrigerator.

436 **Intravenous:** FORTAZ, when constituted as directed with Sterile Water for Injection, maintains
437 satisfactory potency for 24 hours at room temperature or for 7 days under refrigeration. Solutions
438 in Sterile Water for Injection in the infusion vial or in 0.9% Sodium Chloride Injection in
439 VIAFLEX[®] small-volume containers that are frozen immediately after constitution are stable for
440 6 months when stored at -20°C. Do not force thaw by immersion in water baths or by microwave
441 irradiation. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for up
442 to 24 hours at room temperature or for 7 days in a refrigerator. More concentrated solutions in
443 Sterile Water for Injection in the original container that are frozen immediately after constitution
444 are stable for 3 months when stored at -20°C. Once thawed, solutions should not be refrozen.
445 Thawed solutions may be stored for up to 8 hours at room temperature or for 4 days in a
446 refrigerator.

447 FORTAZ is compatible with the more commonly used IV infusion fluids. Solutions at
448 concentrations between 1 and 40 mg/mL in 0.9% Sodium Chloride Injection; 1/6 M Sodium
449 Lactate Injection; 5% Dextrose Injection; 5% Dextrose and 0.225% Sodium Chloride Injection;
450 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride
451 Injection; 10% Dextrose Injection; Ringer's Injection, USP; Lactated Ringer's Injection, USP; 10%
452 Invert Sugar in Water for Injection; and NORMOSOL[®]-M in 5% Dextrose Injection may be stored
453 for up to 24 hours at room temperature or for 7 days if refrigerated.

454 The 1- and 2-g FORTAZ ADD-Vantage vials, when diluted in 50 or 100 mL of 5% Dextrose
455 Injection, 0.9% Sodium Chloride Injection, or 0.45% Sodium Chloride Injection, may be stored for
456 up to 24 hours at room temperature or for 7 days under refrigeration.

457 FORTAZ is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not
458 recommended as a diluent. Solutions of FORTAZ in 5% Dextrose Injection and 0.9% Sodium
459 Chloride Injection are stable for at least 6 hours at room temperature in plastic tubing, drip
460 chambers, and volume control devices of common IV infusion sets.

461 Ceftazidime at a concentration of 4 mg/mL has been found compatible for 24 hours at room
462 temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose

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463 Injection when admixed with: cefuroxime sodium (ZINACEF[®]) 3 mg/mL; heparin 10 or 50 U/mL;
464 or potassium chloride 10 or 40 mEq/L.

465 Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs,
466 including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the
467 concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both
468 drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the
469 IV lines (with 1 of the compatible IV fluids) between the administration of these 2 agents.

470 **Note:** Parenteral drug products should be inspected visually for particulate matter before
471 administration whenever solution and container permit.

472 As with other cephalosporins, FORTAZ powder as well as solutions tend to darken, depending
473 on storage conditions; within the stated recommendations, however, product potency is not
474 adversely affected.

475
476 **HOW SUPPLIED:** FORTAZ in the dry state should be stored between 15° and 30°C (59° and
477 86°F) and protected from light. FORTAZ is a dry, white to off-white powder supplied in vials and
478 infusion packs as follows:

479 NDC 0173-0377-31 500-mg* Vial (Tray of 25)

480 NDC 0173-0378-35 1-g* Vial (Tray of 25)

481 NDC 0173-0379-34 2-g* Vial (Tray of 10)

482 NDC 0173-0380-32 1-g* Infusion Pack (Tray of 10)

483 NDC 0173-0381-32 2-g* Infusion Pack (Tray of 10)

484 NDC 0173-0382-37 6-g* Pharmacy Bulk Package (Tray of 6)

485 NDC 0173-0434-00 1-g ADD-Vantage[®] Vial (Tray of 25)

486 NDC 0173-0435-00 2-g ADD-Vantage[®] Vial (Tray of 10)

487 (The above ADD-Vantage vials are to be used only with Abbott ADD-Vantage diluent containers.)

488 FORTAZ frozen as a premixed solution of ceftazidime sodium should not be stored above
489 -20°C. FORTAZ is supplied frozen in 50-mL, single-dose, plastic containers as follows:

490 NDC 0173-0412-00 1-g* Plastic Container (Carton of 24)

491 NDC 0173-0413-00 2-g* Plastic Container (Carton of 24)

492 *Equivalent to anhydrous ceftazidime.

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2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disc Susceptibility Tests.* (M2-A3). December 1984.
3. Certification procedure for antibiotic sensitivity discs (21 CFR 460.1). *Federal Register.* May 30, 1974;39:19182-19184.
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GlaxoSmithKline
GlaxoSmithKline
FORTAZ[®] (ceftazidime for injection):
GlaxoSmithKline
Research Triangle Park, NC 27709

FORTAZ[®] (ceftazidime sodium injection):
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
by Baxter Healthcare Corporation,
Deerfield, IL 60015

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522 GALAXY and VIAFLEX are registered trademarks of Baxter International Inc.

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TEAR AWAY

FORTAZ[®]
(ceftazidime for injection)

Instructions for Constitution

Vials: 500 mg IM/IV, 1 g IM/IV, 2 g IV

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution will be obtained in 1 to 2 minutes.
3. Invert the vial. Ensuring that the syringe plunger is fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the headspace. The withdrawn solution may contain some bubbles of carbon dioxide.

Note: As with the administration of all parenteral products, accumulated gases should be expressed from the syringe immediately before injection of FORTAZ.

Infusion Pack: 1 g, 2 g

1. Insert the syringe needle through the vial closure and inject 10 mL of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution will be obtained in 1 to 2 minutes.
3. Insert a gas-relief needle through the vial closure to relieve the internal pressure. With the gas-relief needle in position, add the remaining 90 mL of diluent. Remove the gas-relief needle and syringe needle; shake the vial and set up for infusion in the normal way.

Note: To preserve product sterility, it is important that a gas-relief needle is *not* inserted through the

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vial closure before the product has dissolved.

ADD-Vantage[®] Vials: 1 g, 2 g

To Open Diluent Container:

Peel the corner of the ADD-Vantage diluent overwrap and remove flexible diluent container. Some opacity of the plastic flexible container 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.

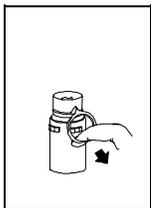


Figure 1

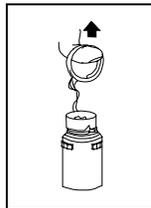


Figure 2

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

2. Screw the vial into the vial port until it will go no further. **THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL.** This occurs approximately one-half 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).

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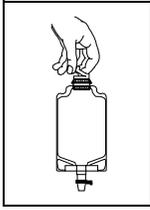


Figure 3

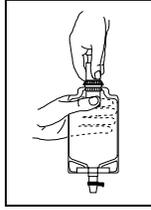


Figure 4

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

To Prepare Admixture:

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.

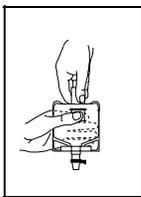


Figure 5

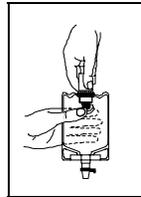


Figure 6

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

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.

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4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
Note: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections.

Pharmacy Bulk Package: 6 g

1. Insert the syringe needle through the vial closure and inject 26 mL of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.
2. Shake to dissolve; a clear solution containing approximately 1 g of ceftazidime activity per 5 mL will be obtained in 1 to 2 minutes.
3. Insert a gas-relief needle through the vial closure to relieve the internal pressure. Remove the gas-relief needle before extracting any solution.

Note: To preserve product sterility, it is important that a gas-relief needle is *not* inserted through the vial closure before the product has dissolved.



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PRODUCT INFORMATION

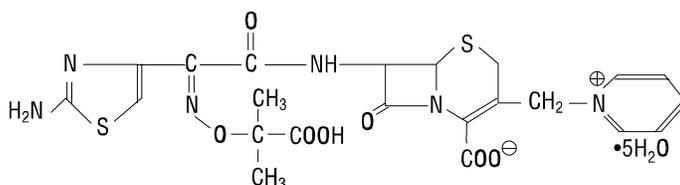
CEPTAZ[®]

(ceftazidime for injection)

L-arginine formulation

For Intravenous or Intramuscular Use

DESCRIPTION: Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for parenteral administration. It is the pentahydrate of pyridinium, 1-[[7-[[[(2-amino-4-thiazolyl)](1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt, [6R-[6 α ,7 β (Z)]]]. It has the following structure:



The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.

CEPTAZ is a sterile, dry mixture of ceftazidime pentahydrate and L-arginine. The L-arginine is at a concentration of 349 mg/g of ceftazidime activity. CEPTAZ dissolves without the evolution of gas. The product contains no sodium ion. Solutions of CEPTAZ range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 7.5.

CLINICAL PHARMACOLOGY: After intravenous (IV) administration of 500-mg and 1-g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500-mg, 1-g, and 2-g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500-mg, 1-g, and 2-g doses to these volunteers

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L-arginine formulation

28 over an 8-hour interval are given in Table 1.

29

30

Table 1

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 h	1 h	2 h	4 h	8 h
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

31

32 The absorption and elimination of ceftazidime were directly proportional to the size of the
33 dose. The half-life following IV administration was approximately 1.9 hours. Less than 10% of
34 ceftazidime was protein bound. The degree of protein binding was independent of concentration.
35 There was no evidence of accumulation of ceftazidime in the serum in individuals with normal
36 renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

37 Following intramuscular (IM) administration of 500-mg and 1-g doses of ceftazidime to
38 normal adult volunteers, the mean peak serum concentrations were 17 and 39 mcg/mL,
39 respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and
40 8 hours after the IM administration of 500-mg and 1-g doses, respectively. The half-life of
41 ceftazidime in these volunteers was approximately 2 hours.

42 The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in
43 individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage
44 adjustment from the normal recommended dosage is not required for patients with hepatic
45 dysfunction, provided renal function is not impaired.

46 Approximately 80% to 90% of an IM or IV dose of ceftazidime is excreted unchanged by the
47 kidneys over a 24-hour period. After the IV administration of single 500-mg or 1-g doses,
48 approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was
49 excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose
50 appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys
51 resulted in high therapeutic concentrations in the urine.

52 The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated

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L-arginine formulation

53 plasma clearance of approximately 115 mL/min indicated nearly complete elimination of
54 ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the
55 elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular
56 filtration and is not actively secreted by renal tubular mechanisms.

57 Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly
58 prolonged in patients with impaired renal function. Consequently, dosage adjustments in such
59 patients as described in the DOSAGE AND ADMINISTRATION section are suggested.

60 Ceftazidime concentrations achieved in specific body tissues and fluids are depicted in
61 Table 2.

62

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63

Table 2: Cefazidime Concentrations in Body Tissues and Fluids

Tissue or Fluid	Dose/ Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg IM	6	0-2 h	2,100.0
	2 g IV	6	0-2 h	12,000.0
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 h	25.6
Peritoneal fluid	2 g IV	8	2 h	48.6
Sputum	1 g IV	8	1 h	9.0
Cerebrospinal fluid (inflamed meninges)	2 g q8h IV	5	120 min	9.8
	2 g q8h IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 h	11.0
Blister fluid	1 g IV	7	2-3 h	19.7
Lymphatic fluid	1 g IV	7	2-3 h	23.4
Bone	2 g IV	8	0.67 h	31.1
Heart muscle	2 g IV	35	30-280 min	12.7
Skin	2 g IV	22	30-180 min	6.6
Skeletal muscle	2 g IV	35	30-280 min	9.4
Myometrium	2 g IV	31	1-2 h	18.7

64

65 **Microbiology:** Cefazidime is bactericidal in action, exerting its effect by inhibition of enzymes
66 responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to
67 cefazidime *in vitro*, including strains resistant to gentamicin and other aminoglycosides. In
68 addition, cefazidime has been shown to be active against gram-positive organisms. It is highly
69 stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced
70 by both gram-negative and gram-positive organisms and, consequently, is active against many
71 strains resistant to ampicillin and other cephalosporins.

72 Cefazidime has been shown to be active against the following organisms both *in vitro* and in

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73 clinical infections (see INDICATIONS AND USAGE).

74 **Aerobes, Gram-negative:** *Citrobacter* spp., including *Citrobacter freundii* and *Citrobacter*
75 *diversus*; *Enterobacter* spp., including *Enterobacter cloacae* and *Enterobacter aerogenes*;
76 *Escherichia coli*; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp.
77 (including *Klebsiella pneumoniae*); *Neisseria meningitidis*; *Proteus mirabilis*; *Proteus vulgaris*;
78 *Pseudomonas* spp. (including *Pseudomonas aeruginosa*); and *Serratia* spp.

79 **Aerobes, Gram-positive:** *Staphylococcus aureus*, including penicillinase- and non-
80 penicillinase-producing strains; *Streptococcus agalactiae* (group B streptococci); *Streptococcus*
81 *pneumoniae*; and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

82 **Anaerobes:** *Bacteroides* spp. (NOTE: many strains of *Bacteroides fragilis* are resistant).

83 Ceftazidime has been shown to be active *in vitro* against most strains of the following
84 organisms; however, the clinical significance of this activity is unknown: *Acinetobacter* spp.,
85 *Clostridium* spp. (not including *Clostridium difficile*), *Haemophilus parainfluenzae*, *Morganella*
86 *morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae*, *Peptococcus* spp.,
87 *Peptostreptococcus* spp., *Providencia* spp. (including *Providencia rettgeri*, formerly *Proteus*
88 *rettgeri*), *Salmonella* spp., *Shigella* spp., *Staphylococcus epidermidis*, and *Yersinia*
89 *enterocolitica*.

90 Ceftazidime and the aminoglycosides have been shown to be synergistic *in vitro* against
91 *Pseudomonas aeruginosa* and the enterobacteriaceae. Ceftazidime and carbenicillin have also
92 been shown to be synergistic *in vitro* against *Pseudomonas aeruginosa*.

93 Ceftazidime is not active *in vitro* against methicillin-resistant staphylococci, *Streptococcus*
94 *faecalis* and many other enterococci, *Listeria monocytogenes*, *Campylobacter* spp., or
95 *Clostridium difficile*.

96 **Susceptibility Tests: Diffusion Techniques:** Quantitative methods that require measurement of
97 zone diameters give an estimate of antibiotic susceptibility. One such procedure¹⁻³ has been
98 recommended for use with disks to test susceptibility to ceftazidime.

99 Reports from the laboratory giving results of the standard single-disk susceptibility test with a
100 30-mcg ceftazidime disk should be interpreted according to the following criteria:

101 Susceptible organisms produce zones of 18 mm or greater, indicating that the test organism
102 is likely to respond to therapy.

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103 Organisms that produce zones of 15 to 17 mm are expected to be susceptible if high dosage
104 is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic
105 levels are attained.

106 Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be
107 selected.

108 Organisms should be tested with the ceftazidime disk since ceftazidime has been shown by *in*
109 *vitro* tests to be active against certain strains found resistant when other beta-lactam disks are
110 used.

111 Standardized procedures require the use of laboratory control organisms. The 30-mcg
112 ceftazidime disk should give zone diameters between 25 and 32 mm for *Escherichia coli*
113 ATCC 25922. For *Pseudomonas aeruginosa* ATCC 27853, the zone diameters should be
114 between 22 and 29 mm. For *Staphylococcus aureus* ATCC 25923, the zone diameters should be
115 between 16 and 20 mm.

116 **Dilution Techniques:** In other susceptibility testing procedures, e.g., ICS agar dilution or the
117 equivalent, a bacterial isolate may be considered susceptible if the minimum inhibitory
118 concentration (MIC) value for ceftazidime is not more than 16 mcg/mL. Organisms are
119 considered resistant to ceftazidime if the MIC is ≥ 64 mcg/mL. Organisms having an MIC value
120 of < 64 mcg/mL but > 16 mcg/mL are expected to be susceptible if high dosage is used or if the
121 infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

122 As with standard diffusion methods, dilution procedures require the use of laboratory control
123 organisms. Standard ceftazidime powder should give MIC values in the range of 4 to 16 mcg/mL
124 for *Staphylococcus aureus* ATCC 25923. For *Escherichia coli* ATCC 25922, the MIC range
125 should be between 0.125 and 0.5 mcg/mL. For *Pseudomonas aeruginosa* ATCC 27853, the MIC
126 range should be between 0.5 and 2 mcg/mL.

127

128 **INDICATIONS AND USAGE:** CEPTAZ is indicated for the treatment of patients with
129 infections caused by susceptible strains of the designated organisms in the following diseases:

130 **1. Lower Respiratory Tract Infections**, including pneumonia, caused by *Pseudomonas*

131 *aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including

132 ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia*

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133 *coli*; *Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae*; and *Staphylococcus aureus*
134 (methicillin-susceptible strains).

135 **2. Skin and Skin-Structure Infections** caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.;
136 *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*;
137 *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and
138 *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

139 **3. Urinary Tract Infections**, both complicated and uncomplicated, caused by *Pseudomonas*
140 *aeruginosa*; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive
141 *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.

142 **4. Bacterial Septicemia** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Haemophilus*
143 *influenzae*, *Escherichia coli*, *Serratia* spp., *Streptococcus pneumoniae*, and *Staphylococcus*
144 *aureus* (methicillin-susceptible strains).

145 **5. Bone and Joint Infections** caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacter*
146 spp., and *Staphylococcus aureus* (methicillin-susceptible strains).

147 **6. Gynecologic Infections**, including endometritis, pelvic cellulitis, and other infections of the
148 female genital tract caused by *Escherichia coli*.

149 **7. Intra-abdominal Infections**, including peritonitis caused by *Escherichia coli*, *Klebsiella* spp.,
150 and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections
151 caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides*
152 *fragilis* are resistant).

153 **8. Central Nervous System Infections**, including meningitis, caused by *Haemophilus influenzae*
154 and *Neisseria meningitidis*. Cefazidime has also been used successfully in a limited number of
155 cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

156 Specimens for bacterial cultures should be obtained before therapy in order to isolate and
157 identify causative organisms and to determine their susceptibility to ceftazidime. Therapy may be
158 instituted before results of susceptibility studies are known; however, once these results become
159 available, the antibiotic treatment should be adjusted accordingly.

160 CEPTAZ may be used alone in cases of confirmed or suspected sepsis. Cefazidime has been
161 used successfully in clinical trials as empiric therapy in cases where various concomitant
162 therapies with other antibiotics have been used.

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163 CEPTAZ may also be used concomitantly with other antibiotics, such as aminoglycosides,
164 vancomycin, and clindamycin; in severe and life-threatening infections; and in the
165 immunocompromised patient (see COMPATIBILITY AND STABILITY). When such
166 concomitant treatment is appropriate, prescribing information in the labeling for the other
167 antibiotics should be followed. The dosage depends on the severity of the infection and the
168 patient's condition.

169

170 **CONTRAINDICATIONS:** CEPTAZ is contraindicated in patients who have shown
171 hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

172

173 **WARNINGS:** BEFORE THERAPY WITH CEPTAZ IS INSTITUTED, CAREFUL INQUIRY
174 SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS
175 HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS,
176 PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO
177 PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE
178 CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN
179 CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A
180 HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEPTAZ
181 OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY
182 REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER
183 EMERGENCY MEASURES, INCLUDING OXYGEN, IV FLUIDS, IV ANTIHISTAMINES,
184 CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS
185 CLINICALLY INDICATED.

186 **Pseudomembranous colitis has been reported with nearly all antibacterial agents,**
187 **including ceftazidime, and may range in severity from mild to life threatening. Therefore, it**
188 **is important to consider this diagnosis in patients who present with diarrhea subsequent to**
189 **the administration of antibacterial agents.**

190 Treatment with antibacterial agents alters the normal flora of the colon and may permit
191 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one
192 primary cause of "antibiotic-associated colitis."

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193 After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic
194 measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug
195 discontinuation alone. In moderate to severe cases, consideration should be given to management
196 with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug
197 clinically effective against *Clostridium difficile* colitis.

198 Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures,
199 encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia (see
200 PRECAUTIONS).

201

202 **PRECAUTIONS:**

203 **General:** High and prolonged serum ceftazidime concentrations can occur from usual dosages in
204 patients with transient or persistent reduction of urinary output because of renal insufficiency.

205 The total daily dosage should be reduced when ceftazidime is administered to patients with renal
206 insufficiency (see DOSAGE AND ADMINISTRATION). Elevated levels of ceftazidime in these
207 patients can lead to seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and
208 myoclonia. Continued dosage should be determined by degree of renal impairment, severity of
209 infection, and susceptibility of the causative organisms.

210 As with other antibiotics, prolonged use of CEPTAZ may result in overgrowth of
211 nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If
212 superinfection occurs during therapy, appropriate measures should be taken.

213 Inducible type I beta-lactamase resistance has been noted with some organisms (e.g.,
214 *Enterobacter* spp., *Pseudomonas* spp., and *Serratia* spp.). As with other extended-spectrum
215 beta-lactam antibiotics, resistance can develop during therapy, leading to clinical failure in some
216 cases. When treating infections caused by these organisms, periodic susceptibility testing should
217 be performed when clinically appropriate. If patients fail to respond to monotherapy, an
218 aminoglycoside or similar agent should be considered.

219 Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include
220 patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a
221 protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at
222 risk and exogenous vitamin K administered as indicated.

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223 CEPTAZ should be prescribed with caution in individuals with a history of gastrointestinal
224 disease, particularly colitis.

225 Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently
226 when administered at 50 times the recommended dose. The effect of lower dosing is not known.

227 Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

228 **Drug Interactions:** Nephrotoxicity has been reported following concomitant administration of
229 cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal
230 function should be carefully monitored, especially if higher dosages of the aminoglycosides are to
231 be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity
232 of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime
233 was given alone in clinical trials.

234 Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, including
235 ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due
236 to the possibility of antagonism *in vivo*, particularly when bactericidal activity is desired, this
237 drug combination should be avoided.

238 **Drug/Laboratory Test Interactions:** The administration of ceftazidime may result in a
239 false-positive reaction for glucose in the urine when using CLINITEST[®] tablets, Benedict's
240 solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose
241 oxidase reactions (such as CLINISTIX[®]) be used.

242 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not
243 been performed to evaluate carcinogenic potential. However, a mouse Micronucleus test and an
244 Ames test were both negative for mutagenic effects.

245 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
246 performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence
247 of impaired fertility or harm to the fetus due to ceftazidime. CEPTAZ at 23 times the human dose
248 was not teratogenic or embryotoxic in a rat reproduction study. There are, however, no adequate
249 and well-controlled studies in pregnant women. Because animal reproduction studies are not
250 always predictive of human response, this drug should be used during pregnancy only if clearly
251 needed.

252 **Nursing Mothers:** Ceftazidime is excreted in human milk in low concentrations. It is not known

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253 whether the arginine component of this product is excreted in human milk. Because many drugs
254 are excreted in human milk and because safety of the arginine component of CEPTAZ in nursing
255 infants has not been established, a decision should be made whether to discontinue nursing or to
256 discontinue the drug, taking into account the importance of the drug to the mother.

257 **Pediatric Use:** Safety of the arginine component of CEPTAZ in neonates, infants, and children
258 has not been established. This product is for use in patients 12 years and older. If treatment with
259 ceftazidime is indicated for neonates, infants, or children, a sodium carbonate formulation should
260 be used.

261
262 **ADVERSE REACTIONS:** The following adverse effects from clinical trials were considered to
263 be either related to ceftazidime therapy or were of uncertain etiology. The most common were
264 local reactions following IV injection and allergic and gastrointestinal reactions. No
265 disulfiramlike reactions were reported.

266 **Local Effects,** reported in fewer than 2% of patients, were phlebitis and inflammation at the site
267 of injection (1 in 69 patients).

268 **Hypersensitivity Reactions,** reported in 2% of patients, were pruritus, rash, and fever.
269 Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients.
270 Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been
271 reported with cephalosporin antibiotics, including ceftazidime. Angioedema and anaphylaxis
272 (bronchospasm and/or hypotension) have been reported very rarely.

273 **Gastrointestinal Symptoms,** reported in fewer than 2% of patients, were diarrhea (1 in 78),
274 nausea (1 in 156), vomiting (1 in 500), and abdominal pain (1 in 416). The onset of
275 pseudomembranous colitis symptoms may occur during or after treatment (see WARNINGS).

276 **Central Nervous System Reactions** (fewer than 1%) included headache, dizziness, and
277 paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In
278 addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been
279 reported in renally impaired patients treated with unadjusted dosage regimens of ceftazidime (see
280 PRECAUTIONS: General).

281 **Less Frequent Adverse Events** (fewer than 1%) were candidiasis (including oral thrush) and
282 vaginitis.

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283 **Hematologic:** Rare cases of hemolytic anemia have been reported.

284 **Laboratory Test Changes** noted during ceftazidime clinical trials were transient and included:
285 eosinophilia (1 in 13), positive Coombs' test without hemolysis (1 in 23), thrombocytosis (1 in
286 45), and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase
287 (AST, SGOT) (1 in 16), alanine aminotransferase (ALT, SGPT) (1 in 15), LDH (1 in 18), GGT (1
288 in 19), and alkaline phosphatase (1 in 23). As with some other cephalosporins, transient
289 elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed
290 occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and
291 lymphocytosis were seen very rarely.

292
293 **POSTMARKETING EXPERIENCE WITH CEPTAZ PRODUCTS:** In addition to the
294 adverse events reported during clinical trials, the following events have been observed during
295 clinical practice in patients treated with CEPTAZ and were reported spontaneously. For some of
296 these events, data are insufficient to allow an estimate of incidence or to establish causation.

297 **General:** Anaphylaxis; allergic reactions, which, in rare instances, were severe (e.g.,
298 cardiopulmonary arrest); urticaria; pain at injection site.

299 **Hepatobiliary Tract:** Hyperbilirubinemia, jaundice.

300 **Renal and Genitourinary:** Renal impairment.

301 **Cephalosporin-Class Adverse Reactions:** In addition to the adverse reactions listed above that
302 have been observed in patients treated with ceftazidime, the following adverse reactions and
303 altered laboratory tests have been reported for cephalosporin-class antibiotics:

304 *Adverse Reactions:* Colitis, toxic nephropathy, hepatic dysfunction including cholestasis,
305 aplastic anemia, hemorrhage.

306 *Altered Laboratory Tests:* Prolonged prothrombin time, false-positive test for urinary
307 glucose, pancytopenia.

308
309 **OVERDOSAGE:** Ceftazidime overdose has occurred in patients with renal failure. Reactions
310 have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma.
311 Patients who receive an acute overdose should be carefully observed and given supportive
312 treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in

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313 the removal of ceftazidime from the body.

314

315 **DOSAGE AND ADMINISTRATION:**

316 **Dosage:** The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8
317 to 12 hours. The dosage and route should be determined by the susceptibility of the causative
318 organisms, the severity of infection, and the condition and renal function of the patient.

319 The guidelines for dosage of CEPTAZ are listed in Table 3. The following dosage schedule is
320 recommended.

321

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322

Table 3: Recommended Dosage Schedule

	Dose	Frequency
Patients 12 years and older*		
Usual recommended dosage	1 gram IV or IM	q8-12h
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 grams IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8-12h
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 gram IV or IM	q8h
Serious gynecologic and intra-abdominal infections	2 grams IV	q8h
Meningitis	2 grams IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8h
Lung infections caused by <i>Pseudomonas</i> spp. in patients with cystic fibrosis with normal renal function [†]	30-50 mg/kg IV to a maximum of 6 grams per day	q8h

323 * This product is for use in patients 12 years and older. If treatment with ceftazidime is
 324 indicated for patients less than 12 years old, a sodium carbonate formulation should
 325 be used.

326 [†] Although clinical improvement has been shown, bacteriologic cures cannot be
 327 expected in patients with chronic respiratory disease and cystic fibrosis.

328

329 **Impaired Hepatic Function:** No adjustment in dosage is required for patients with hepatic
 330 dysfunction.

331 **Impaired Renal Function:** Ceftazidime is excreted by the kidneys, almost exclusively by
 332 glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration
 333 rate [GFR]<50 mL/min), it is recommended that the dosage of ceftazidime be reduced to
 334 compensate for its slower excretion. In patients with suspected renal insufficiency, an initial
 335 loading dose of 1 gram of CEPTAZ may be given. An estimate of GFR should be made to
 336 determine the appropriate maintenance dosage. The recommended dosage is presented in Table 4.

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337

338 **Table 4: Recommended Maintenance Dosages of CEPTAZ in Renal Insufficiency**

339 **NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN**
340 **THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS**
341 **OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.**

Creatinine Clearance (mL/min)	Recommended Unit Dose of CEPTAZ	Frequency of Dosing
50-31	1 gram	q12h
30-16	1 gram	q24h
15-6	500 mg	q24h
<5	500 mg	q48h

342

343 When only serum creatinine is available, the following formula (Cockcroft's equation)⁴ may be
344 used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal
345 function:

346

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

348

349 Females: 0.85 x male value

350

351 In patients with severe infections who would normally receive 6 grams of CEPTAZ daily were
352 it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or
353 the dosing frequency may be increased appropriately. Further dosing should be determined by
354 therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

355 In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by
356 1 gram after each hemodialysis period.

357 CEPTAZ can also be used in patients undergoing intraperitoneal dialysis and continuous
358 ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of CEPTAZ may be
359 given, followed by 500 mg every 24 hours. It is not known whether or not CEPTAZ can be safely
360 incorporated into dialysis fluid.

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361 **Note:** Generally CEPTAZ should be continued for 2 days after the signs and symptoms of
362 infection have disappeared, but in complicated infections longer therapy may be required.

363 **Administration:** CEPTAZ may be given intravenously or by deep IM injection into a large
364 muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.
365 Intra-arterial administration should be avoided (see PRECAUTIONS).

366 ***Intramuscular Administration:*** For IM administration, CEPTAZ should be constituted with
367 one of the following diluents: Sterile Water for Injection, Bacteriostatic Water for Injection, or
368 0.5% or 1% Lidocaine Hydrochloride Injection. Refer to Table 5.

369 ***Intravenous Administration:*** The IV route is preferable for patients with bacterial septicemia,
370 bacterial meningitis, peritonitis, or other severe or life-threatening infections, or for patients who
371 may be poor risks because of lowered resistance resulting from such debilitating conditions as
372 malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is
373 present or pending.

374 ***For direct intermittent IV administration,*** constitute CEPTAZ as directed in Table 5 with
375 Sterile Water for Injection, 5% Dextrose Injection, or 0.9% Sodium Chloride Injection. Slowly
376 inject directly into the vein over a period of 3 to 5 minutes or give through the tubing of an
377 administration set while the patient is also receiving one of the compatible IV fluids (see
378 COMPATIBILITY AND STABILITY).

379 ***For IV infusion,*** constitute the 1- or 2-gram infusion pack with 100 mL of Sterile Water for
380 Injection or one of the compatible IV fluids listed under the COMPATIBILITY AND
381 STABILITY section. Alternatively, constitute the 1- or 2-gram vial and add an appropriate
382 quantity of the resulting solution to an IV container with one of the compatible IV fluids.

383 ***Intermittent IV infusion with a Y-type administration set*** can be accomplished with
384 compatible solutions. However, during infusion of a solution containing ceftazidime, it is
385 desirable to discontinue the other solution.

386

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387

Table 5: Preparation of Solutions of CEPTAZ

Size	Amount of Diluent to Be Added (mL)	Volume to Be Withdrawn (mL)	Approximate Ceftazidime Concentration (mg/mL)
Intramuscular			
1-gram vial	3.0	Total	250
Intravenous			
1-gram vial	10.0	Total	90
2-gram vial	10.0	Total	170
Infusion pack			
1-gram vial	100	—	10
2-gram vial	100	—	20
Pharmacy bulk package			
10-gram vial	40	Amount needed	200

388

389 Solutions of CEPTAZ, like those of most beta-lactam antibiotics, should not be added to
 390 solutions of aminoglycoside antibiotics because of potential interaction.

391 However, if concurrent therapy with CEPTAZ and an aminoglycoside is indicated, each of
 392 these antibiotics can be administered separately to the same patient.

393 **Instructions for Constitution:** Vials of CEPTAZ as supplied are under a slightly reduced
 394 pressure. This may assist entry of the diluent. No gas-relief needle is required when adding the
 395 diluent, except for the infusion pack where it is required during the latter stages of addition (in
 396 order to preserve product sterility, a gas-relief needle should not be inserted until an overpressure
 397 is produced in the vial). No evolution of gas occurs on constitution. When the vial contents are
 398 dissolved, vials other than infusion packs may still be under a reduced pressure. This reduced
 399 pressure is particularly noticeable for the 10-gram pharmacy bulk package.

400

401 **COMPATIBILITY AND STABILITY:**

402 **Intramuscular:** CEPTAZ, when constituted as directed with Sterile Water for Injection,

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403 Bacteriostatic Water for Injection, or 0.5% or 1% Lidocaine Hydrochloride Injection, maintains
404 satisfactory potency for 18 hours at room temperature or for 7 days under refrigeration. Solutions
405 in Sterile Water for Injection that are frozen immediately after constitution in the original
406 container are stable for 6 months when stored at -20°C. Components of the solution may
407 precipitate in the frozen state and will dissolve on reaching room temperature with little or no
408 agitation. Potency is not affected. Frozen solutions should only be thawed at room temperature.
409 Do not force thaw by immersion in water baths or by microwave irradiation. Once thawed,
410 solutions should not be refrozen. Thawed solutions may be stored for up to 12 hours at room
411 temperature or for 7 days in a refrigerator.

412 **Intravenous: *Ceftazidime concentration greater than 100 mg/mL (2-g vial or 10-g pharmacy***
413 ***bulk package):*** CEPTAZ, when constituted as directed with Sterile Water for Injection, 0.9%
414 Sodium Chloride Injection, or 5% Dextrose Injection, maintains satisfactory potency for 18 hours
415 at room temperature or for 7 days under refrigeration. Solutions of a similar concentration in
416 Sterile Water for Injection that are frozen immediately after constitution in the original container
417 are stable for 6 months when stored at -20°C. Components of the solution may precipitate in the
418 frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency
419 is not affected. Frozen solutions should only be thawed at room temperature. Do not force thaw
420 by immersion in water baths or by microwave irradiation. Once thawed, solutions should not be
421 refrozen. Thawed solutions may be stored for up to 12 hours at room temperature or for 7 days in
422 a refrigerator.

423 ***Ceftazidime concentration of 100 mg/mL or less (1-g vial or infusion packs):*** CEPTAZ,
424 when constituted as directed with Sterile Water for Injection, 0.9% Sodium Chloride Injection, or
425 5% Dextrose Injection, maintains satisfactory potency for 24 hours at room temperature or for
426 7 days under refrigeration. Solutions, prepared by a pharmacist, of the approved arginine
427 formulation of ceftazidime of a similar concentration in Sterile Water for Injection, 0.9% Sodium
428 Chloride Injection, or 5% Dextrose Injection in the original container or in 0.9% Sodium
429 Chloride Injection in VIAFLEX[®] (PL 146[®] Plastic) small-volume containers that are frozen
430 immediately after constitution by the pharmacist are stable for 6 months when stored at -20°C.
431 Solutions in the PL 146 Plastic small-volume containers are in contact with the polyvinyl chloride
432 layer of this container and can leach out certain chemical components of the plastic in very small

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433 amounts within the expiration period. The suitability of the plastic has been confirmed in tests in
434 animals according to USP biological tests for plastic containers as well as by tissue culture
435 toxicity studies. Stability of the frozen solution in other containers has not been confirmed.
436 Frozen solutions should only be thawed at room temperature. Do not force thaw by immersion in
437 water baths or by microwave irradiation. For the larger volumes of IV infusion solutions where it
438 may be necessary to warm the frozen product, care should be taken to avoid heating after thawing
439 is complete. Once thawed, solutions should not be refrozen. Thawed solutions may be stored for
440 up to 18 hours at room temperature or for 7 days in a refrigerator.

441 Components of the solution may precipitate in the frozen state and will dissolve on reaching
442 room temperature with little or no agitation. Potency is not affected. Check for minute leaks in
443 plastic containers by squeezing bag firmly. Discard bag if leaks are found as sterility may be
444 impaired. Do not add supplementary medication to bags. Do not use unless solution is clear and
445 seal is intact.

446 Use sterile equipment.

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

450 ***Preparation for Administration:***

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

454 CEPTAZ is compatible with the more commonly used IV infusion fluids. Solutions at
455 concentrations between 1 and 40 mg/mL in 0.9% Sodium Chloride Injection; 1/6 M Sodium
456 Lactate Injection; 5% Dextrose Injection; 5% Dextrose and 0.225% Sodium Chloride Injection;
457 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride
458 Injection; 10% Dextrose Injection; Ringer's Injection, USP; Lactated Ringer's Injection, USP;
459 10% Invert Sugar in Sterile Water for Injection; and Normosol[®]-M in 5% Dextrose Injection may
460 be stored for up to 24 hours at room temperature or for 7 days if refrigerated.

461 CEPTAZ is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not
462 recommended as a diluent. Solutions of CEPTAZ in 5% Dextrose Injection and 0.9% Sodium

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463 Chloride Injection are stable for at least 6 hours at room temperature in plastic tubing, drip
464 chambers, and volume control devices of common IV infusion sets.

465 Ceftazidime at a concentration of 4 mg/mL has been found compatible for 24 hours at room
466 temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose
467 Injection when admixed with: cefuroxime sodium (ZINACEF[®]) 3 mg/mL; heparin sodium in
468 concentrations up to 50 U/mL; or potassium chloride in concentrations up to 40 mEq/L.

469 Ceftazidime may be constituted at a concentration of 20 mg/mL with metronidazole injection
470 5 mg/mL, and the resultant solution may be stored for 24 hours at room temperature or for 7 days
471 under refrigeration. Ceftazidime at a concentration of 20 mg/mL has been found compatible for
472 24 hours at room temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection
473 or 5% Dextrose Injection when admixed with 6 mg/mL clindamycin (as clindamycin phosphate).

474 Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs,
475 including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the
476 concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both
477 drugs are to be administered by intermittent IV infusion, that they be given separately, flushing
478 the IV lines (with one of the compatible IV fluids) between the administration of these two
479 agents.

480 **Note:** Parenteral drug products should be inspected visually for particulate matter before
481 administration whenever solution and container permit.

482 As with other cephalosporins, CEPTAZ powder as well as solutions tend to darken, depending
483 on storage conditions; within the stated recommendations, however, product potency is not
484 adversely affected.

485 **Directions for Dispensing: *Pharmacy Bulk Package—Not for Direct Infusion:*** The pharmacy
486 bulk package is for use in a pharmacy admixture service only under a laminar flow hood. Entry
487 into the vial must be made with a sterile transfer set or other sterile dispensing device, and the
488 contents dispensed in aliquots using aseptic technique. The use of syringe and needle is not
489 recommended as it may cause leakage (see DOSAGE AND ADMINISTRATION). GOOD
490 PHARMACY PRACTICE DICTATES THAT THE CLOSURE BE PENETRATED ONLY
491 ONE TIME AFTER CONSTITUTION. AFTER INITIAL PENETRATION OF THE CLOSURE,
492 USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE

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493 DISCARDED WITHIN 18 HOURS OF CONSTITUTION.

494

495 **HOW SUPPLIED:** CEPTAZ in the dry state should be stored between 15° and 30°C (59° and
496 86°F) and protected from light. CEPTAZ is a dry, white to off-white powder supplied in vials and
497 infusion packs as follows:

498 NDC 0173-0414-00 1-g* Vial (Tray of 25)

499 NDC 0173-0415-00 2-g* Vial (Tray of 25)

500 NDC 0173-0416-00 1-g* Infusion Pack (Tray of 10)

501 NDC 0173-0417-00 2-g* Infusion Pack (Tray of 10)

502 NDC 0173-0418-00 10-g* Pharmacy Bulk Package (Tray of 6)

503 *Equivalent to anhydrous ceftazidime.

504

505 **REFERENCES:**

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517 GlaxoSmithKline

518 Research Triangle Park, NC 27709

519 Made in England

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Janice Soreth
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