PRODUCT INFORMATION

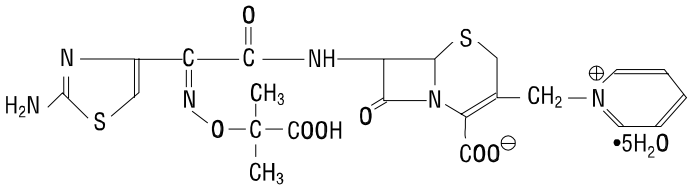
CEPTAZ®

(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-[6α,7β(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

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

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

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

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

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

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

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

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

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

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

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

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

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

clinical infections (see INDICATIONS AND USAGE).

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

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

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

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

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

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

Susceptibility Tests: *Diffusion Techniques:* Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure[1-3] has been recommended for use with disks to test susceptibility to ceftazidime.

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

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

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

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

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

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

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

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

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

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including ampicillin-resistant strains; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia*

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

2. **Skin and Skin-Structure Infections** caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible strains); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).
3. **Urinary Tract Infections**, both complicated and uncomplicated, caused by *Pseudomonas aeruginosa*; *Enterobacter* spp.; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Klebsiella* spp.; and *Escherichia coli*.
4. **Bacterial Septicemia** caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Haemophilus influenzae*, *Escherichia coli, Serratia* spp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible strains).
5. **Bone and Joint Infections** caused by *Pseudomonas aeruginosa, Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible strains).
6. **Gynecologic Infections,** including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli*.
7. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).
8. **Central Nervous System Infections,** including meningitis, caused by *Haemophilus influenzae* and *Neisseria meningitidis*. Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

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

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

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

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

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

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

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

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

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

PRECAUTIONS:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hematologic: Rare cases of hemolytic anemia have been reported.

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

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

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

Hepatobiliary Tract: Hyperbilirubinemia, jaundice.

Renal and Genitourinary: Renal impairment.

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

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

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

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

the removal of ceftazidime from the body.

DOSAGE AND ADMINISTRATION:

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

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

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 *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function†	30-50 mg/kg IV to a maximum of 6 grams per day	q8h

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

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

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

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

Table 4: Recommended Maintenance Dosages of CEPTAZ in Renal Insufficiency

NOTE: IF THE DOSE RECOMMENDED IN TABLE 3 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS 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

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

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

Females: 0.85 x male value

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

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

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

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

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

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

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

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

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

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

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

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

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

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

COMPATIBILITY AND STABILITY:

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

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

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

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

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

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

Use sterile equipment.

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

Preparation for Administration:

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

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

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

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

Ceftazidime at a concentration of 4 mg/mL has been found compatible for 24 hours at room temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose Injection when admixed with: cefuroxime sodium (ZINACEF®) 3 mg/mL; heparin sodium in concentrations up to 50 U/mL; or potassium chloride in concentrations up to 40 mEq/L. Ceftazidime may be constituted at a concentration of 20 mg/mL with metronidazole injection 5 mg/mL, and the resultant solution may be stored for 24 hours at room temperature or for 7 days under refrigeration. Ceftazidime at a concentration of 20 mg/mL has been found compatible for 24 hours at room temperature or for 7 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose Injection when admixed with 6 mg/mL clindamycin (as clindamycin phosphate).

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

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

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

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

DISCARDED WITHIN 18 HOURS OF CONSTITUTION.

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

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

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

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

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

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

*Equivalent to anhydrous ceftazidime.

REFERENCES:

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2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disc Susceptibility Tests*. (M2-A3). December 1984.
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4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

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/s/

Janice Soreth
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