ABL3899BU1

Ceftazidime for Injection, USP

PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

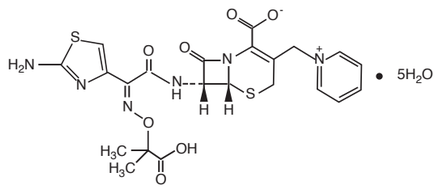
SAGENT™

℞ only

For Intravenous Use
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftazidime for injection and other antibacterial drugs, ceftazidime for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

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 structural formula:



The molecular formula is $C_{22}H_{32}N_6O_{12}S_2$, representing a molecular weight of 636.6.
Ceftazidime for injection, USP is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity.
Ceftazidime for injection, USP is a white to cream-colored crystalline powder. Solutions of ceftazidime for injection, USP 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 8.
Ceftazidime in sterile crystalline form is supplied in 6 gram Pharmacy Bulk Package bottles equivalent to 6 grams of anhydrous ceftazidime.
The Pharmacy Bulk Package bottle contains 708 mg of sodium carbonate. The sodium content is approximately 54 mg (2.3 mEq) per gram of ceftazidime.
The 6 g Pharmacy Bulk Package bottle is a container of sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous use. THE 6 g PHARMACY BULK PACKAGE IS NOT FOR DIRECT INFUSION. FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY

After 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. Average Serum Concentrations of Ceftazidime

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 hr	1 hr	2 hr	4 hr	8 hr
500 mg	42	25	12	6	2
1g	60	39	23	11	3
2g	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.
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 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.
Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids.

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	2 g IV	6	0 to 2 hr	12,000
Bile	2 g IV	3	90 min	36.4
Synovial fluid	2 g IV	13	2 hr	25.6
Peritoneal fluid	2 g IV	8	2 hr	48.6
Sputum	1 g IV	8	1 hr	9
Cerebrospinal fluid	2 g q8hr IV	5	120 min	9.8
(inflamed meninges)	2 g q8hr IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1 to 3 hr	11
Blister fluid	1 g IV	7	2 to 3 hr	19.7
Lymphatic fluid	1 g IV	7	2 to 3 hr	23.4
Bone	2 g IV	8	0.67 hr	31.1
Heart muscle	2 g IV	35	30 to 280 min	12.7
Skin	2 g IV	22	30 to 180 min	6.6
Skeletal muscle	2 g IV	35	30 to 280 min	9.4
Myometrium	2 g IV	31	1 to 2 hr	18.7

Microbiology

Mechanism of Action
Ceftazidime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Ceftazidime has activity in the presence of some beta-lactamases, both penicillinases and cephalosporinases, of Gram-negative and Gram-positive bacteria.

Mechanism of Resistance
Resistance to ceftazidime is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), and decreased permeability.

Interaction with Other Antimicrobials
In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftazidime.
Ceftazidime has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Gram-negative bacteria
- *Citrobacter* species
- *Enterobacter* species
- *Escherichia coli*
- *Klebsiella* species
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Pseudomonas aeruginosa*
- *Serratia* species

Gram-positive bacteria
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*

Anaerobic bacteria
- *Bacteroides* species (Note: many isolates of *Bacteroides* species are resistant)

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftazidime. However, the efficacy of ceftazidime in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria
- *Acinetobacter* species
- *Citrobacter diversus*
- *Citrobacter freundii*
- *Providencia* species (including *Providencia rettgeri*)
- *Salmonella* species
- *Shigella* species
- *Haemophilus parainfluenzae*
- *Morganella morganii*
- *Neisseria gonorrhoeae*
- *Yersinia enterocolitica*

Gram-positive bacteria
- *Staphylococcus epidermidis*

Anaerobic bacteria
- *Clostridium* species (Not including *Clostridium difficile*)
- *Peptostreptococcus* species

Susceptibility Test Methods
When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution techniques
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,2]. The MIC values should be interpreted according to criteria provided in *Table 3*.

Diffusion techniques
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method[2,3]. This procedure uses paper disks impregnated with 30 mcg ceftazidime to test the susceptibility of microorganisms to ceftazidime. The disk diffusion interpretive criteria are provided in *Table 3*.

Table 3. Susceptibility Test Interpretive Criteria for Ceftazidime

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameters (mm)		
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae§	≤ 4	8	≥ 16	≥ 21	18 to 20	≤ 17
Haemophilus influenzae[a]	≤ 2	-	-	≥26	-	-
*Pseudomonas aeruginosa**	≤ 8	-	≥ 16	≥ 18	-	≤ 17

§ Susceptibility interpretive criteria for *Enterobacteriaceae* are based on a dose of 1 gram q 8h. For isolates with intermediate susceptibility, use a dose of 2 grams every 8 hours in patients with normal renal function.
* For *P. aeruginosa*, susceptibility interpretive criteria are based on a dose of 2 grams IV every 8 hours in patients with normal renal function.
[a] The current absence of data on resistant isolates precludes defining any category other than 'Susceptible'. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing. Susceptibility of staphylococci to ceftazidime may be deduced from testing only penicillin and either cefoxitin or oxacillin.

A report of "Susceptible" indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection; other therapy should be selected.

Quality Control
Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test[1,2,3,4]. Standard ceftazidime powder should provide the following range of MIC values noted in *Table 4*. For the diffusion technique using the 30 mcg disk, the criteria in *Table 4* should be achieved.

Table 4. Acceptable Quality Control Ranges for Ceftazidime

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone diameters (mm)
Escherichia coli ATCC 25922	0.06 to 0.5	25 to 32
Staphylococcus aureus ATCC 25923	-----	16 to 20
Staphylococcus aureus ATCC 29213	4 to 16	-----
Haemophilus influenzae ATCC 49247	0.12 to 1	27 to 35
Neisseria gonorrhoeae ATCC 49226	0.03 to 0.12	35 to 43
Pseudomonas aeruginosa ATCC 27853	1 to 4	22 to 29

INDICATIONS AND USAGE

Ceftazidime for injection, USP 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 for injection, USP has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

Ceftazidime for injection, USP may be used alone in cases of confirmed or suspected sepsis. Ceftazidime for injection, USP has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used.
Ceftazidime for injection, USP 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. When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftazidime for injection, USP and other antibacterial drugs, ceftazidime for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ceftazidime for injection is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFTAZIDIME FOR INJECTION 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 CEFTAZIDIME FOR INJECTION 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.
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftazidime for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.
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 ceftazidime 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 and 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.
Ceftazidime should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime. Prescribing ceftazidime for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be counseled that antibacterial drugs, including ceftazidime for injection, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ceftazidime for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ceftazidime for injection or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.
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 aminoglycoside 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.
In common with other antibiotics, ceftazidime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.
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 for injection. 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. Caution should be exercised when ceftazidime is administered to a nursing woman.
Pediatric Use
See DOSAGE AND ADMINISTRATION.
Geriatric Use
Of the 2,221 subjects who received ceftazidime in 11 clinical studies, 824 (37%) were 65 and older while 391 (18%) were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiram-like reactions were reported.
The following adverse effects from clinical trials were considered to be either related to ceftazidime therapy or were of uncertain etiology:
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 dosing 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 clinical trials with ceftazidime 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 Ceftazidime Products
In addition to the adverse events reported during clinical trials, the following events have been observed during clinical practice in patients treated with ceftazidime 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.

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 every 8 to 12 hours. The dosage 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 ceftazidime for injection are listed in *Table 5*. The following dosage schedule is recommended.

Table 5. Recommended Dosage Schedule

	Dose	Frequency
Adults		
Usual recommended dosage	**1 gram IV**	**q8 to 12hr**
Uncomplicated urinary tract infections	250 mg IV	q12hr
Bone and joint infections	2 grams IV	q12hr
Complicated urinary tract infections	500 mg IV	q8 to 12hr
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg to 1 gram IV	q8hr
Serious gynecologic and intra-abdominal infections	2 grams IV	q8hr
Meningitis	2 grams IV	q8hr
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8hr
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30 to 50 mg/kg IV to a maximum of 6 grams per day	q8hr
Neonates (0 to 4 weeks)	30 mg/kg IV	q12hr
Infants and children (1 month to 12 years)	30 to 50 mg/kg IV to a maximum of 6 grams per day**	q8hr

*Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.
**The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.

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 ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in *Table 6*.

Table 6. Recommended Maintenance Dosages of Ceftazidime for Injection in Renal Insufficiency
NOTE: IF THE DOSE RECOMMENDED IN *TABLE 5* ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN *TABLE 6*, THE LOWER DOSE SHOULD BE USED.

Creatinine Clearance (mL/min)	Recommended Unit Dose of Ceftazidime for Injection	Frequency of Dosing
50 to 31	1 gram	q12hr
30 to 16	1 gram	q24hr
15 to 6	500 mg	q24hr
<5	500 mg	q48hr

When only serum creatinine is available, the following formula (Cockcroft's equation)[5] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

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

Females: 0.85 x male value

In patients with severe infections who would normally receive 6 grams of ceftazidime for injection 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 pediatric patients as for adults, the creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.
In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period.
Ceftazidime for injection can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of ceftazidime for injection may be given, followed by 500 mg every 24 hours. In addition to IV use, ceftazidime for injection can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.
Note: Generally ceftazidime for injection 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
Ceftazidime for injection may be given intravenously. Intra-arterial administration should be avoided (see PRECAUTIONS).
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.
Directions for Proper Use of a Pharmacy Bulk Package
Not for direct infusion. This Pharmacy Bulk Package is for use in a hospital pharmacy admixture service, only in a suitable work area, such as a laminar flow hood. Using aseptic technique, the container closure may be penetrated only one time using a suitable sterile dispensing set or transfer device that allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 4 HOURS from initial closure entry is permitted to complete fluid transfer operations. This time limit should begin with the introduction of the solvent or diluent into the Pharmacy Bulk Package. DISCARD ANY UNUSED PORTION AFTER 4 HOURS. NOT FOR DIRECT INFUSION. THIS PHARMACY BULK PACKAGE IS NOT INTENDED TO BE DISPENSED AS A UNIT.

For IV infusion, constitute the 6 g Pharmacy Bulk Package bottle with Sterile Water for Injection and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids listed under the COMPATIBILITY AND STABILITY section.
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.

Freezing solutions of ceftazidime for injection is not recommended.

Table 7. Preparation of Solutions of Ceftazidime for Injection

Size	Amount of Diluent to be Added (mL)	Approximate Available Volume (mL)	Approximate Ceftazidime Concentration (mg/mL)
Pharmacy bulk package bottle 6 grams	26	30	200

All Pharmacy Bulk Package bottles of ceftazidime for injection as supplied are under reduced pressure. When ceftazidime for injection is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use please follow the recommended techniques of constitution described on the detachable Instructions for Constitution section of this insert.
Solutions of ceftazidime for injection, 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 ceftazidime for injection and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

COMPATIBILITY AND STABILITY

Intravenous
Ceftazidime for injection, when constituted as directed with Sterile Water for Injection, should have the contents withdrawn within 4 hours. Solutions in 0.9% Sodium Chloride Injection in VIAFLEX® small-volume containers that are frozen immediately after constitution are stable for 3 months when stored at -20°C. 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 3 days in a refrigerator.
Ceftazidime 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 Water for Injection; and NORMOSOL®-M in 5% Dextrose Injection may be stored for up to 12 hours at room temperature or for 3 days if refrigerated.
Ceftazidime for injection is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not recommended as a diluent. Solutions of ceftazidime for injection 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 12 hours at room temperature or for 3 days under refrigeration in 0.9% Sodium Chloride Injection or 5% Dextrose Injection when admixed with: cefuroxime sodium 3 mg/mL, heparin 10 or 50 U/mL, or potassium chloride 10 or 40 mEq/L.
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 1 of the compatible IV fluids) between the administration of these 2 agents.
Note: Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit.
As with other cephalosporins, ceftazidime for injection powder, as well as solutions, tend to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

HOW SUPPLIED
Ceftazidime for injection, USP in the dry state should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] and protected from light. Ceftazidime for Injection, USP is a white to cream-colored crystalline powder supplied in Pharmacy Bulk Package Bottles as follows:

NDC	Ceftazidime for Injection, USP	Package Factor
25021-129-99	6g* Pharmacy Bulk Package Bottle	6 bottles per carton

*Equivalent to anhydrous ceftazidime.

Sterile, Nonpyrogenic, Preservative-free
The container closure is not made with natural rubber latex.

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition.* CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement*, CLSI document M100-S24. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*, CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
4. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eighth Edition.* CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.

SAGENT™

Mfd. for SAGENT Pharmaceuticals
Schaumburg, IL 60195 (USA)
Made in Brazil

Revised: December 2014 ABL3899BU1

TEAR AWAY

CEFTAZIDIME FOR INJECTION, USP

Instructions for Constitution

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.

SAGENT™

Mfd. for SAGENT Pharmaceuticals
Schaumburg, IL 60195 (USA)
Made in Brazil
©2014 Sagent Pharmaceuticals, Inc.

Revised: December 2014 ABL3899BU1