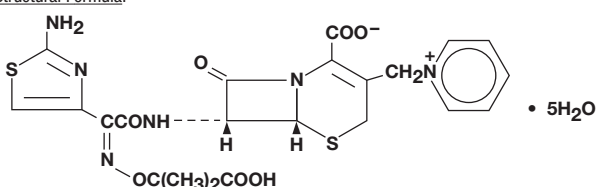


**Ceftazidime** for Injection, USP  
**Antibiotic**

**PHARMACEUTICAL INFORMATION**

**Chemical Name:** 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, pentahydrate, [6R-[6 $\alpha$ ,7 $\beta$ (Z)]].

**Structural Formula:**



**Molecular Formula:** C<sub>22</sub>H<sub>22</sub>N<sub>6</sub>O<sub>7</sub>S<sub>2</sub>•5H<sub>2</sub>O

**Molecular Weight:** 636.65

**Description:**

Ceftazidime is a white to cream-coloured crystalline powder. It is soluble in acid, alkali and dimethyl sulfoxide; slightly soluble in water, methanol and dimethylformamide; insoluble in 95% ethanol, ethyl acetate, acetone, 1,4-dioxan, diethyl ether, toluene, petroleum spirit and chloroform.

**Composition:**

Ceftazidime for Injection, USP vials contain a mixture of ceftazidime 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).

Solutions of Ceftazidime for Injection, USP range in colour from light yellow to amber, depending upon the diluent and volume used. The pH of freshly reconstituted solutions usually ranges from 5.0 to 7.5.

**ACTION**

*In vitro* studies indicate that the bactericidal action of ceftazidime results from inhibition of bacterial cell wall synthesis.

**INDICATIONS AND CLINICAL USES**

Ceftazidime for Injection, USP may be indicated for the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

**Pneumonia** caused by *Pseudomonas aeruginosa*, *H. influenzae* (including ampicillin-resistant strains), *Klebsiella* sp., *Enterobacter* sp., *Proteus mirabilis*, *E. coli*, *Serratia* sp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible strains).

**Skin and skin-structure infections** caused by *Pseudomonas aeruginosa*, *Klebsiella* sp., *E. coli*, *Proteus mirabilis*, *Enterobacter* sp., *Staphylococcus aureus* (methicillin-susceptible strains), and *Streptococcus pyogenes*.

**Urinary tract infections** caused by *Pseudomonas aeruginosa*, *Enterobacter* sp., *Proteus* sp. (indole-positive and negative), *Klebsiella* sp., and *E. coli*.

**Bacteremia/Septicemia** caused by *Pseudomonas aeruginosa*, *Klebsiella* sp., *E. coli*, *Serratia* sp., *Streptococcus pneumoniae*, *Staphylococcus aureus* (methicillin-susceptible strains) and *Staphylococcus epidermidis*.

**Bone infections** caused by *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Enterobacter* sp., and *Staphylococcus aureus* (methicillin-susceptible strains).

**Peritonitis** caused by *E. coli*, *Klebsiella* sp., *Peptostreptococcus* sp. and *Bacteroides* sp. (most strains of *B. fragilis* are resistant).

Specimens for bacteriologic cultures should be obtained prior to therapy in order to isolate and identify causative organisms and to determine their susceptibilities 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.

Due to the nature of the underlying conditions which usually predispose patients to pseudomonal infections of the lower respiratory and urinary tracts, a good clinical response accompanied by bacterial eradication may not be achieved despite evidence of *in vitro* sensitivity.

**CONTRAINDICATIONS**

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

**WARNINGS**

BEFORE THERAPY WITH CEFTAZIDIME FOR INJECTION, USP IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. CEFTAZIDIME FOR INJECTION SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PATIENTS WITH TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. 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 TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics, including Ceftazidime for Injection, USP. Therefore, it is important to consider its diagnosis in patients administered ceftazidime who develop diarrhea. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics including Ceftazidime for Injection, USP may alter 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.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the administration of ceftazidime has been discontinued, or when it is severe, consideration should be given to the administration of oral vancomycin or other suitable therapy.

**PRECAUTIONS**

Ceftazidime for Injection, USP dosage should be reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). High and prolonged serum antibiotic concentrations can occur from normal 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 such patients to avoid the clinical consequences, e.g., seizures, encephalopathy, asterixis, and neuromuscular excitability due to elevated levels of antibiotics (see **DOSAGE AND ADMINISTRATION**). Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

Chloramphenicol in combination with cephalosporins, including ceftazidime, has been shown to be antagonistic *in vitro*. Due to the possibility of antagonism *in vivo*, this combination should be avoided.

As with other antibiotics, prolonged use of Ceftazidime for Injection, USP may result in the overgrowth of non-susceptible organisms including species originally sensitive to the drug. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. Resistance has developed during therapy with ceftazidime by *Staphylococcus aureus*, *Enterobacteriaceae*, *Acinetobacter* species, and *Pseudomonas* species.

Ceftazidime for Injection, USP should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics or potent diuretics, such as furosemide. Although transient elevations of BUN and serum creatinine have been observed in clinical studies, there is no evidence that ceftazidime, when administered alone, is significantly nephrotoxic.

**Pregnancy:**

The safety of Ceftazidime for Injection, USP in the treatment of infections during pregnancy has not been established. If the administration of ceftazidime to pregnant patients is considered necessary, its use requires that the potential benefits be weighed against the possible hazards to the fetus.

**Nursing Mothers:**

Ceftazidime is excreted in human milk in low concentrations (3.8 - 5.2 mg/mL). Caution should be exercised when Ceftazidime for Injection, USP is administered to a nursing woman.

**Neonates:**

Safety in infants 1 month of age or younger has not been established.

**Elderly Patients:**

The elimination of ceftazidime may be reduced due to impairment of renal function.

**Laboratory Test Changes:**

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinifast tablets. As with some other cephalosporins, transient

elevations of blood urea, blood urea nitrogen, and/or serum creatinine, hepatic enzymes [aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH) and alkaline phosphatases] were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis were very rarely seen.

## ADVERSE REACTIONS

The most common adverse reactions associated with the administration of Ceftazidime for Injection, USP in clinical trials are listed below:

**Local effects**, reported in < 2% of patients, were phlebitis, thrombophlebitis, pain and inflammation at the site of injection or infusion.

**Hypersensitivity reactions**, reported in 2% of patients, were pruritus, urticaria, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Angioedema and anaphylaxis (0.2% of patients; bronchospasm and/or hypotension) have been reported very rarely.

**Gastrointestinal symptoms**, reported in < 2% of patients, were diarrhea, colitis, nausea, vomiting, and abdominal pain. Pseudomembranous colitis has been reported (see **WARNINGS**).

**Central nervous system reactions** (less than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins including ceftazidime (see **PRECAUTIONS**).

**Less frequent adverse events**: (< 1%) were candidiasis (including oral thrush) and vaginitis.

**Hepatic**: < 4% of patients experienced transient elevations of hepatic values, these included: SGOT, SGPT, LDH, and alkaline phosphatase.

**Renal**: transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were noted in < 1% of patients.

**Hematopoietic effects** were noted and included eosinophilia (3.4%), positive Coombs' test without hemolysis (5.1%). Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, thrombocytosis, and lymphocytosis were seen in < 1% of patients.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

**Signs and Symptoms** – Overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, and neuromuscular excitability. 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. It is reported that the administration of large doses of parenteral cephalosporins may cause dizziness, paresthesias, and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur.

Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs' test, thrombocytosis, thrombocytopenia, eosinophilia, leukopenia, and prolongation of the prothrombin time.

**Treatment** – If seizures occur, the drug should be discontinued promptly and anticonvulsant therapy may be administered if clinically indicated. The patient's airway should be protected and ventilation and perfusion supported. The patient's vital signs, blood gases, serum electrolytes, etc. should be meticulously monitored and maintained, within acceptable limits.

In cases of severe overdosage, especially in a patient with renal failure, combined hemodialysis and hemoperfusion may be considered if response to more conservative therapy fails. However, no clinical data supporting such therapy of Ceftazidime for Injection, USP overdosage are available.

## DOSAGE AND ADMINISTRATION

Ceftazidime for Injection, USP may be administered intravenously or intramuscularly after reconstitution. Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms, and condition and renal function of the patient.

### DOSAGE

#### Adults:

The usual recommended daily dose of Ceftazidime for Injection, USP is 1 g to 6 g in divided doses; 250 mg to 2 g every 8 to 12 hours.

Type of infection	Dosage	Frequency and Route
Uncomplicated urinary tract infections	250 mg	q12h IM or IV
Skin and skin structure infections and uncomplicated pneumonia	500 mg - 1 g	q8h IM or IV
Bone infections	2 g	q12h IV
Life-threatening infections (those commonly needing antibiotics in higher doses e.g., peritonitis or septicemia) or infections due to less susceptible organisms	2 g	q8h IV

A normal course of treatment should continue until 48-72 hours after the patient defervesces or after bacterial eradication has been obtained, usually 10-14 days, except for bone infections where treatment can continue for 6 weeks. In the treatment

of beta-hemolytic streptococcal infections, Ceftazidime for Injection, USP should be administered for at least 10 days.

#### Adults With Impaired Renal Function:

A reduced dosage must be employed and the serum levels closely monitored. After an initial dose of 1 g, a maintenance dosage schedule should be followed (see Table 2 below). The maintenance dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

Males:

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

Females: 0.85 x above value

MAINTENANCE DOSAGE GUIDE FOR PATIENTS WITH RENAL IMPAIRMENT		
Creatinine Clearance (mL/min.)	Recommended Dose of Ceftazidime for Injection	Frequency
50-31	1 g	q12h
30-16	1 g	q24h
15-6	500 mg	q24h
≤ 5	500 mg	q48h

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

In patients undergoing hemodialysis, a loading dose of 0.5 - 1 g of ceftazidime is recommended, followed by 0.5 - 1 g after each hemodialysis period.

Ceftazidime for Injection, USP can also be used in patients undergoing intraperitoneal dialysis (IPD) and continuous ambulatory peritoneal dialysis (CAPD). In such patients, a loading dose of 1 g of ceftazidime may be given, followed by 500 mg every 24 hours. In addition to intravenous use, ceftazidime can be incorporated in the dialysis fluid at a concentration of 250 mg/2 L of dialysis fluid.

#### Children With Impaired Renal Function:

In children, as in 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.

#### Impaired Hepatic Function:

No adjustment in dosage is required for patients with hepatic dysfunction provided renal function is not impaired.

#### Infants and Children:\*

The following dosage schedule (not to exceed the maximum adult dose) is recommended, although renal status and seriousness of infection must be considered:

Age	Dosage	Frequency
1 month - 2 months	12.5 - 25 mg/kg	q12h IV
2 months - 12 years	10 - 33 mg/kg	q8h IV

\*Safety and efficacy have not been established in infants less than 1 month of age.

Due to the nature of the underlying conditions which usually predispose patients to *Pseudomonas* infections of the lower respiratory and urinary tracts, a good clinical response accompanied by bacterial eradication may not be achieved despite evidence of *in vitro* sensitivity.

## ADMINISTRATION

#### Intramuscular:

Ceftazidime for Injection, USP should be injected well within the body of a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

#### Intravenous:

The intravenous route is preferable for patients with septicemia, peritonitis, or other severe or life-threatening infections.

#### Intermittent Intravenous Administration:

The reconstituted solution may be slowly injected into the vein over a period of 3 to 5 minutes or given through the tubing of an administration set. During the infusion of the solution containing ceftazidime, the administration of other solutions should be discontinued temporarily.

#### Continuous Intravenous Infusion:

Ceftazidime for Injection, USP may also be administered over a longer period of time.

**NOTE:** If therapy with Ceftazidime for Injection, USP is carried out in combination with an aminoglycoside antibiotic, either each of these antibiotics should be administered at different sites, or ceftazidime and aminoglycosides may

be administered sequentially by intermittent intravenous infusion. After the administration of one of the two drugs, the tubing is carefully and thoroughly flushed with an approved solution for reconstitution and then the other drug solution is administered. An aminoglycoside should not be mixed with Ceftazidime for Injection, USP in the same container.

**RECONSTITUTION:**

**NOTE:** Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution or container permits. Every container whose contents show evidence of contamination with visible foreign matter is to be rejected.

For Intramuscular Use:

Solutions for Reconstitution:

Sterile Water for Injection or, if required, Bacteriostatic Water for Injection, 0.5 to 1.0% Lidocaine Hydrochloride Injection.

Reconstitution Table:

Vial Size	Diluent to be added to Vial	Approximate Available Volume	Approximate Average Concentration
1.0 g, Vial (VL7231)	3.0 mL	3.6 mL	280 mg/mL

Shake well until dissolved. Refer to **STABILITY AND STORAGE RECOMMENDATIONS** for recommended storage conditions for both dry state and reconstituted solutions.

For Intravenous Use:

Solutions for Reconstitution:

Sterile Water for Injection.

Reconstitute as follows:

Reconstitution Table:

Vial Size	Diluent to be added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g, Vial (VL7231)	5 or 10 mL	5.6 or 10.6 mL	180 or 95 mg/mL
2 g, Vial (VL7234)	10 mL	11.2 mL	180 mg/mL

Shake well until dissolved. The prepared solution may be further diluted to the desired volume with any of the solutions for IV infusion listed below. Refer to **STABILITY AND STORAGE RECOMMENDATIONS** for recommended storage conditions for both dry state and reconstituted solutions.

For Direct Intravenous Injection: Reconstitute as directed above.

For Intermittent Intravenous Infusion: Reconstitute as directed above for 1 g or 2 g vials of Ceftazidime for Injection, USP.

For Continuous Intravenous Infusion:

Reconstitute 1 g or 2 g vials of Ceftazidime for Injection, USP with 10 mL Sterile Water for Injection. The appropriate quantity of the reconstituted solution may be added to an intravenous bottle containing any of the solutions listed below.

Pharmacy Bulk Vial:

THE AVAILABILITY OF THE BULK PHARMACY VIAL IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

Ceftazidime for Injection, USP does not contain any preservatives. The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture.

Reconstitution Table:

Vial Size	Diluent to be added to Vial	Approximate Available Volume	Approximate Average Concentration
6g, Vial (VL7241)	26 mL 56 mL	30 mL 60 mL	200 or 100 mg/mL

For the 6 g vial (VL7241), following reconstitution with Sterile Water for Injection, the solution should be dispensed and further diluted for use within 8 hours if stored at room temperature (not exceeding 25°C) and 48 hours if refrigerated (2° - 8°C). Any unused reconstituted solution should be discarded after 8 hours if stored at room temperature and after 48 hours if refrigerated. Refer to **STABILITY AND STORAGE RECOMMENDATIONS** for recommended storage conditions for both dry state and reconstituted solutions.

Solutions for IV Infusion:

- 0.9% Sodium Chloride Injection
- M/6 Sodium Lactate Injection
- Ringer's Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 10% Dextrose Injection
- Normosol®-M in 5% Dextrose Injection

When Ceftazidime for Injection, USP is dissolved, carbon dioxide is released and a positive pressure develops. For ease of use, please follow the recommended techniques of reconstitution described below.

Solutions of ceftazidime, 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 and an aminoglycoside is indicated, each of these antibiotics should be administered in different sites.

Instructions for Reconstitution:

For 1 g IM/IV, and 2 g IV vials

1. Inject the diluent and shake well to dissolve.
2. Carbon dioxide is released as the antibiotic dissolves, generating pressure within the vial. The solution will become clear within 1 to 2 minutes.
3. Invert the vial, and completely depress the syringe plunger prior to insertion.
4. Insert the needle through the vial stopper. Be sure the needle remains within the solution, and withdraw contents of the vial in the usual manner. Pressure in the vial may aid withdrawal.
5. The withdrawn solution may contain carbon dioxide bubbles which should be expelled from the syringe before injection.

For 6 g Pharmacy Bulk Package

1. When diluent is being added, the vial must be vented to prevent buildup of pressure due to release of carbon dioxide formed as the antibiotic dissolves. Use standard venting procedures outlined in the venting card for Ceftazidime for Injection, USP.
2. Inject 26 mL of diluent to provide a solution containing approximately 1 g of ceftazidime activity per 5 mL. Inject 56 mL of diluent to provide a solution containing approximately 1 g of ceftazidime activity per 10 mL.
3. Dissolve the antibiotic by gently agitating the solution.
4. Allow sufficient time (1 - 2 minutes) for carbon dioxide to vent before dispensing solution.
5. After storage, relieve any additional pressure which may develop in the vial before dispensing.

**STABILITY AND STORAGE RECOMMENDATIONS**

Dry Powder:

Ceftazidime for Injection, USP in the dry state should be stored between 15 and 30°C and protected from light.

Solutions:

1 g (VL7231) and 2 g (VL7234) Vials: Reconstituted solutions should be administered within 12 hours when stored at room temperature, (not exceeding 25°C), and within 48 hours when refrigerated (2° - 8°C), from the time of reconstitution.

6 g (VL7241) Vial: Reconstituted solution and further dilutions, should be administered within 8 hours when stored at room temperature (not exceeding 25°C) and within 48 hours if refrigerated (2° - 8°C) from the time of reconstitution. Any unused reconstituted solution should be discarded after 8 hours if stored at room temperature and after 48 hours if refrigerated.

Incompatibility:

Ceftazidime for Injection, USP should not be added to blood products, protein hydrolysates or amino acids. Ceftazidime for Injection, USP should not be mixed together with an aminoglycoside.

**AVAILABILITY OF DOSAGE FORMS**

Vial stoppers do not contain natural rubber latex.

VL 7231: Ceftazidime for Injection, USP 1 g, equivalent to 1 g ceftazidime and 118 mg sodium carbonate, 20 mL vial. (Dry Powder.)

VL 7234: Ceftazidime for Injection, USP 2 g, equivalent to 2 g ceftazidime and 236 mg sodium carbonate, 50 mL vial. (Dry Powder.)

Pharmacy Bulk Vial

VL 7241: Ceftazidime for Injection, USP 6 g, equivalent to 6 g ceftazidime and 708 mg sodium carbonate, 100 mL vial. (Dry Powder.)

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