PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]CEFTAZIDIME FOR INJECTION, USP

1 g / vial, 2 g / vial, 6 g / vial

Sterile Powder for Solution

For Intramuscular or Intravenous Use

Antibiotic

ATC Code: J01DD02

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Date of Initial Authorization:
MAR 24, 2015

Date of Revision:
FEB 17, 2022

Submission Control Number: 254560

RECENT MAJOR LABEL CHANGES

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1 INDICATIONS	[02/2022]
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	[02/2022]
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

Lower Respiratory Tract infections

Pneumonia caused by *Pseudomonas aeruginosa*, *H. influenzae* (including ampicillin-resistant strains), *Klebsiella* sp., *Enterobacte*r 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.

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 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.

1.1 Pediatrics

Pediatrics (age 1 month – 18 years):

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Ceftazidime for Injection, USP in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use(age 1 month – 18 years). See 7.1.3 Pediatrics.

Pediatrics (age 0-1 month):

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Ceftazidime for Injection, USP in pediatric patients age 0-1 month has not been established. Therefore, Health Canada has not authorized an indication for pediatric use (age 0-1 month). See 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Ceftazidime for Injection, USP is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

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.

4.2 Recommended Dose and Dosage Adjustment

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 (see Table 1).

Table 1

Type of infection	Dosage	Frequency and Route
Uncomplicated urinary tract infections	250 mg	q12h Intramuscular or Intravenous
Skin and skin structure infections and uncomplicated pneumonia	500 mg - 1 g	q8h Intramuscular or Intravenous
Bone infections	2 g	q12h Intravenous
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 Intravenous

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.

For the treatment of infections caused by *Staphylococcus* species, a dosage of 1 or 2 g administered every 8 hours is recommended. For the treatment of infections (except those confined to the urinary tract) caused by *Enterobacter* species, a dosage of at least 1 g administered every 8 hours is recommended.

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:

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

Females: 0.85 x above value

Table 2 Maintenance Dosage Guide for Patients with Renal Impairment

Creatinine Clearance (mL/min.)	Recommended Dose of Ceftazidime for Injection, USP	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:

Table 3

Age	Dosage	Frequency
1 month - 2 months	25 - 50 mg/kg	q12h Intravenous
2 months - 12 years	30 – 50 mg/kg	q8h Intravenous
12 – 18 years	Children >40kg weight - Same as adults. See Table 1.	
* Safety and efficacy have not been established in infants less than 1 month of age.		

Use in Elderly:

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. In acutely ill elderly patients with reduced renal clearance of ceftazidime, the daily dosage should not exceed 3 g.

4.3 Reconstitution

NOTE: As with all parenteral drug products, intravenous admixtures should be inspected for clarity of solutions, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

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 g	3.0 mL	3.6 mL	280 mg/mL

Shake well until dissolved. See 11 STORAGE, STABILITY AND DISPOSAL for recommended storage conditions for both dry state and reconstituted solutions.

For Intravenous Use

- **Solutions for Reconstitution:**

Sterile Water for Injection.

Reconstitution Table:

Vial Size	Diluent to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	5 or 10 mL	5.6 or 10.6 mL	180 or 95 mg/mL
2 g	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 intravenous infusion listed below. see 11 STORAGE, STABILITY AND DISPOSAL 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
6 g	26 mL	30 mL	200 or
	56 mL	60 mL	100 mg/mL

For 6 g vial, 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 to 8 °C). Any unused reconstituted solution should be discarded after 8 hours if stored at room temperature and after 48 hours if refrigerated. See 11 STORAGE, STABILITY AND DISPOSAL for recommended storage conditions for both dry state and reconstituted solutions.

- **Solutions for Intravenous 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.

Instructions for Reconstitution:

- **For 1 g Intramuscular/Intravenous, and 2 g Intravenous 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 for injection 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.

4.4 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.

5 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular or Intravenous	Sterile Powder for Solution 1 g / vial, 2 g / vial, 6 g / vial	sodium carbonate

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).

Availability of dosage forms:

The vial stoppers are not made with natural rubber latex.

Ceftazidime for Injection, USP 1 g, equivalent to 1 g ceftazidime and 118 mg sodium carbonate, 20 mL rubber-stoppered vial (Dry Powder).

Ceftazidime for Injection, USP 2 g, equivalent to 2 g ceftazidime and 236 mg sodium carbonate, 50 mL rubber-stoppered vial (Dry Powder).

Pharmacy Bulk Vial: Ceftazidime for Injection, USP 6 g, equivalent to 6 g ceftazidime and 708 mg sodium carbonate, 100 mL rubber-stoppered vial (Dry Powder).

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

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 (see 16 NON-CLINICAL TOXICOLOGY, Mutagenicity Studies).

Gastrointestinal

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

- ***Clostridium difficile*-associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including Ceftazidime for Injection, USP. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see 8 ADVERSE REACTIONS).

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.

Hematologic

- **Hemolytic Anemia**

Ceftazidime for Injection, USP should not be used in patients with a history of cephalosporin-associated hemolytic anemia since the recurrence of hemolysis is much more severe.

An immune mediate hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials, including Ceftazidime for Injection, USP. Severe cases of hemolytic anemia, including

fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2 - 3 weeks subsequent to the administration of Ceftazidime for Injection, USP, the diagnosis of a cephalosporin-associated anemia should be considered and the drug discontinued until the etiology is determined.

Patients may benefit from periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing, where appropriate (see 8 ADVERSE REACTIONS).

Immune

- **Hypersensitivity**

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, USP 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 β-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, USP occurs, discontinue treatment with the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Monitoring and Laboratory Tests

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with CLINITEST® 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.

Renal

Ceftazidime for Injection, USP dosage should be reduced in patients with impaired renal function (see 4.2 Recommended Dose and Dosage Adjustment). 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 4.2 Recommended Dose and Dosage Adjustment and 5 OVERDOSAGE). Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

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.

Sensitivity/Resistance

- **Development of Drug-Resistant Bacteria**

Prescribing Ceftazidime for Injection, USP in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria. Development of resistance during the administration of Ceftazidime for Injection, USP has been observed for Staphylococcus aureus, members of the Enterobacteriaceae family, Acinetobacter species, Pseudomonas species, and Serratia species.

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance and prevalence of extended spectrum beta lactamase (ESBLs) producing organisms is desirable, particularly when treating severe infections.

- **Potential for Microbial Overgrowth**

Prolonged treatment with Ceftazidime for Injection, USP may result in the overgrowth of nonsusceptible 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.

Skin

- **Severe Cutaneous Adverse Reactions**

Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, Ceftazidime for Injection, USP should be discontinued and appropriate therapy and/or measures should be taken.

Sodium Content

Each 1 g of ceftazidime contains 52 mg of sodium. The sodium content must be taken into account in patients requiring sodium restriction.

7.1 Special Populations

7.1.1 Pregnant Women

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.

Reproduction studies have been performed in mice and rats employing ceftazidime doses of up to 25 times those usually administered to humans. These studies have revealed no evidence of impaired fertility or harm of the fetus caused by ceftazidime. Animal reproduction studies, however, are not always predictive of human response.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Safety in infants 1 month of age or younger has not been established. Therefore, Health Canada has not authorized an indication for use in pediatric patients under the age of 1 month.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. The elimination of ceftazidime may be reduced due to age related impairment of renal function.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse effects have been local reactions following intravenous injection, allergic reactions, and gastrointestinal reactions. Other adverse effects have been encountered less frequently.

8.2 Clinical Trial 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 2.8% of patients

Phlebitis, thrombophlebitis, pain and inflammation at the site of injection or infusion.

Hypersensitivity reactions reported in 2.7% of patients

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 (see 7.WARNINGS AND PRECAUTIONS, Immune).

Gastrointestinal symptoms reported in < 4% of patients

Diarrhea, colitis, nausea, vomiting, and abdominal pain. Pseudomembranous colitis has been reported (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

Central nervous system reactions (less than 1%)

Headache, dizziness, paresthesia, hallucinations, and lethargy. There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy and coma occurring in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced. Seizures have been reported with several cephalosporins including ceftazidime (see 7 WARNINGS AND PRECAUTIONS and 5 OVERDOSAGE).

8.3 Less Common Clinical Trial Adverse Reactions

Less frequent adverse events: (< 1%)

Blurred vision, flushing, candidiasis (including oral thrush) and vaginitis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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.

Hematologic: Cases of hemolytic anemia have been reported (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

8.5 Post-Market Adverse Reactions

In addition to adverse events reported during clinical trials, the following events have been identified during clinical practice in patients treated with ceftazidime and were reported spontaneously. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Blood and lymphatic system disorders

Lymphocytosis, hemolytic anemia, and agranulocytosis.

Immune system disorders

Anaphylaxis (including bronchospasm and/or hypotension).

Nervous system disorders

Paraesthesia.

Gastrointestinal disorders

Bad taste.

Hepatobiliary disorders

Jaundice.

Skin and subcutaneous tissue disorders

Angioedema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function. See 7 WARNINGS AND PRECAUTIONS, Renal.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table Established or Potential Drug-Drug Interactions

Drug or Drug class	Effect / Clinical comment
Aminoglycosides	The concomitant administration of aminoglycosides and some cephalosporins has caused nephrotoxicity. 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. However, the effect of administering Ceftazidime concomitantly with aminoglycosides is not known.
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.

Drug or Drug class	Effect / Clinical comment
Oral contraceptives.	In common with other antibiotics, ceftazidime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.
Potent diuretics, such as furosemide and ethacrynic acid	Studies suggest that the concomitant use of potent diuretics, such as furosemide and ethacrynic acid, may increase the risk of renal toxicity with cephalosporins.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established

9.7 Drug-Laboratory Test Interactions

Ceftazidime may cause a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution). As a false negative result may occur in the ferricyanide test, it is Ceftazidime for Injection USP recommended that either glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Ceftazidime for Injection USP.

Ceftazidime does not interfere in the alkaline picrate assay for creatinine. A positive Coombs' test has been reported during treatment with cephalosporins. This phenomenon can interfere with cross matching of blood.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ceftazidime is a bactericidal agent that inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

10.2 Pharmacodynamics

In vitro studies indicate that the bactericidal action of ceftazidime results from inhibition of bacterial cell wall synthesis. Ceftazidime has a high affinity for the Penicillin-Binding Protein-3 (PBP-3) and moderate affinity for the PBP-1a of certain Gram negative organisms such as *Escherichia coli* and *Pseudomonas aeruginosa*. The affinity for PBP-1b is much less than that for either PBP-3 or PBP-1a. PBP-3 is involved in the process of cross-wall formation (septation). Binding to this protein results in formation of filaments

and eventual death of the bacterium. PBP-1a and PBP-1b are involved in longitudinal wall synthesis (elongation) prior to septation. Binding to these proteins results in spheroplast formation followed by rapid lysis.

Ceftazidime has high affinity for PBP-1 and PBP-2 of *Staphylococcus aureus*. However, the drug's affinity for PBP-3 is very much less in this organism.

10.3 Pharmacokinetics

Absorption

- **Intramuscular Injection:**

Following intramuscular administration of 500 mg and 1 g doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations at approximately 1 hour were 17 mg/L and 39 mg/L respectively. Serum concentration-time curves are shown below.

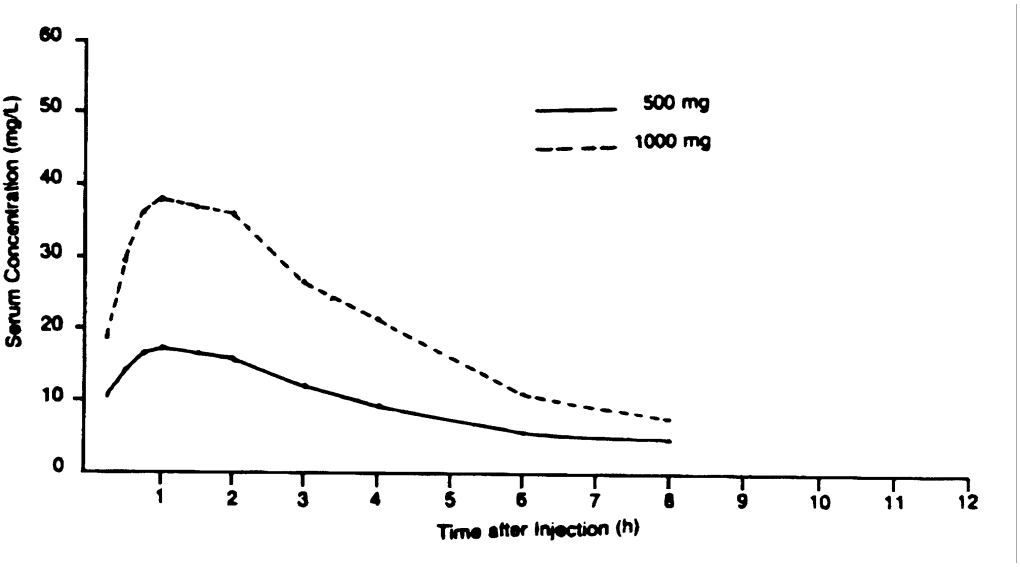


Figure 1

The average urinary concentration, following 500 mg intramuscular administration to 6 patients, was 2100 mg/L. Mean urinary recovery over 24 hours ranged from 78.9% of a 1g intramuscular dose to 84.6% of a 500 mg intramuscular dose.

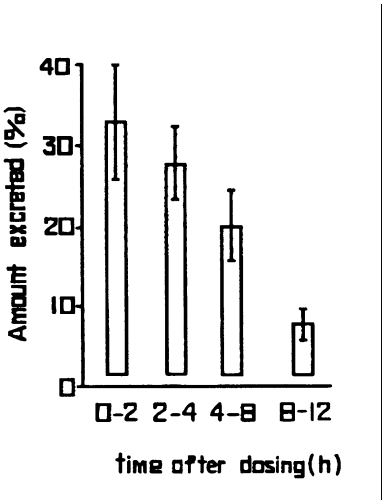


Figure 2

Table 4 Pharmacokinetic Profile of Ceftazidime after intramuscular Injection

Dose	Peak Serum Conc. (mg/L)	Apparent Volume of Distribution (L)	Serum Half-life (h)	Urinary Recovery (%, 24h)	Renal Clearance (mL/min)
Single 500mg	17	21	2.2	85	90
Single 1g	39	17	2.0	79	76
Multiple 1g	44	17	2.2	-	-

No drug accumulation was noted after repeated single intramuscular dosing over 10 days. Pharmacokinetic parameters remained unchanged. The addition of lidocaine did not alter the kinetics (see Table 4).

- **Intravenous Administration:**

Single doses of 250 mg, 500 mg, 1000 mg and 2000 mg ceftazidime were infused over 30 minutes to six male volunteers. Serum concentration time curves (Figure 3) follow a biexponential decay.

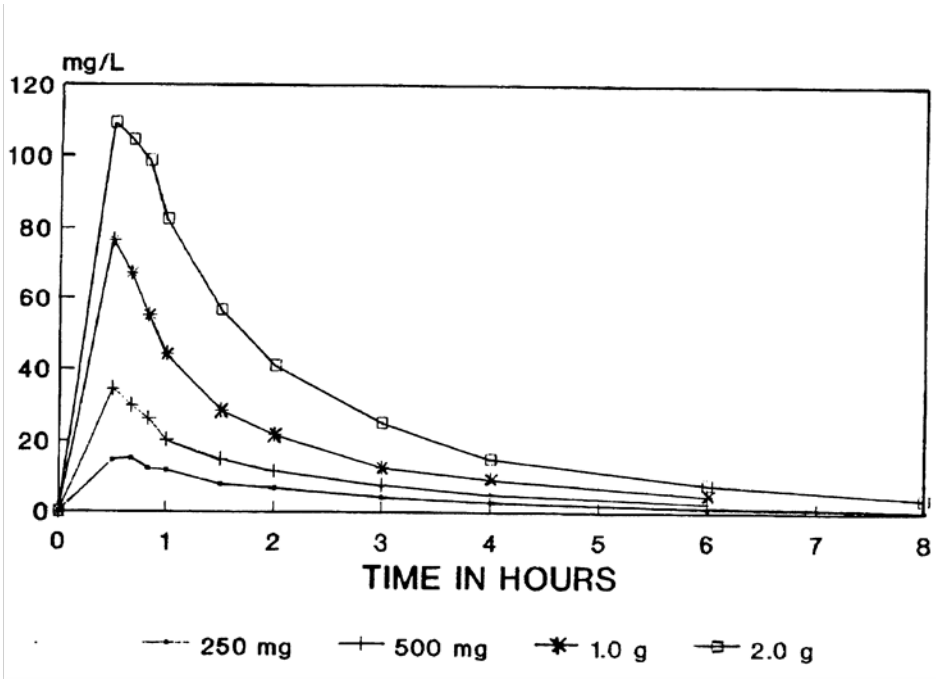


Figure 3

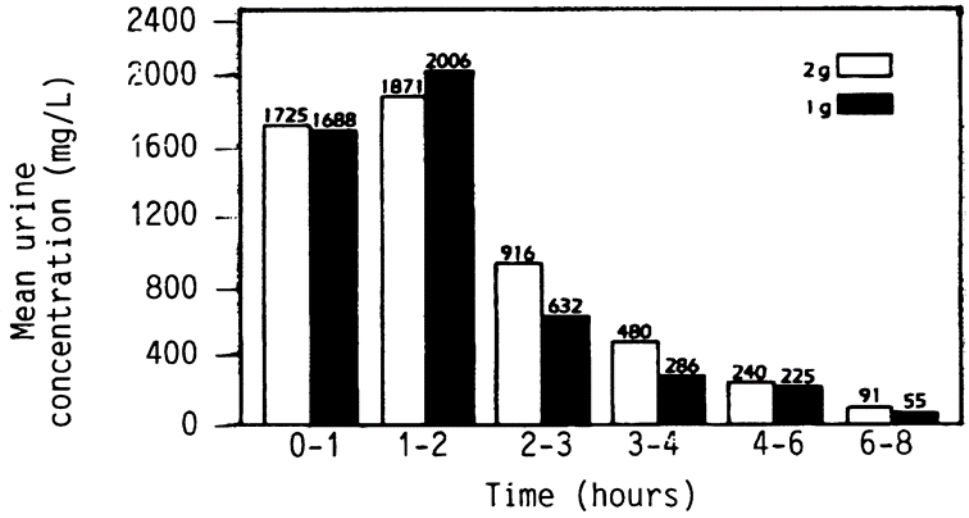


Figure 4

Mean urinary recovery of unchanged drug over 24 hours was approximately 85%, with over 50% being excreted in the first two to four hours. Figure 4 shows urinary concentrations of two doses of ceftazidime for various collection intervals after infusion.

Table 5 Average pharmacokinetic parameters of ceftazidime after intravenous infusion

Dose/ Route	Peak Serum Conc.	Apparent volume of distribution	Area under serum level / time curve	Serum half-life	Dose recovered in urine to 24h	Renal Clearance	Plasma Clearance
(Intravenous -Infusion)	(mg/L)	(L)	(mg/L/h)	(h)	(%)	(mL/min)	(mL/min)
250 mg	15.2	16.2	33.5	1.5	77.5	100	126
500 mg	34.5	20.2	68.7	1.9	63.2	77	122
1 g	76.8	19.7	134.6	1.8	69.6	88	126
2 g	114.2	22.5	235.6	1.8	53.8	79	146

Maximum serum concentrations following rapid intravenous infusions (3 to 5 minutes) were higher than those measured at the conclusion of 30 - 60 minute infusions. The maximum concentration and the area under the curve (AUC) increased proportionately with increasing doses while the elimination half-life (range of 1.5 - 2.01 hours) and renal excretion remained constant. In subjects receiving up to ten days of intravenous ceftazidime, there was no evidence of accumulation or alteration of pharmacokinetics. Addition of probenecid did not alter pharmacokinetics. The apparent volume of distribution and plasma and renal clearance rates remained within the same range as the intramuscular doses. Proportional increases in AUC with increasing doses show that ceftazidime follows linear kinetics.

Distribution

- **Protein Binding**

In vitro studies with human serum revealed that 5 - 23% of ceftazidime is protein bound and is independent of drug concentration.

- **Tissue Concentrations**

Therapeutic concentrations of ceftazidime in tissues and body fluids are presented in Table 6.

Table 6 Ceftazidime Concentration in Tissues and Body Fluids

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Post-Dose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	500 mg Intramuscular	6	0 - 2 hr	2100
	2 g Intravenous	6	0 - 2 hr	12000
Bile	2 g Intravenous	3	90 min	36.4
Synovial fluid	2 g Intravenous	13	2 hr	25.6

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Post-Dose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Peritoneal fluid	2 g Intravenous	8	2 hr	48.6
Sputum	1 g Intravenous	8	1 hr	9
Cerebrospinal fluid (inflamed meninges)	2 g q 8 hr Intravenous	5	120 min	9.4
Aqueous humor	2 g Intravenous	13	1 - 3 hr	11
Blister fluid	1 g Intravenous	7	2 - 3 hr	19.7
Lymphatic fluid	1 g Intravenous	7	2 - 3 hr	23.4
Bone	2 g Intravenous	8	0.67 hr	31.1
Heart muscle	2 g Intravenous	35	30 - 280 min	12.7
Skin	2 g Intravenous	22	30 - 280 min	6.6
Skeletal Muscle	2 g Intravenous	35	30 - 280 min	9.4
Myometrium	2 g Intravenous	31	1 - 2 hr	18.7

Concentrations of ceftazidime in the breast milk of 11 puerperal women following intravenous administration of 2 g doses every 8 hours for 5 days were determined by bioassay. Mean (± S.D.) concentrations of ceftazidime averaged 3.8 ± 2.0 mcg/mL (before the next dose), 5.2 ± 3.0 mcg/mL (1 hour after dosing) and 4.5 ± 1.7 mcg/mL (3 hours after dosing). Excretion of ceftazidime into breast milk remained constant between days 2 and 4 of therapy.

Metabolism

Ceftazidime is not metabolized. Metabolites were not detected either in the serum or in the urine.

Elimination

Hepatic clearance (i.e., biliary excretion) accounts for less than 1% of the non-renal clearance of ceftazidime in the presence of normally functioning kidneys.

The mean renal clearance of ceftazidime was 86 mL/min (range 46 to 145 mL/min). The calculated plasma clearance of 130 mL/min (range 103 to 199 mL/min) indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid prior to dosing had no effect on the elimination of kinetics of ceftazidime, suggesting elimination by glomerular filtration and not by renal tubular secretion.

Special Populations and Conditions

- **Pediatrics**

Neonates and Infants

Fifty-three neonates and infants (1 day to 12 months of age) were administered ceftazidime as a single intravenous bolus injection at a mean dose of 31 mg/kg (25.0 - 35.7 mg/kg) in addition to other antimicrobial therapy. Serum levels are presented in Table 7. The mean serum half-life for babies ages 2 months or younger was prolonged (4.2 ± 1.6 h). Those aged greater than 2 months had a half-life of 2.0 ± 0.6h.

Table 7

	Serum levels (mcg/mL) at hours after dose (mean ± S.D.)				
Age	**3**	**5**	**6**	**7**	**8**
<2 months (n=30)	54.1 ± 28.7	-	31.2 ± 17.9	-	18.6 ± 12.1
2-12 months (n=23)	26.5 ± 10.7	12.3 ± 7.6	-	6.4 ± 6.0	3.3 ± 4.2

In another study pediatric patients (1-6 years) with Gram-negative infections received a single intravenous infusion over 15 minutes of either 15 mg/kg (8 patients) or 50 mg/kg (5 patients) of ceftazidime. Serum levels were measured by bioassay. Pharmacokinetic data are presented in Table 8.

Table 8 Pharmacokinetic Parameters in Children

Patient Group	**n**	**Mean Age (months)**	**Dose (mg/Kg)**	**Peak Serum Conc. (mg/L)**	**Serum half-life (h)**	**Vol. of Distribution (L/Kg)**	**Plasma Clearance (mL/min/Kg)**
A	8	22.5	15	37.8	1.65	0.73	5.03
B	5	57.4	50	186.4	1.72	0.52	3.75

- **Geriatrics**

Ceftazidime, at a dose of 2g b.i.d., was administered as a bolus intravenous injection to 13 elderly patients with a mean age of 77 years (63 - 83 years) and to 6 younger volunteers (24 - 32 years). A mean serum half-life of 2.9 hours was observed for the elderly patients and 1.75 hours in the young volunteers. The elderly patients were continued on treatment and no accumulation was noted on day 7.

- **Sex**

Females had a smaller volume of distribution than males attributed to a smaller extra-cellular volume. The time to maximum serum concentration was slightly prolonged in females, and peak serum concentrations were higher than in men following the same dosing.

- **Pregnancy and Breastfeeding**

Intramuscular injections to pregnant women scheduled for abortions following diagnosis of fetal Cooley's anemia resulted in serum levels of ceftazidime approximately 50% lower than similar doses given to non-pregnant females.

- **Renal Insufficiency**

The relationship between serum elimination half-life and glomerular filtration rate (GFR) is curvilinear. The half-life increases steeply at GFR's less-than 50mL/min/1.73 m2 (see Figure 5).

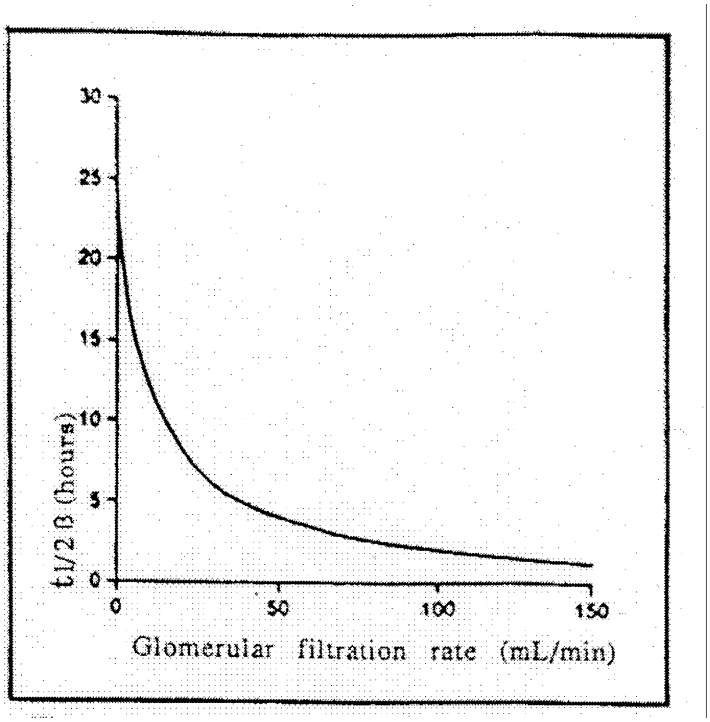


Figure 5 **Relationship between the ceftazidime half-life of elimination (t1/2β) and glomerular filtration rate**

Pharmacokinetics of patients having various degrees of renal insufficiency were compared to those of normal patients following intravenous administration of a 1g bolus dose of ceftazidime to 14 patients (mean age 49 years) with severely impaired renal function and those from 8 healthy volunteers (mean age 35 years).

Table 9 **Mean Pharmacokinetic Parameters after 1g Ceftazidime intravenous**

Group	**C_0 (mg/h/L)**	**AUC_T (mg/h/L)**	**B (h-1)**	**$T_{1/2ß}$ (h)**	**V_{dB} (L)**	**U_R (%)**	**GFR (mL/min)**
Volunteers (8)	108	152	0.378	1.9	17.8	88	115
Patients (8)	70	1360	0.061	16.7	19.2	24	12
Patients on Dialysis (6)	82	292	0.176	4.6	22.2	0	-

Group	C_0 (mg/h/L)	AUC_T (mg/h/L)	B (h-1)	$T_{1/2ß}$ (h)	V_{dB} (L)	U_R (%)	GFR (mL/min)
C_0 = Fictive serum concentration at time zero							
AUC_T = Area under the serum concentration/time curve to infinity							
B = Serum elimination rate constant							
$T_{1/2B}$ = Serum half-life							
V_{dB} = Volume of distribution during the post-distributive phase							
U_R = Urinary recovery over 24h							

In another study, six normal volunteers and four end-stage renal disease (ESRD) patients on hemodialysis were administered a single 1g intravenous dose of ceftazidime. The apparent volumes of distribution were similar in both groups. The terminal half-life in the normal subjects ranged from 1.3 to 1.7 hours, while in the ESRD patients it ranged from 25.5 to 35.4 hours. Dialysis clearance ranged from 27 to 50mL/min, while the total body clearance in the normal volunteers ranged from 98 to 184 mL/min.

The elimination half-life measured after peritoneal dialysis was comparable to the value obtained in the post dialysis period of patients undergoing hemodialysis.

- **Cystic Fibrosis**

The pharmacokinetics of an intravenous infusion (20 min) of 50 mg/kg ceftazidime were studied in 10 patients (20.8 ± 4.8 yr, 4 female, 6 males) with cystic fibrosis and 10 normal volunteers (21.6 ± 1.9 yr, 3 females, 7 males). Serum elimination half-lives were 1.76 ± 0.21h in controls and 1.50 ± 0.19h in cystic fibrosis patients. Total body clearance was 41.9% greater in the cystic fibrosis group (142.4 ±16.9mL/min/1.73m2) compared to controls (100.5 ± 10.3mL/min/1.73m2). Although the fraction of the dose recovered in urine was the same in each group, renal clearance was 40.9% greater in patients with cystic fibrosis (130.1 ± 11.4 and 92.7 ± 11.6mL/min/1.73m2 respectively).

The mechanisms responsible for the altered renal clearance of ceftazidime in cystic fibrotic patients is not known.

11 STORAGE, STABILITY AND DISPOSAL

Dry Powder

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

Solutions

1 g and 2 g 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 °C to 8 °C), from the time of reconstitution.

6 g 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 °C to 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.

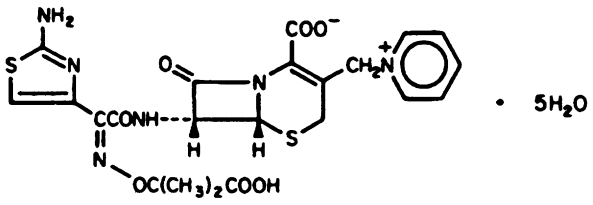
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Ceftazidime
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-[6α,7β(Z)]].
Molecular Formula:	C22H22N6O7S2.5H2O
Molecular Mass:	636.65 g/mol
Structural Formula:	
Physicochemical properties:	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. Solutions of ceftazidime for injection 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.

14 CLINICAL TRIALS

The clinical trial data on which the indications were originally authorized is not available.

15 MICROBIOLOGY

The in vitro activity of ceftazidime against various Gram-positive and Gram-negative aerobic and anaerobic organisms is shown in Table 10.

Table 10

Organism	No. of Strains	Cumulative % of strains inhibited at indicated concentrations (g/mL)										
		0.06	**0.13**	**0.25**	**0.5**	**1.0**	**2.0**	**4.0**	**8.0**	**16.0**	**31.0**	**62.0**
GRAM-NEGATIVE AEROBES												
Acinetobacter species	32	--	--	--	--	3	7	34	78	100		
Bordetella pertussis	9	--	--	78	100							
Branhamella catarrhalis	7	43	100									
Citrobacter freundii	21	10	29	62	76	90	--	95	--	100		
Citrobacter species	18	39	78	94	100							
Enterobacter aerogenes	7	14	--	43	71	86	--	100				
Enterobacter cloacae	62	10	22	70	81	86	87	92	--	94	95	98
Escherichia coli	125	43	74	92	96	--	97	98	100			
Haemophilus ducreyi	42	67	100									
Haemophilus influenzae	51	39	82	90	98	--	--	100				
Klebsiella pneumoniae	103	17	--	27	79	94	99	--	--	100		
Klebsiella species	18	28	44	72	83	94	100					
*Legionella pneumophila**	4	--	--	--	100							
Morganella morganii	34	71	85	94	--	--	--	97	--	100		
Neisseria gonorrhoea	19	84	--	89	--	--	--	95	100			
Neisseria meningitidis	80	2	100									
Proteus mirabilis	106	99	100									
Proteus rettgeri	8	61	74	87	--	--	100					
Proteus vulgaris	38	87	--	97	--	100						
Providencia species	46	30	70	78	89	98	100					
Pseudomonas aeruginosa	127	2	--	5	18	52	85	97	100			
Pseudomonas species	94	2	4	6	13	52	88	99	100			
Salmonella species	25	--	8	96	--	100						
Serratia marcescens	31	34	66	97	100							
Serratia species	69	51	71	87	100							
Shigella species	10	10	50	70	--	--	90	100				

Organism	No. of Strains	Cumulative % of strains inhibited at indicated concentrations (g/mL)										
		0.06	**0.13**	**0.25**	**0.5**	**1.0**	**2.0**	**4.0**	**8.0**	**16.0**	**31.0**	**62.0**
GRAM-POSITIVE AEROBES												
Listeria monocytogenes	10	--	--	--	--	--	--	--	--	--	--	--
Micrococcus species	13	--	--	--	--	8	23	31	46	100		
Staphylococcus epidermidis	9	--	--	--	--	--	22	78	100			
Staphylococcus species (methicillin-sensitive)	36	--	--	--	--	3	--	64	100			
Staphylococcus species (methicillin-resistant)	24	--	--	--	--	--	--	4	--	8	64	100
Streptococcus agalactiae Gr.B.	5	--	100									
Streptococcus faecalis	29	--	--	--	--	--	--	--	--	62	69	76
Streptococcus pneumoniae	6	17	83	100								
Streptococcus pyogenes	8	75	100									
GRAM-NEGATIVE ANAEROBES												
Bacteroides fragilis	62	--	--	--	--	--	--	--	--	--	21	55
Bacteroides thetaiotamicron	8	--	--	--	--	--	--	--	--	--	--	--
Fusobacterium species	15	--	21	--	--	--	--	36	--	50	79	86
Veillonella species	22	--	9	--	--	14	--	36	41	64	86	91
GRAM-POSITIVE ANAEROBES												
Actinomyces	10	--	--	--	--	10	30	40	60	--	80	100
Bifidobacterium species	7	--	--	--	--	14	29	43	--	71	86	--
Clostridium difficile	10	--	--	--	--	--	--	--	--	--	10	20
Clostridium perfringens	29	--	4	--	--	7	--	18	57	86	96	100
Peptococcus species	46	--	7	--	26	37	43	63	74	89	98	100
Peptostreptococcus species	21	--	33	--	48	52	76	--	86	--	95	100
Propionibacterium acnes	91	--	--	--	--	--	13	46	76	98	100	

*Legionnaires' Disease has been observed to progress in patients treated with antimicrobial agents possessing demonstrated in vitro activity against Legionnaires' Disease bacterium.

Inoculum Effect

The MIC's of ceftazidime against aerobic bacteria are not significantly affected by changes in inoculum size in the range 102 to 105 CFU/mL. However, increasing the inoculum size to 107 CFU/mL has a pronounced effect on the MIC's for some organisms. In one study, when the inocula of various Enterobacteriaceae (10 Citrobacter species, 10 Enterobacter species, 20 indole-positive Proteus species) were increased in size from 105 to 107 CFU/mL, MIC values increased 8- to 128-fold. The ratios of MBC to MIC are shown in Table 11.

Table 11 Ceftazidime MIC's and MBC's Tested against 110 Bacterial Isolates from 11 Genera

	MIC (mcg/mL)		**MBC (mcg/mL)**		**Ratio of Means**
Organisms (No. Tested)	Mean	90 %	Mean	90 %	MBC/MIC
Citrobacter spp. (10)	0.35	1.0	0.33	1.0	0.94
E. coli (10)	0.16	0.12	0.18	0.25	0.13
Enterobacter spp. (10)	0.60	8.0	0.65	8.0	1.08
K. pneumoniae (10)	0.18	0.12	0.19	0.12	1.06
*Proteus Providencia-** *Morganella spp. (20)*	0.15	0.06	0.20	0.12	1.33
Pr. mirabilis (10)	0.05	0.06	0.05	0.06	1.00
Ser. marcescens (10)	0.25	0.25	0.30	0.5	1.20
Ps. aeruginosa (10)	2.40	4.0	2.80	4.0	1.17
Staph. aureus (10)	9.60	16	12.80	16	1.33
Str. faecalis (10)	230	>256	>230	>256	1.00
*Includes *Pr. vulgaris* (6), *Prov. rettgeri* (7) and *Morg. morganii* (7).					

The rates of hydrolysis of ceftazidime and 2 other cephalosporins relative to those of cephaloridine (value 100) by various beta-lactamases are shown in Table 12.

Table 12

Name	**Source**	**CFZ**	**CFX**	**CAZ**
TEM-1	*E. coli*	18	<1	0
TEM-2	*E. coli*	19	0	0
SHV-1	*K. pneumoniae*	<1	0	0
OXA-1	*E. coli*	13	22	7
OXA-2	*E. coli*	150	0	0
OXA-3	*E. coli*	800	0	0

Name	Source	CFZ	CFX	CAZ
K1	*K. pneumoniae*	161	7	3
P99	*E. cloacae*	128	3	>1
2046E	*C. intermedius b*	36	15	>1
STH4	*B. fragilis*	61	0	1
PSE-1	*P. aeruginosa*	14	27	0
PSE-2	*P. aeruginosa*	30	16	30
PSE-3	*P. aeruginosa*	41	<1	8
PSE-4	*P. aeruginosa*	10	1	2
S and A	*P. aeruginosa*	112	15	<1
PC-1	*S. aureus*	115	0	30
Abbreviations: CFZ, cefazolin; CFX, cefoxitin; CAZ, ceftazidime.				

Development of Resistance

Resistance to ceftazidime has been induced in *E. cloacae* and *C. freundii* through successive daily subcultures. *Pseudomonas aeruginosa* rendered ceftazidime-resistant exhibited cross-resistance to other beta-lactam antibiotics but not to aminoglycosides.

Susceptibility Testing

The standard single-disc susceptibility test (using the 30 mcg ceftazidime disc) and dilution susceptibility should be interpreted according to the criteria in Table 13.

Table 13

	Zone diameter (30 mcg ceftazidime disc)	Approximate MIC correlation (mg/L)
Susceptible (susceptible to the usual doses)	=18	≤ 8
Moderately Susceptible (intermediate)	15 - 17	9 - 31
Resistant	≤ 14	=32

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

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

The effects produced by single doses of ceftazidime have been studied in mice, rats, dogs, and Rhesus monkeys using intravenous and subcutaneous administration. The results are shown in Table 14.

In the intravenous studies one animal of each species died at the high dose with only minimal signs of toxicity observed, limited to the day of dosing. No deaths or signs of toxicity occurred when ceftazidime was administered subcutaneously to rats.

A single intravenous dose of 1500 mg ceftazidime/kg administered to dogs and monkeys was tolerated with signs of toxicity limited to vomiting and salivation in dogs and soft stools in monkeys.

A comparative study using Glaxo and Lilly ceftazidime was conducted in mice with a single intravenous dose of 2000 mg/kg in mice. Results with both products were similar.

Sub chronic Toxicity

- **Rats:**

Daily intravenous doses of 100, 300, or 900 mg ceftazidime were administered to rats (15/sex/group) for one month. Doses for this study showed demonstrable toxicity but no deaths at 900 mg/kg.

There were no deaths or toxicologically significant changes in body weight gain, food consumption, or clinical chemistry values. Changes in hematology, slight in degree, including decreases in values of erythrocyte parameters and activated partial thromboplastin time occurred in all dose groups. Slight increases in liver and kidney weight also occurred. Cecomegaly and hyaline droplet formation in the renal cortical tubules were the only treatment-related lesions observed.

Daily intramuscular injections for 12 weeks were well tolerated by rats. All animals survived treatment and no abnormal physical or behavioral symptoms were seen.

Table 14 Acute Toxicity Studies

Species	Animals		Duration of Study (Days)	Administration	Dose Levels (mg/kg)	Signs of Toxicity	Results (LD_{50} mg/kg)
	M	F					
Ceftazidime							
Mouse	50	50	14	Intravenous	516 - 5163	Leg weakness and tremors	> 5163
Rat	30	30	14	Intravenous	1033 or 2581	Leg weakness	> 2581
Rat	-	30	14	Subcutaneous	1033 or 2581	None	LDo > 2581
Dog	1	1	14	Intravenous	1500	Vomiting and salivation	LDo > 1500

Species	Animals		Duration of Study (Days)	Administration	Dose Levels (mg/kg)	Signs of Toxicity	Results (LD_{50} mg/kg)
	M	F					
Rhesus Monkey	1	1	14	Intravenous	1500	Soft stools and diarrhea	LDo > 1500
Mouse	-	20	14	Intravenous	2000[a]	Leg weakness, poor grooming	> 2000
Mouse	-	20	14	Intravenous	2000[b]	Leg weakness, poor grooming, hypoactivity	> 2000
a Glaxo ceftazidime b Lilly ceftazidime							

Erythrocyte counts increased in the 900 mg/kg/day females and decreased in males. Other laboratory parameter changes at the same dose were: decreases in serum alkaline phosphatase, SGPT, hematocrit, and hemoglobin; increases in serum creatinine, bilirubin, potassium, BUN and SGOT; and inconsistent changes in lymphocyte and neutrophil counts.

Increases in serum cholesterol; inconsistent changes in serum proteins; and increases in urinary volume and pH and decreases in specific gravity were observed in both 300 and 900 mg/kg/day groups.

- **Dogs:**

Daily intravenous doses of ceftazidime of 250, 500, or 1000 mg/kg were administered to dogs (2/sex/group) for one month. All dogs survived the study and all treated dogs vomited, salivated and had soft and/or mucoid stools. No effects were observed on body weight, clinical chemistry, urinalysis, bone marrow differential counts, or organ weights. A few large platelets and moderate decreases in numbers of platelets in the high dose dogs and mild injection site reactions were the only treatment-related effects. Accumulation of the antibiotic was not observed.

Chronic Toxicity

- **Rats:**

Daily subcutaneous doses of 60, 250, or 1000 mg/kg were administered to rats (15/sex/group) for six months. There were no deaths or toxicologically significant changes in food consumption, clinical chemistry, or urinalysis values. Treatment-related effects occurred primarily at the high dose and included depressed weight gain, decreased erythrocyte parameters with compensatory increases in reticulocyte counts and systemic hematopoiesis, increased activated partial thromboplastin time, increased organ weights, cecomegaly, injection site irritation, hemosiderin deposition in renal tubules, renal tubular vacuolar degeneration and the presence of phagocytized amorphous material in renal cortical tubular cytoplasm and in Kupffer cells of the liver.

- **Dogs:**

Ceftazidime was administered to dogs (4/sex/group) in daily intravenous doses of 0, 125, 250, or 500 mg/kg for six months. All dogs survived the treatment. No vomiting occurred at any doses, and abnormal stools were seen in the middle and high dose groups. Increases in liver weights and pigmentation of renal cortical tubular epithelium were seen in the middle and high dose groups. In a second six month study in dogs using intravenous doses up to 850 mg/kg/day, adverse effects of treatment included principally discomfort during injection, salivation and vomiting. Laboratory abnormalities in the mid and high dose groups consisted of decreases in serum gamma-globulin and SGPT, and increases in cholesterol, albumin, and total protein. Post-mortem examinations revealed hepatomegaly, injection phlebitis, proteinaceous droplets in proximal convoluted tubular cells, and infiltration of the prostate.

Mutagenicity Studies

Ceftazidime was evaluated in a battery of in vitro and in vivo tests including Ames test, a modified fluctuation test, a yeast conversion test, DNA repair in rat hepatocytes and mouse micronucleus test. No mutagenic effects were observed.

Reproduction and Teratology Studies

Teratology:

- **Mouse:**

Pregnant mice were given subcutaneous injections of ceftazidime at 1500, 3250 or 6500 mg/kg/day during the period of organogenesis (gestation days 6 - 15). Eight mice from the control group and eight from the 6500 mg/kg/day group were allowed to give birth and raise their young to weaning. The other mice were sacrificed on day 18 of pregnancy and examined.

The overall incidence of skeletal abnormalities was 15% (controls), 20% (3250 mg/Kg ceftazidime) and 24% (6500 mg/kg ceftazidime). These consisted mainly of obliquely fused sternebrae. The incidence of rib variance was significantly higher in the high dose group than in the control group. In the group treated with the high dose (6500 mg/kg), one fetus had extra ribs on cervical vertebrae 6 and 7 and one fetus had a bifid hyoid bone.

The number of live pups/litter and the weights of litters born to mice treated with the high-dose (6500 mg/kg) was significantly lower when compared to controls.

- **Rabbit:**

Female Dutch rabbits were given intramuscular injections of 0, 25 mg/kg, 50 mg/kg, 100 mg/kg or 200 mg/kg ceftazidime daily from day 6 to day 18 of pregnancy. On day 29, the rabbits were sacrificed and the uterine contents examined.

Twenty-nine rabbits dosed with ceftazidime were either found dead (18) or had to be destroyed (11) due to ill-health (diarrhea and emaciation) or because they had aborted their fetuses. One rabbit in the control group was found dead on day 10 of pregnancy. The incidence of death was not dose-related (highest incidence occurred in the group given 25 mg/kg/day).

A decrease in body weight was noted during the first week of dosing and continued for the duration of the study in those rabbits receiving doses greater than 25 mg/kg of ceftazidime per day.

Results of the examination of the uterine contents are presented in Table 15 (see below).

Table 15

Observation	Control	25 mg/kg ceftazidime	50 mg/kg ceftazidime	100 mg/kg ceftazidime	200 mg/kg ceftazidime
Implantations	7	6	6	6	6
Resorptions	1	1	2	2	4
Live Fetuses	6	5	4	4	3
Live Litter Weight (g)	191	153	136	141	138
Within Litter Mean Live Fetuses Weight (g)	31.4	30.2	28.6	26.9	24.5
Within Litter Mean Practical Weight (g)	3.93	4.56	3.56	3.87	2.91

Two dead fetuses were reported - one in the control group (flexed forepaws) and one in 25 mg/kg/day group. Three fetuses (25 mg/kg group) from a litter of 5 had one or more of the following gross external abnormalities: anencephaly, gastroschisis, 1st and 3rd toes absent from both forepaws, 4th toe on right hind paw absent, tail twisted, craniorachischisis, lower jaw absent, eyes open, fore and hind limb buds present, tail and anogenital papilla present, thoracic and abdominal organs exposed.

Peri- and Postnatal Study

Groups of 20 female rats received a daily subcutaneous injection of either 0, 100, 500 or 2500 mg/kg ceftazidime. Animals were dosed from day 17 of pregnancy to the day of parturition and subsequently on days 1 - 21 inclusive postpartum.

No significant adverse reactions were seen during pregnancy with the exception of the high dose (2500 mg/kg) group which produced large quantities of soft wet feces. During the second and third week of the lactation period the dams treated with ceftazidime gained weight more rapidly than in the control group and this effect was dose-related. At termination (day 21 postpartum), pups in the high-dose group (2500 mg/kg) had gained significantly ($p < 0.05$) less weight (47.95 g) than controls (52.23 g). This was observed through lactation.

Fertility and Reproduction

Groups of 20 male and 40 female mice received subcutaneous injections of either saline or ceftazidime daily through gametogenesis and mating and in the case of females through pregnancy. Males were treated for 60 days prior to mating and females for 14 days. Half of the pregnant mice were sacrificed on day 18 of pregnancy while the remainder were allowed to litter and rear their young for 21 days. Two pups from each litter were retained to study any effects on fertility of the F1 generation.

Treatment with ceftazidime had no adverse effect on the fertility of either male or female mice.

A high incidence of skeletal variants seen in all of the groups was due to the large number of fetuses with supernumerary ribs. The incidence of bone variants was significantly higher in the high-dose group (6500 mg/kg/day) as compared to the controls. Throughout lactation, the mean pup weights (F1 generation) for the mid- and high-dose groups (3250 and 6500 mg/kg/day) were lower than the corresponding control values but the differences did not achieve statistical significance.

There were no significant differences in pregnancy rates for any of the F1 generation groups.

The mean pup weights (F2 generation) during lactation in the high-dose group were consistently less than those of controls but the differences were not statistically significant and this was attributed to the lighter weights of the dams.

Miscellaneous Studies

- **Nephrotoxicity Studies in Rabbits:**

In a comparative study in rabbits, single doses of 354 or 708 mg/kg ceftazidime or 400 or 800 mg/kg cefazolin sodium were administered subcutaneously. Serum concentrations of urea nitrogen, creatinine, glucose, total bilirubin and the activity of alkaline phosphatase and alanine transaminase were used as the indicators of nephrotoxicity. At those doses, there was evidence of nephrotoxicity with cefazolin but not ceftazidime.

In a similar study, 2000 mg/kg doses of ceftazidime, cefazolin sodium, cefamandole nafate, or cephalothin sodium were given by intravenous infusion. Rabbits treated with cefazolin sodium and cefamandole nafate exhibited severe and mild nephrotoxicity, respectively; while rabbits treated with ceftazidime or cephalothin sodium had no evidence of renal toxicity.

In female mice single subcutaneous doses of 8000 and 10 000 mg/kg ceftazidime produced coagulative necrosis of inner cortical tubules. Male rats given ≥ 4000 mg/kg produced acute tubular necrosis (inner cortex) and elevations in serum urea nitrogen.

The addition of an aminoglycoside to ceftazidime treatment of male rats did not potentiate the nephrotoxicity of either drug given alone, but involved less outer cortical tubular necrosis than caused by the aminoglycoside alone.

- **Intramuscular Irritation in Rabbits:**

In a study in which single intramuscular doses of 0.5 mL sterile water, or 25% aqueous solutions of ceftazidime or cefamandole nafate were given to rabbits, all substances tested, including sterile water, caused muscle necrosis and inflammation. Ceftazidime produced more muscle irritation than sterile water (measured by CPK and histologic endpoints) but less than that produced by cefamandole nafate.

- **Intravenous Irritation:**

Postmortem examinations following the 28 week intravenous dose study in dogs demonstrated injection phlebitis.

- **Hemolysis and Serum Flocculation Tests:**

These studies were conducted due to the proposed parenteral route of administration. No flocculation was detected in rat or dog blood at a concentration of 250 mg ceftazidime/mL. The same concentration produced only slight in vitro hemolysis in dog blood and no hemolysis in rat blood.

- **Studies of Ceftazidime Containing Polymer:**

The possibility that some lots of ceftazidime could generate polymeric impurities was noted in a nephrotoxicity study in rabbits in which unexpected deaths occurred at high doses. Subsequent analytical work showed that the observed toxicity was associated with a high molecular weight polymer. A series of studies in rats, mice and dogs, up to one month in duration, were conducted with ceftazidime containing various levels of polymer. In addition to an apparent enhancement of acute toxicity in mice when administered at a dose of 5000 mg/kg, the most significant finding was foreign material phagocytized in Kupffer cells of the liver. This was found in dogs given 500 or 1000 mg/kg/day of ceftazidime containing 0.6% polymer intravenously for one month. No effects occurred in the 100 mg/kg group. A polymer specification of not more than 0.3% was set for the product based on this study.

17 SUPPORTING PRODUCT MONOGRAPHS

CEFTAZIDIME FOR INJECTION BP, Sterile Powder for Solution, 1 g/vial, 2 g/vial, 3 g/vial, 6 g/vial, submission control 227800, Product Monograph, SteriMax Inc. (MAY 27, 2019).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCEFTAZIDIME FOR INJECTION, USP

Sterile powder for solution

Read this carefully before you start taking **Ceftazidime for Injection, USP.** This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Ceftazidime for Injection, USP**.

What is Ceftazidime for Injection, USP used for?

Ceftazidime for Injection, USP is used to treat the following infections that are proven to be or strongly suspected to be cause by certain bacteria:

- pneumonia (lung infection)
- skin infections
- bladder (urinary tract) infections
- blood infections
- bone infections
- infections around the inner organs (peritonitis)

Antibacterial drugs like Ceftazidime for Injection, USP treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, Ceftazidime for Injection, USP should be taken exactly as directed. Misuse or overuse of Ceftazidime for Injection, USP could lead to the growth of bacteria that will not be killed by Ceftazidime for Injection, USP (resistance). This means that Ceftazidime for Injection, USP may not work for you in the future. Do not share your medicine.

How does Ceftazidime for Injection, USP work?

Ceftazidime for Injection, USP contains a medicine called ceftazidime. Ceftazidime is an antibiotic that kill the bacteria in your body.

What are the ingredients in Ceftazidime for Injection, USP?

Medicinal ingredient: ceftazidime

Non-medicinal ingredient: sodium carbonate

Ceftazidime for Injection, USP comes in the following dosage forms:

Powder for solution

- 1 g / vial
- 2 g / vial
- 6 g / vial

Do not use Ceftazidime for Injection, USP if:

- You are allergic to ceftazidime, cephalosporin antibiotics, or any of the other ingredients in Ceftazidime for Injection, USP. See **What are the ingredients in Ceftazidime for Injection, USP?**

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ceftazidime for Injection, USP. Talk about any health conditions or problems you or your child may have, including if you:

- have a history of intestinal problems such as colitis (inflammation of the colon)
- have or develop severe diarrhea as this may be a sign of a more serious condition
- have or have had anemia (low blood iron) after taking antibiotics
- have kidney problems
- are 65 years of age or older
- have had allergic reactions to other medicines such as antibiotics
- are taking any diuretics such as furosemide
- have restrictions on how much sodium you can have
- are pregnant, think you could be pregnant, or are planning to become pregnant
- are breastfeeding. Ceftazidime for Injection, USP is excreted into breastmilk.

Other warnings you should know about:

Monitoring and Laboratory Tests: Ceftazidime for Injection, USP may impact the results of blood and urine tests. It may also cause a false-positive reaction for sugar in the urine.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Ceftazidime for Injection, USP:

- Other antibiotics (such as chloramphenicol)
- Diuretics such as furosemide
- Oral Contraceptives

How to take Ceftazidime for Injection, USP:

- Ceftazidime for Injection, USP will be first mixed into a solution.

- Your healthcare professional will check the solution to make sure it is not cloudy or leaking.
- Ceftazidime for Injection, USP will be given to you by a healthcare professional either as an injection into a vein, infusion (slow drip) through a vein, or as an injection into a muscle.

Usual dose:

The usual dose and how long you are given Ceftazidime for Injection, USP will be different for everyone. Your healthcare professional will decide on the dose that is right for you. Your dose and how often you take it will depend on:

- your age
- the type of infection you have
- how severe your infection is
- other conditions or illnesses you have, including if you have kidney problems

Ask your healthcare professional if you have any questions about how many doses of Ceftazidime for Injection, USP you will need or when you will receive them.

Overdose:

If you think you have taken too much Ceftazidime for Injection, USP, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using Ceftazidime for Injection, USP?

These are not all the possible side effects you may have when taking Ceftazidime for Injection, USP. If you experience any side effects not listed here, tell you healthcare professional.

Side effects may include:

- swelling, redness, or pain near the injection site
- diarrhea, nausea, vomiting, stomach ache
- white spots in the mouth or throat (yeast infection, thrush)
- vaginal yeast infection (in women)
- headache, dizziness
- flushing (redness)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.	X		
Pseudomembranous colitis (inflammation of the large intestine): severe diarrhea, usually with blood and mucus, stomach pain and fever.			X
VERY RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			X
Nervous System problems: tremors, twitching, seeing things that are not there, tingling.			X
Seizures (fit): uncontrollable shaking with or without loss of consciousness.			X
Liver problems: yellowing of the skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness.	X		
Hemolytic Anemia (breakdown of red blood cells): pale skin, feeling tired or weak, dizziness, fainting, thirst, rapid breathing.			X
Infection: fever, high heart rate, feeling unwell, or other signs of new or ongoing infection.			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish); swelling and redness of eyes or face; flu-like feeling, fever, chills, body aches, swollen glands, cough; shortness of breath, chest pain or discomfort.			X
***Clostridium difficile* colitis (bowel inflammation):** severe or persistent diarrhea, abdominal pain, nausea and vomiting, fever			X
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing.		X	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains and flu-like symptoms		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Ceftazidime for Injection, USP powder at 15 °C to 30 °C. Protect from light.

Keep out of reach and sight of children.

If you want more information about Ceftazidime for Injection, USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.fresenius-kabi.com/en-ca), or by calling 1-877-821-7724.

This leaflet was prepared by:

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Last Revised: FEB 17, 2022