PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]cefTAZidime for Injection BP

Powder for Solution,1 g, 2 g, 3 g and 6 g of ceftazidime (as ceftazidime pentahydrate) per vial

Intravenous, Intramuscular

BP

Antibiotic

SteriMax Inc.
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RECENT MAJOR LABEL CHANGES

Sections	Date
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	05/2023
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Consideration, 4.2 Recommended Dose and Dosage Adjustment, 4.3 Reconstitution, 4.4 Administration	05/2023
7 WARNINGS AND PRECAUTIONS, Clostridium difficile-Associated Disease, Immune, Neurologic, Renal, Skin	05/2023
8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions	05/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Ceftazidime for Injection BP (Ceftazidime pentahydrate) is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

Lower Respiratory Tract Infections
Pneumonia caused by *Pseudomonas aeruginosa*; *Haemophilus influenzae* including ampicillin-resistant strains; *Klebsiella* species; *Enterobacter* species; *Proteus mirabilis; Escherichia coli, Serratia* species, *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin susceptible) strains.

Urinary Tract Infections
Caused by *Pseudomonas aeruginosa; Enterobacter* species; *Proteus* species (indole positive and negative); *Klebsiella* species, and *Escherichia coli.*

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.

Skin Structure Infections
Caused by *Pseudomonas aeruginosa; Klebsiella* species; *Escherichia coli; Proteus mirabilis; Enterobacter* species; *Staphylococcus aureus* (methicillin susceptible) strains; and *Streptococcus pyogenes*.

Bacteremia/Septicemia
Caused by *Pseudomonas aeruginosa; Klebsiella* species; *Escherichia coli; Serratia* species; *Streptococcus pneumoniae; Staphylococcus aureus* (methicillin susceptible) strains; and *Staphylococcus epidermidis.*

Bone Infections
Caused by *Pseudomonas aeruginosa; Proteus mirabilis; Entero*bacter species; and *Staphylococcus aureus* (methicillin susceptible) strains.

Peritonitis
Caused by *Escherichia coli; Klebsiella* species; and *Peptostreptococcus* species. Patients infected with *Bacteroides* species have also responded.

Meningitis
Caused by *Haemophilus influenzae* and *Neisseria meningitidis*. Ceftazidime for Injection BP has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa*.

Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibilities to Ceftazidime for Injection BP. Therapy may be instituted before results of susceptibility testing are known. However, modification of the treatment may be required once these results become available.

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 BP and other antibacterial drugs, Ceftazidime for Injection BP 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

Health Canada has authorized an indication for pediatric use (age 0 month – 18 years). See 4.2 Recommended Dose and Dosage Adjustment, Infants and Children and 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 BP is contraindicated for patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hemolytic Anemia:** Ceftazidime for Injection BP should not be used in patients with a history of cephalosporin-associated hemolytic anemia since the recurrence of hemolysis is much more severe. See 7 WARNINGS AND PRECAUTIONS, Hemolytic Anemia, 8.4 Abnormal Laboratory Findings, and 8.5 Post-Market Adverse Reactions.
- **Hypersensitivity:** Serious and occasionally fatal hypersensitivity (anaphylactic) and severe cutaneous adverse reactions (SCAR) have been reported in patients receiving therapy with beta-lactams. See 7 WARNINGS AND PRECAUTIONS, Hypersensitivity and 7 WARNINGS AND PRECAUTIONS, Skin.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Ceftazidime for Injection BP may be administered either intravenously or intramuscularly after reconstitution. Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organism(s), 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 recommended daily dosage of Ceftazidime for Injection BP is 0.5 to 6 g administered in equally divided doses every 8 to 12 hours (see Table 1).

TABLE 1

TYPE OF INFECTION	DAILY DOSE IN GRAMS	FREQUENCY AND ROUTE
uncomplicated pneumonia or skin structure infection	1.5 – 3	0.5 – 1 g IM. or IV q8h
uncomplicated urinary tract infections	0.5	250 mg IM or IV q12h

TYPE OF INFECTION	DAILY DOSE IN GRAMS	FREQUENCY AND ROUTE
complicated urinary tract infections	1.0 – 1.5	500 mg IM or IV q8h or q12h
bone infections	4	2 g IV q12h
peritonitis or septicemia	6	2 g IV q8h
meningitis	6	2 g IV q8h

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 BP 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:
Ceftazidime is excreted almost exclusively by glomerular filtration. In patients in whom the glomerular filtration rate (GFR) is less than or equal to 50 mL/min (0.83 mL/s), the dosage of Ceftazidime for Injection BP must be reduced to compensate for its slower excretion. After an initial loading dose of 1 g of Ceftazidime for Injection BP, a maintenance dosage schedule should be followed (see Table 2).

TABLE 2: Recommended Maintenance Doses of Ceftazidime for Injection BP in Renal Insufficiency

Creatinine Clearance		Recommended Unit Dose of Ceftazidime for Injection BP		Frequency of Dosing*
mL/min/1.73 m^2	mL/s/1.73 m^2	Moderate Infections	Severe Infections	
31- 50	0.51 – 0.83	1 g	1.5 g	q12h
16 – 30	0.26 – 0.5	1 g	1.5 g	q24h
6 -15	0.10 – 0.25	500 mg	750 mg	q24h
<5	<0.09	500 mg	750 mg	q48h

* If the severity of the infection necessitates an increase in the dosing frequency, serum concentrations of ceftazidime should be used as guidelines.

When only serum creatinine levels are known, the following formulae may be used to estimate creatinine clearance. The serum creatinine must represent a steady state of renal function:

Males

$$\text{Creatinine clearance (mL/s)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{49 \times \text{serum creatinine (mcmol/L)}}$$

OR

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

Females

0.85 X above value.

Mean serum half-life of ceftazidime in patients with no kidney function was reduced from a range of 24 - 35.4 h between dialysis sessions to a range of 2.8 - 4.6 h during hemodialysis. Therefore, a loading dose of 1 g is recommended followed by 0.5 to 1 g after each hemodialysis period. Serum concentrations of ceftazidime should be carefully monitored and used as a basis to adjust the dosage.

Ceftazidime for Injection BP can also be used in patients undergoing peritoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of Ceftazidime for Injection BP (1 g) is suggested, followed by 500 mg every 24 hours. Serum concentrations of ceftazidime should be carefully monitored and used as a basis to adjust the dosage.

For patients in renal failure receiving low-flux haemofiltration, the dosage as recommended under impaired renal function should be followed. For patients in renal failure receiving continuous arteriovenous haemodialysis or high-flux haemofiltration, 1 g of Ceftazidime for Injection BP daily either as a single dose or in divided doses may be administered.

Clinical studies on safety and efficacy of Ceftazidime for Injection BP in patients on continuous venovenous hemofiltration (CVVH) and continuous venovenous haemodialysis (CVVHD) have not been conducted. Pharmacokinetic modelling data from a limited number of patients with end stage renal disease suggest that ceftazidime clearance is dependent on the ultrafiltration rate and residual renal function in patients receiving CVVH. However, in patients receiving CVVHD, ceftazidime clearance is dependent on ultrafiltration rate, diluent volume, and residual renal function. Therefore, a loading dose of 1 g - 2 g followed by a maintenance dosage of 0.25 - 2 g every 12 hours (total daily dose 0.5- 4 g) and 0.5 g -2 g every 12 hours (total daily dose 1- 4 g) may be considered in patients on CVVH or CVVHD, respectively.

A clinical judgement for individual patient dose optimization should be considered based on severity of the infection, susceptibility of the causative organism and therapeutic monitoring. Dosage should be adjusted to maintain drug levels ≥4 times the minimum inhibitory concentration (MIC) for gram negative susceptible pathogens.

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 (see 10 CLINICAL PHARMACOLOGY).

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

Type of Infection	Age group dosage	Dosage
Infections other than meningitis	1 month – 2 months	25 – 50 mg/kg IV q12h to a maximum of 6 g/day
	2 months – 12 years	30 – 50 mg/kg IV q8h to a maximum of 6 g/day
Meningitis	1 month – 12 years	50 mg/kg IV q8h to a maximum of 6 g/day

The maximum daily dose in children is 6 g.

Neonates (aged 0-28 days)
In children aged one month or less the recommended dose is 25-50 mg/kg of Ceftazidime for Injection BP given twice daily.

Data indicates that half-life of ceftazidime in neonates increases with decreasing gestational age and can be 3-4 times that in adults. An adjustment in dosing interval may be necessary with an increasing degree of prematurity. Additionally, clearance may increase rapidly in the first 2-3 weeks of life necessitating a readjustment of dose and/or dosing interval.

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

CAUTION: Mixture (solution) should be inspected visually for clarity, particulate matter, precipitation, discolourations, and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Ensure adequate venting, addition of diluent generates a positive pressure.

For Intramuscular Use

- **Solutions for Reconstitution:**

Sterile Water for Injection or, if required Bacteriostatic Water for Injection with Benzyl Alcohol (not for use in neonates), 0.5 w/v to 1% w/v Lidocaine Hydrochloride Injection.

Reconstitution Table

Vial Size	Diluent to be added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	3 mL	3.9 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

- **Solution 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	10 mL	10.9 mL	100 mg/mL
2 g	10 mL	11.7 mL	175 mg/mL

Shake well until dissolved. The prepared solution may be further diluted to the desired volume with any of the solutions listed under "Solutions for IV Infusion". 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 and 2 g vials of Ceftazidime for Injection BP.

For Continuous Intravenous Infusion: Reconstitute 1 g and 2 g vials of Ceftazidime for Injection BP 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 under "Solutions for IV Infusion".

6 g and 3 g Pharmacy Bulk Vial

The availability of the pharmacy bulk vials is restricted to hospitals with a recognized intravenous admixture program.

Ceftazidime for Injection BP does not contain any preservatives. The Pharmacy Bulk Vials are intended for multiple dispensing for intravenous use only, employing a single puncture. Reconstitute with 13 mL and 26 mL Sterile Water for Injection for the 3 g and 6 g vials, respectively.

Reconstitution Table

Vial Size	Diluent to be added to Vial	Approximate Available Volume	Approximate Average Concentration
6 g	26 mL	30 mL	200 mg/mL
3 g	13 mL	15 mL	200 mg/mL

Shake well until dissolved. Following reconstitution with Sterile Water for Injection, the solution should be dispensed and diluted for use within 8 hours at room temperature (15-25°C). Any unused reconstituted solution should be discarded after 8 hours. The appropriate quantity of the reconstituted solution may be added to an intravenous bottle containing any of the solutions listed below. See 11 STORAGE, STABILITY AND DISPOSAL 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
  Ringers Injection USP
  Lactated Ringers Injection USP
  5% Dextrose Injection
  5% Dextrose and 0.225% Sodium Chloride Injection
  5% Dextrose and 0.45% Sodium Chloride Injection
  5% Dextrose and 0.9% Sodium Chloride Injection
  10% Dextrose Injection
  10% Invert Sugar in Water for Injection
  Normosol-M in 5% Dextrose Injection
  Sterile Water for Injection

When Ceftazidime for Injection BP 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 and 2 g Intramuscular/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 and 3 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.
2. For 6 g vial, inject 26 mL of diluent and for 3 g vial, inject 13 mL of diluent to provide a solution containing approximately 1 g of ceftazidime for injection activity per 5 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 BP may be administered by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or vastus lateralis. The maximum dose of Ceftazidime for Injection BP should be one (1) gram for a single intramuscular injection.

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

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 for Injection BP, the administration of other solutions should be discontinued temporarily.

Continuous Intravenous Infusion
Ceftazidime for Injection BP may also be administered over a longer period of time.

NOTE: If therapy with Ceftazidime for Injection BP is carried out in combination with an aminoglycoside antibiotic, each should be administered at different sites because of a physical incompatibility. 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 BP 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 overdosage are available.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredient
Intramuscular or Intravenous	Sterile Powder for Solution 1 g/vial, 2 g/vial, 3 g/vial, 6 g/vial	Sodium Carbonate

Ceftazidime for Injection BP vials contain a mixture of ceftazidime pentahydrate and sodium carbonate. When constituted, this mixture provides a solution of ceftazidime sodium.

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 52 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 BP for intramuscular or direct intravenous injection
Vials containing the equivalent of 1 g ceftazidime are available in packs of ten.

Ceftazidime for Injection BP for intravenous injection or infusion
Vials containing the equivalent of 1 g and 2 g ceftazidime are available in packs of ten.
Vials containing the equivalent of 6 g ceftazidime are available in single packs.
Vials containing the equivalent of 3 g ceftazidime are available in single packs.

7 WARNINGS AND PRECAUTIONS

General

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.

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 BP should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

- ***Clostridium difficile*-Associated Disease**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including ceftazidime. 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. C. 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 BP 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 BP 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 mediated hemolytic anemia has been observed in patients receiving cephalosphorin class antibacterials, including ceftazidime. 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 BP, the diagnosis of a cephalosphorin-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 BP is instituted, careful enquiry should be made to determine whether the patient has had previous hypersensitivity reactions to ceftazidime, cephalosporins, penicillins, or other drugs. Ceftazidime for Injection BP should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams. 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 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 BP occurs, treatment should be discontinued and standard agents (e.g. epinephrine, antihistamines, corticosteroids) administered as necessary. Elevated levels of ceftazidime in patients with renal insufficiency can lead to convulsions. (See 7 WARNINGS AND PRECAUTIONS).

Monitoring and Laboratory Tests

Ceftazidime may cause a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution).

Ceftazidime has shown, transient elevations of blood urea, blood urea nitrogen and serum creatinine, serum bilirubin, alkaline phosphatase, LDH, AST (SGOT), ALT (SGPT) and GGT.

Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis were very rarely seen.

Periodically monitor hematological parameters or drug-induced antibody where appropriate.

Neurologic

Cephalosporins have been associated with the occurrence of seizures. A known risk factor is renal impairment without dosage adjustment; however, seizures have also been described in individuals without a preceding history of renal impairment whose renal function deteriorates while taking the cephalosporin. If seizures associated with Ceftazidime for Injection BP occur, the drug should be discontinued if clinically appropriate. Anticonvulsant therapy can be given if clinically indicated.

Renal

Patients with impaired renal function (i.e. creatinine clearance of 50mL/min/1.73m^2 or less) should be placed on the special dosage schedule for Ceftazidime for Injection BP recommended under 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 BP 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 BP 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 BP 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 BP should be discontinued and appropriate therapy and/or measures should be taken.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of ceftazidime in pregnancy has not been established. The use of ceftazidime in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and 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/L). The clinical significance of this is unknown, therefore, caution should be exercised when ceftazidime is administered to a nursing mother.

7.1.3 Pediatrics

In children aged one month or less the recommended dose is 25-50 mg/kg of Ceftazidime for Injection BP given twice daily.

Data indicates that half-life of ceftazidime in neonates increases with decreasing gestational age and can be 3-4 times that in adults. An adjustment in dosing interval may be necessary with an increasing degree of prematurity. Additionally, clearance may increase rapidly in the first 2-3 weeks of life necessitating a readjustment of dose and/or dosing interval.

7.1.4 Geriatrics

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.

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 BP in clinical trials are listed below:

Local effects reported in 2.8% of patients
Thrombophlebitis or phlebitis and pain with intravenous administration. Pain after intramuscular injection.

Hypersensitivity reactions reported in 2.7% of patients
Pruritus, urticaria, macropapular rash, allergic exanthema, 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, nausea, vomiting, colitis and abdominal pain. Pseudomembranous colitis has been reported (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal). Oral thrush has been reported very rarely.

Central Nervous system reactions reported in <1% of patients
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. (7 WARNINGS AND PRECAUTIONS and 5 OVERDOSAGE).

Hematopoietic
Eosinophilia (3.4%), positive Direct Coombs' Test (5.1%), and with an incidence of <1%: thrombocytosis, transient leukopenia, neutropenia, thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS).

8.3 Less Common Clinical Trial Adverse Reactions

Less frequent adverse events: (<1% of patients)
Blurred vision, flushing, candidiasis, 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: serum bilirubin, alkaline phosphatase, LDH, AST (SGOT), ALT (SGPT) and GGT.

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

Hematopoietic effects: Eosinophilia (3.4%), positive Direct Coombs' test (5.1%). thrombocytosis, transient leukopenia, neutropenia, thrombocytopenia were seen in < 1% of patients (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Hematologic: Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children (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 and ethacrynic acid) may increase the risk of renal toxicity. 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 5 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 for Injection BP, when administered alone, is significantly nephrotoxic. However, the effect of administering Ceftazidime for Injection BP concomitantly with aminoglycosides is not known.
Chloramphenicol	Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of

Drug or Drug class	Effect / Clinical comment
	ceftazidime with chloramphenicol is proposed, the possibility of antagonism should be considered.
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. 7 WARNINGS AND PRECAUTIONS, Renal.

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 recommended that either glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Ceftazidime for Injection BP.

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, a semisynthetic cephalosporin antibiotic, 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

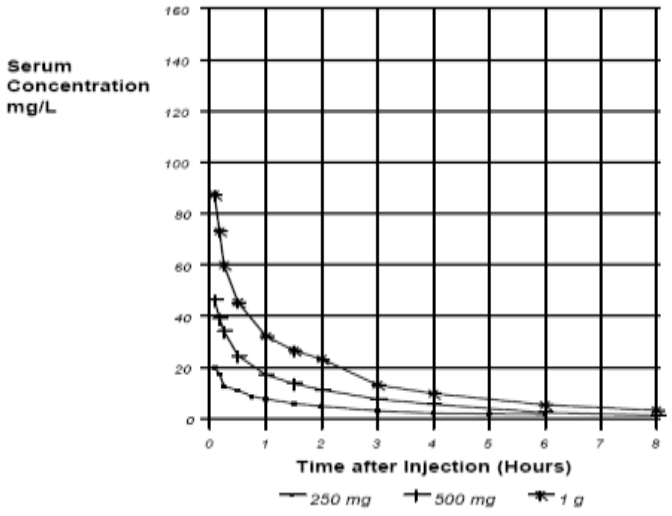
Absorption

Human
Ceftazidime is poorly absorbed when given orally (e.g. following a 250 mg dose the average urinary recovery was less than 1% of the dose).

- **Intravenous Administration**

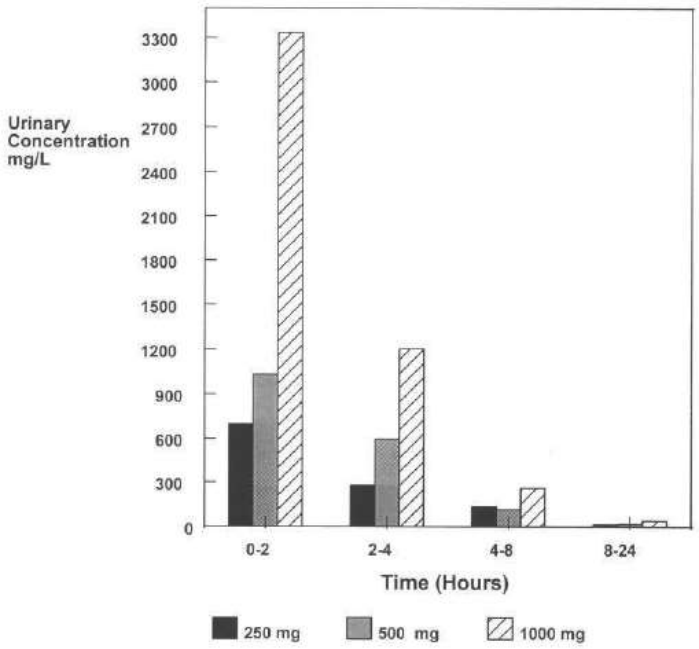
Bolus Injections
Ceftazidime was administered as single bolus injections (over 1 min) to 22 healthy male volunteers in three doses: 250 mg (6 subjects, mean age 34 years), 500 mg (8 subjects, mean age 33 years) and 1000 mg (8 subjects, mean age 35 years). Serum concentration-time curves follow a biexponential decay (see Figure 1).

FIGURE 1: Serum concentrations of ceftazidime administered intravenously over 1 minute



Mean urinary recovery of unchanged drug over 24 hours ranged from 77.4 to 85.5% (Table 6) with over 50% being excreted in the first two to four hours. Figure 2 shows urinary concentrations of ceftazidime for various collection intervals following injection. Derived pharmacokinetic indices (based on a two-compartment model) are summarized in Table 6.

FIGURE 2: Urinary concentrations of ceftazidime after single bolus intravenous injections



No accumulation of drug occurred during repeated administrations of ceftazidime (2 g t.i.d., 10 days). Trough serum level did not increase after dose 2 and urinary recoveries over the first eight hours averaged 81.2% after dose 1 and 76.3% after dose 28. Pharmacokinetic parameters remained unchanged (see Table 6).

TABLE 6: Average pharmacokinetic parameters of ceftazidime after IV bolus administration

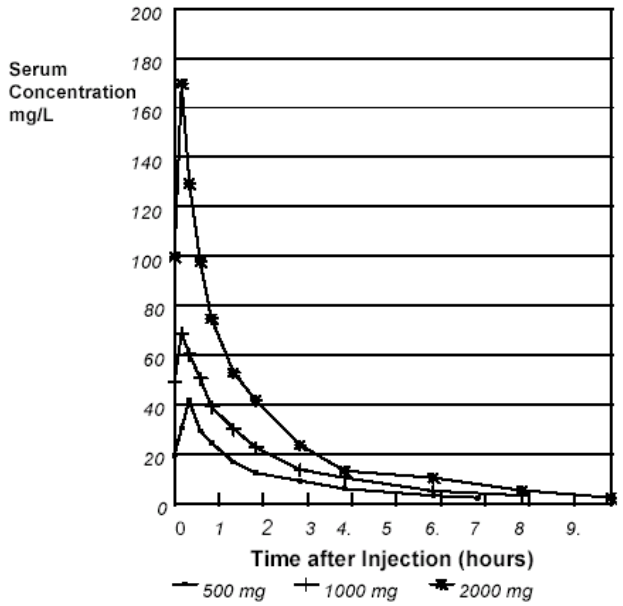
Dose/ Route	Peak Serum Conc (mg/L)	Apparent Volume of distribution (L)	Area under serum level/time curve (mg/L/h)	Serum half-life (h)	Dose recovered in urine to 24 h (%)	Renal Clearance (mL/min)	Plasma Clearance (mL/min)
250 mg IV bolus	28.7	18.9	30.2	1.8	77.4	109	139
500 mg IV bolus	57.6	16.9	71.9	1.9	85.5	100	116
1 g IV bolus	119.1	17.1	135.8	1.8	85.1	109	128
2 g IV dose 1	182.8	19.7	279.4	1.9	81.2*	102	-
2 g IV dose 28	156.7	18.0	274.7	1.7	76.3*	95	-

* 8h collection only

Intravenous Infusion

Single intravenous infusions of 500 mg (6 subjects, mean age 35 years), 1000 mg (7 subjects, mean age 33 years) and 2000 mg (7 subjects, mean age 30 years) of ceftazidime were administered over 20 to 30 minutes to normal adult male volunteers. Serum concentration-time curves (Figure 3) follow a biexponential decay.

FIGURE 3: Serum concentrations of ceftazidime infused intravenously over 20-30 minutes



Mean urinary recovery of unchanged drug over 24 hours ranged from 83.7 to 87.1% (Table 7) with over 50% being excreted in the first two to four hours. Figure 4 shows urinary concentrations of ceftazidime for various collection intervals following infusion. Derived pharmacokinetic indices (based on a two-compartment model) are summarized in Table 7.

FIGURE 4: Urinary concentrations of ceftazidime after single intravenous infusions over 20-30 minutes

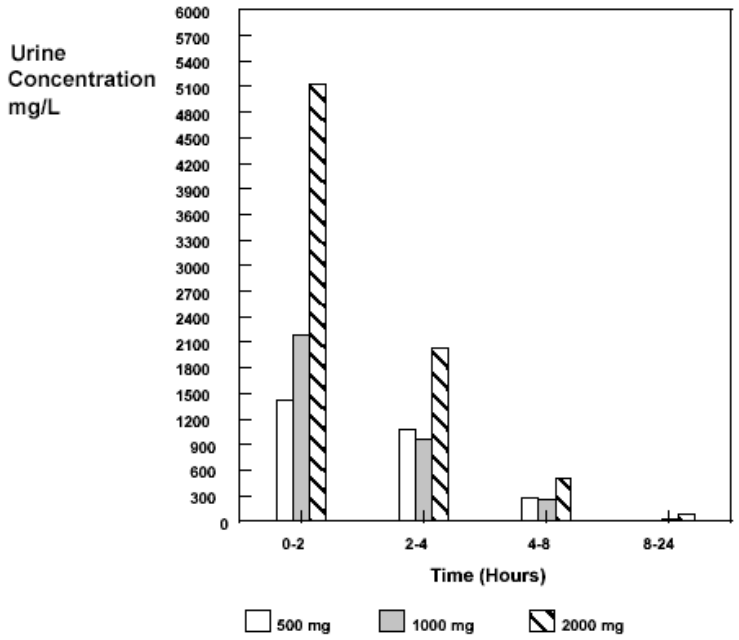


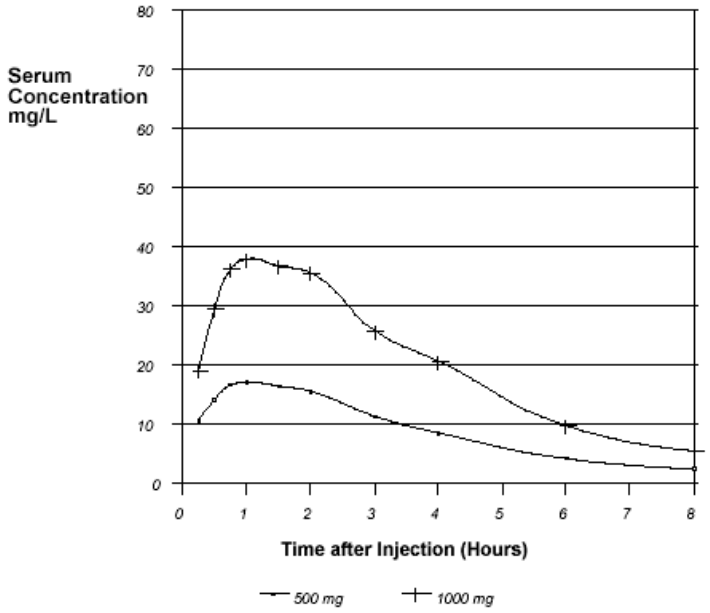
TABLE 7: Average pharmacokinetic parameters of ceftazidime after IV infusion

Dose/ Route	Peak Serum Conc (mg/L)	Apparent Volume of distribution (L)	Area under serum level/time curve (mg/L/h)	Serum half-life (h)	Dose recovered in urine to 24 h (%)	Renal Clearance (mL/min)	Plasma Clearance (mL/min)
500 mg IV infusion	41.5	16.3	82	1.9	86.8	89	102
1 g IV infusion	72.1	19.9	143.2	1.9	83.7	98	117
2 g IV infusion	170	19.9	266	1.9	87.1	110	126

- **Intramuscular Injection**

Serum concentration-time curves following intramuscular injection of 500 mg (8 subjects, mean age 32 years) or 1000 mg (8 subjects, mean age 34 years) of ceftazidime is shown in Figure 5.

FIGURE 5: Serum concentrations of ceftazidime administered intramuscularly



Mean urinary recovery of ceftazidime over 24 hours ranged from 78.9 to 84.6% (Table 8). Figure 6 shows urinary concentrations of ceftazidime for various collection intervals following injection. Derived pharmacokinetic indices (based on a one-compartment model) are summarized in Table 8.

FIGURE 6: Urinary concentrations of ceftazidime after single intramuscular injections

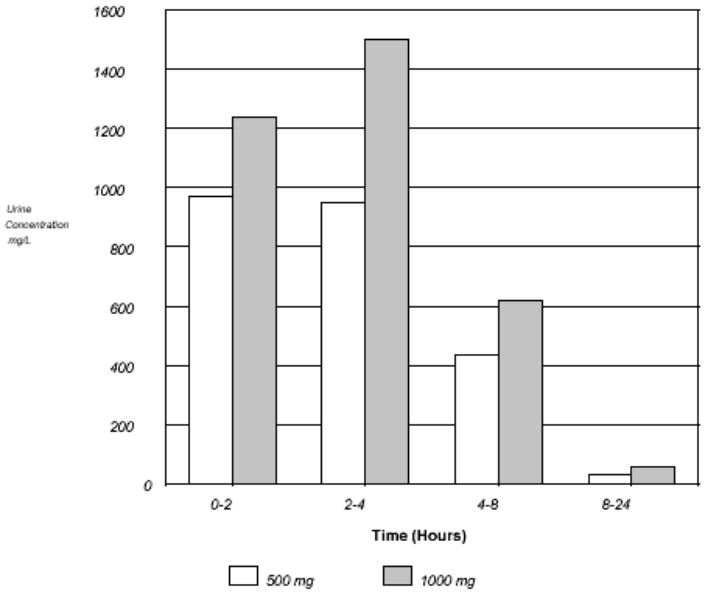


Table 8: Average pharmacokinetic parameters of ceftazidime after IM administration

Dose/ Route	Peak Serum Conc (mg/L)	Apparent Volume of distribution (L)	Area under serum level/time curve (mg/L/h)	Serum half-life (h)	Dose recovered in urine to 24 h (%)	Renal Clearance (mL/min)	Plasma Clearance (mL/min)
500 mg IM injection	17.4	21.2	79	2.2	84.6	90	106
1 g IM injection	38.8	16.7	174.7	2	78.9	76	97
1 g IM dose 1	38.5	16.7	174	2	-	-	97
1 g IM dose 2	44	17.1	186	2.2	-	-	97

No accumulation of drug was noted during repeated intramuscular doses of ceftazidime (1 g, t.i.d., 10 days). Pharmacokinetic parameters remained unchanged (Table 8).

The pharmacokinetic parameters of 1 g of ceftazidime in 1% lidocaine (6 healthy male volunteers, mean age 37 years) did not differ significantly from those obtained without the use of lidocaine.

When ceftazidime was administered to two subjects (750 mg IM) in the recumbent position, average peak serum levels were lower (20.8 mg/L) and serum half-life was longer (2.6 hours)

when compared to the two mobile volunteers (36.4 mg/L and 1.8 hours, respectively). The area-under-the-curve was not significantly affected by physical activity.

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 and Body Fluid Concentrations**

Therapeutic concentrations of ceftazidime in tissues and body fluids other than serum are presented in Table 9.

TABLE 9: Ceftazidime Concentration in Body Tissues and Fluids

TISSUE OR FLUID	DOSE/ROUTE	NO. PATIENTS	TIME OF SAMPLE POST-DOSE	AVERAGE TISSUE OR FLUID LEVEL CONCENTRATION (mcg/mL or mcg/g)
Aqueous humour	2 g IV	21	1-3 h	11 ± 4
Bile	2 g IV	3	90 min	36.4
Blister fluid	1 g IV	7	2-3 h	19.7 ± 2.3
Bone	2 g IV	5	40 min	31.1 ± 1.7
Cerebrospinal fluid (inflamed meninges)	2 g q8h IV 2 g q8h IV	5 6	120 min 180 min	9.8 ± 11.4 9.4 ± 4.0
Endometrium	2 g IV	6	1-2 h	18.7 ± 4.7
Fat	2 g IV	39	30-280 min	9.2
Heart Muscle	2 g IV	35	30-280 min	12.7
Lymphatic fluid	1 g IV	7	2-3 h	23.4 ± 1.2
Myometrium	2 g IV	9	1-2 h	18.9 ± 4.9
Peritoneal fluid	2 g IV	8	2 h	48.6
Pleural fluid	2 g IV	5	4 h	28 ± 2
Salpinges	2 g IV	6	1-2 h	18.8 ± 5.4

TISSUE OR FLUID	DOSE/ROUTE	NO. PATIENTS	TIME OF SAMPLE POST-DOSE	AVERAGE TISSUE OR FLUID LEVEL CONCENTRATION (mcg/mL or mcg/g)
Skeletal muscle	2 g IV	35	30-280 min	9.4
Skin	2 g IV	22	30-180 min	6.6
Sputum*	35 mg/kg IV	6	**	2.7
Subcutaneous tissue	2 g IV	2	1-2 h	6.9 ± 6.3
Synovial fluid	2 g IV	13	2 h	25.6 ± 1.8

* Cystic fibrosis patients

** Sputum collected for 8h period

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 by HPLC or in the urine by chromatography or bioautography.

Elimination

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

The mean renal clearance of ceftazidime was 97.6 mL/min (range 76 to 110 mL/min). The calculated plasma clearance of 116.4 mL/min (range 97 - 139 mL/min) indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid prior to dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Special Populations and Conditions

- **Pediatrics**

Neonates and Infants

Two studies were conducted in neonates (aged 0-29 days) which indicated that the serum half-life of ceftazidime in neonates could be 3-4 times that of an adult.

In the first study, 56 neonates (aged less than 29 days) were administered ceftazidime at a dose of 25 mg/kg every 12 hours. The mean serum half-life was 7.57 hours.

In the second study 29 neonates (aged less than 12 days) were dosed with 30-50 mg/kg of ceftazidime every 12 hours had an overall elimination half-life of 4.28 hours. The 30 mg/kg bid dose gave sustained serum levels of ceftazidime throughout the dosing interval and was found to be appropriate for the neonate population.

In another study, conducted in both neonates and infants (1 day to 12 months of age) 53 patients 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 10. The mean serum half-life for babies aged 2 months or younger was prolonged (4.2 ± 1.6h). Those aged greater than 2 months had a half-life of 2 ± 0.6h.

TABLE 10

	Serum levels (mcg/mL) at hrs after dose (mean ± S.D.)				
Age	**3**	**5**	**6**	**7**	**9**
< 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 (mean age, 3.5 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 11.

TABLE 11: Pharmacokinetic Parameters in Children

Patient Group	**n**	**Mean Age (Months)**	**Dose (mg/kg)**	**Peak Conc. (mg/L)**	**$t1/2_\beta$ (h)**	**V_d (L/kg)**	**C1 (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 2 g 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**

The peripheral comparative volume of distribution was smaller in females (mean 3.5 ± 0.5 L) than in males (6.7 ± 0.6 L) following intravenous administration (1 g, bolus injection).

Following intramuscular administration (1 g), the time to peak concentration occurred earlier in the men (1 ± 0.1h - vastus lateralis and 1.1 ± 0.1h - gluteus maximus) than in women (1.3 ± 0.03h and 1.5 ± 0.2h, respectively). Peak serum concentrations were greater in women (37.2 ± 0.2 mg/L - vastus lateralis and 34.0 ± 2.3 mg/L – gluteus maximus) than in men (29.4 ± 1.6 mg/L and 27.6 ± 2.3 mg/L, respectively).

- **Pregnancy and Breastfeeding**

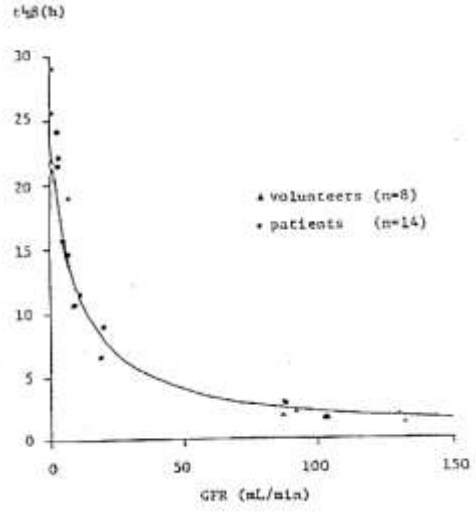
Intramuscular injections of at least three doses of ceftazidime (1 g t.i.d.) were administered to 9 pregnant women (mean age 25.6 yr; mean gestational age 20.2 weeks) scheduled for abortion following diagnosis of fetal Cooley's anemia.

Amniotic fluid levels of 1 - 5.5 mcg/mL were observed between 2 and 6 hours after dosing. Serum levels of ceftazidime were approximately 50% lower in pregnant than 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 50 mL/min/1.73m^2 (see Figure 7).

FIGURE 7: The relationship between serum elimination half-life and glomerular filtration rate



The pharmacokinetic parameters obtained following intravenous administration of a 1 g 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) are given in Table 12.

TABLE 12: Mean Pharmacokinetic Parameter after 1 g Ceftazidime IV

Group	C_0 (mg/L)	AUC_T (mg/h/L)	B (h^{-1})	t1/2β (h)	Vdβ (L)	UR (%)	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	-

Co = Fictive serum concentration at time zero
AUCT = Area under the serum concentration/time curve to infinity
β = Serum elimination rate constant
t1/2β = Serum half-life
Vdβ = Volume of distribution during the post-distributive phase
UR = Urinary recovery over 24 h

Mean maximum urine levels ranged between 0.2 g/L in patients with a GFR of <5 mL/min to 0.8 g/L with a GFR of 88 mL/min.

In another study, six normal volunteers and four end-stage renal disease (ESRD) patients on hemodialysis were administered a single 1 g IV 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 50 mL/min, while the total body clearance in the normals ranged from 98 to 184 mL/min. In another study single bolus doses of ceftazidime (15 mg/kg IV) were administered to 5 normal volunteers and 19 uremic patients (See Table 13). Four of the latter patients received an additional dose during hemodialysis.

TABLE 13: Pharmacokinetic parameters of ceftazidime in healthy volunteers and in patients with impaired renal function

Group (n)		Cl_{cr} (mL/min)	t1/2β(h) (mean ± S.D.)	VD (L)
I - Healthy Volunteers	(5)	>80	1.5 ± 0.2	17.8 ± 1.2
II - Uremic Patients	(5)	30-80	3.6 ± 0.7	17.5 ± 3.1
III -Uremic Patients	(6)	13-29	9.0 ± 1	16.1 ± 3.4

Group (n)		Cl_{cr} (mL/min)	t1/2β(h) (mean ± S.D.)	VD (L)
IV - Uremic Patients	(4)	2-12	16.1 ± 4	19.1 ± 8.4
V - Hemodialysis Patients - during dialysis - between dialysis sessions	(4)	--	 2.8 ± 0.2 25.5 ± 4.6	--

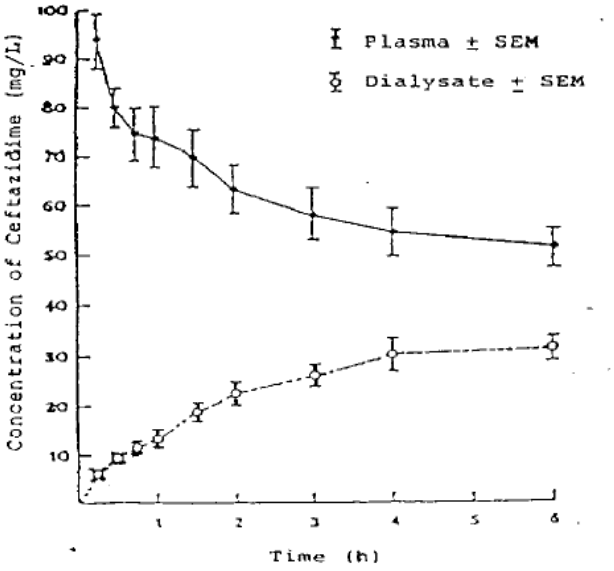
CIcr = creatinine clearance VD = volume of distribution

The pharmacokinetics of ceftazidime were studied in 12 patients with end-stage chronic renal failure during peritoneal dialysis. Mean serum levels (mg/L) following the IV administration of ceftazidime (1 g) to 5 patients at 0.25, 2 and 12 hours after starting peritoneal dialysis were 50.6 ± 11.2, 35.6 ± 3.7 and 22.7 ± 7.9 respectively. The mean serum half-life during and after peritoneal dialysis was 8.7 ± 3.1 hours and 26.9 ± 11 hours respectively.

Four patients were administered ceftazidime (1 g) via an intraperitoneal catheter. The mean serum levels (mg/L) at 0.25, 2 and 8 hours were 14.2 ± 3.1, 40 ± 3.1 and 32.5 ± 6.4 respectively.

Five male and one female patient undergoing continuous ambulatory peritoneal dialysis (CAPD) were administered 1 g ceftazidime. Two liters of dialysis fluid were used every six hours. The mean concentrations of ceftazidime in plasma and dialysate are shown in Figure 8. Using a dwell time of 4 to 6 hours, approximately 10% of a dose of ceftazidime is removed. The data indicate that the half-life of ceftazidime is reduced to approximately 12 hours.

FIGURE 8: Mean ceftazidime levels in plasma and dialysate of CAPD patients



- **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 ± 0.21 h in controls and 1.50 ± 0.19 h in cystic fibrotics. Total body clearance was 41.9% greater in the cystic fibrosis group (142.4 ± 16.9 mL/min/1.73m^2) compared to controls (100.5 ± 10.3 mL/min/1.73m^2). 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 ± 11.6 mL/min/1.73m^2 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 BP as powder for solution should be stored between 15-30°C and protected from light.

Solutions

1g and 2g Single Dose Vials: Use reconstituted and further diluted solution within 12 hours if kept at room temperature (15-25°C) or 48 hours if refrigerated (2-8°C). Single Use. Discard unused portion.

3g and 6g Pharmacy Bulk Vial: Ceftazidime for Injection BP as powder for solution should be stored between 15-30°C and protected from light.

Following reconstitution with Sterile Water for Injection, the solution should be dispensed and diluted for use within 8 hours at room temperature (15-25ºC). Any unused reconstituted solution should be discarded after 8 hours. Further diluted solutions should be administered within 12 hours when stored at room temperature (15-25°C), and within 48 hours when refrigerated (2-8°C). Single Use. Discard unused portion.

Incompatibility

Ceftazidime for Injection BP should not be added to blood products, protein a hydrolysates or amino acids. Ceftazidime for Injection BP should not be mixed together with an aminoglycoside. Ceftazidime for Injection BP is less stable in Sodium Bicarbonate Injection than in other intravenous fluids, therefore it is not recommended as a diluent. Precipitation has been reported when vancomycin has been added to Ceftazidime for Injection BP in solution. Therefore, it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

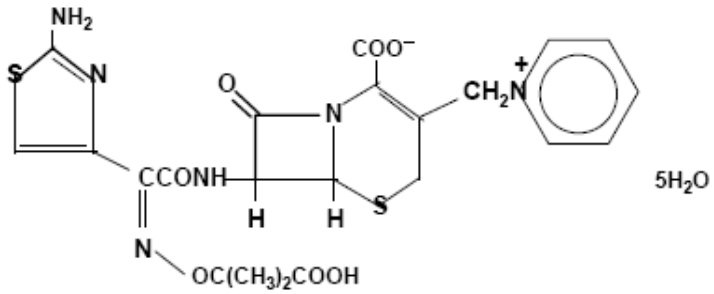
Drug Substance :

Proper Name: Ceftazidime pentahydrate

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 and Molecular Mass: $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$ and 636.6 (as pentahydrate)

Structural Formula:



Physicochemical Properties: Ceftazidime pentahydrate is a white to cream-coloured 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 BP 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

Spectrum of Activity

Ceftazidime has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections (see 1 INDICATIONS).

Table 14

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			

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
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				
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

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
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.												

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

Ceftazidime is not active in vitro against methicillin-resistant staphylococci, *Enterococcus* species, Listeria monocytogenes, *Campylobacter* species, *Clostridium difficile*, *Bacteroides* species, *Chlamydia* species, *Mycoplasma* species and *Legionella* species.

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 15.

Table 15 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

	MIC (mcg/mL)		MBC (mcg/mL)		Ratio of Means
Organisms (No. Tested)	Mean	90 %	Mean	90 %	MBC/MIC
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 16.

Table 16

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
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 is primarily through hydrolysis by beta-lactamase, alteration of penicillin-binding proteins (PBPs), outer membrane impermeability, and presence of bacterial efflux pumps.

Susceptibility Test Methods
Susceptibility to ceftazidime will vary with geography and time (see 7 WARNINGS AND PRECAUTIONS). Local susceptibility data should be consulted where available.

Dilution Technique:
Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar). The disc diffusion Interpretive criteria are based on the CLSI M100-S24 interpretive criteria as provided in Table 17.

Diffusion Technique:
Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. These procedures use paper discs impregnated with 30 mcg ceftazidime to test the susceptibility of bacteria to ceftazidime. The disc diffusion interpretive criteria are provided in Table 17.

TABLE 17 Disk and MIC breakpoints for ceftazidime susceptibility testing

Organism	Zone Diameter Interpretive Criteria* (mm) (30 mcg disk)			MIC Interpretive Criteria* (mcg/mL)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≥21	18-20	≤17	≤4	8	≥16
Hemophilus influenzae	≥26	-	-	≤2	-	-
Pseudomonas aeruginosa	≥18	15-17	≤14	≤8	16	≥32
Staphylococcus spp.	Susceptibility may be deduced from testing either cefoxitin or oxacillin.					
Streptococcus pneumonia	Penicillin-susceptible *S. pneumoniae* can be considered susceptible to ceftazidime.					
Streptococcus pyogenes	Penicillin-susceptible *S. pyogenes* can be considered susceptible to ceftazidime.					

*Interpretive criteria based on CLSI M100-S24 interpretive criteria

A report of “Susceptible” indicates the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the bacterium is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in

body sites where the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control:
Standard ceftazidime powder should provide the range of MIC values noted in Table 18. The Quality Control should be performed and evaluated according to the CLSI M100-S24 published QC ranges as provided in Table 18.

TABLE 18 Disk and MIC QC ranges for ceftazidime susceptibility testing

QC Strain	Disk Range* (mm) (30 mcg disk)	MIC Range* (mcg/mL)
Escherichia coli ATCC 25922	25-32	0.06-0.5
Pseudomonas aeruginosa ATCC 27853	22-29	1-4
Staphylococcus aureus ATCC 29213	-	4-16
Staphylococcus aureus ATCC 25923	16-20	-
Haemophilus influenzae ATCC 49247	27-35	0.12-1

*Disk and MIC QC ranges as published from CLSI M100-S24

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

TABLE 19

ANIMAL	AGE	SEX	ROUTE	DOSES (g/kg)	ANIMALS /DOSE	LENGTH OF OBSERVATION	LD_{50} (g/kg)
mouse	3 days	M F	IP	2.1,3.0,4.2,5.9,8.2 2.1,3.0,4.2,5.9,8.2,11.5	8 8	18 days 18 days	4.6 ± 0.6 6.1 ± 0.9
	14 days	M F	IP IP IP	3.6,4.3,5.2,6.2,7.4,8.9 3.6,4.3,5.2,6.2,7.4,8.9	8 8	14 days 14 days	4.9 ± 0.3 4.8 ± 0.2
	21 days	M F	IP IP IV	4.7,5.7,6.8,8.2,9.8,11.8 4.7,5.7,6.8,8.2,9.8,11.8	8 8	14 days 14 days	9.0 ± 0.8 8.4 ± 0.6
	adult	M	IV	5.0,6.25,7.5,8.8,10.0	5	14 days	7.0± 1.1

ANIMAL	AGE	SEX	ROUTE	DOSES (g/kg)	ANIMALS /DOSE	LENGTH OF OBSERVATION	LD_{50} (g/kg)
		F		5.0,5.6,6.25,6.9,7.5,8.8	5	14 days	6.3 ± 0.6
rat	3 days	M	IP SC	3.9,4.6,5.6,6.7,8.0,9.6	8	14 days	5.7 ± 0.4
			IP	4.8,5.8,6.9	8	14 days	6
		F	SC	3.9,4.6,5.6,6.7	8	14 days	5.7 ± 0.4
			IP	4.8,5.8,6.9,8.3	8	14 days	6
	14 days	M	SC	4.2,5.0,6.0,7.3,8.7,10.5	8	14 days	5.9 ± 0.6
			IP	4.7,5.6,6.7,7.8,8.1,9.7,11.6	8	14 days	6.6 ± 0.4
		F	SC	3.5,4.2,5.0,6.0,7.3,8.7	8	14 days	5.8 ± 0.4
			IP	4.7,5.6,6.7,8.1,9.7,11.6	8	14 days	7.2 ± 0.4
	21 days	M	SC	5.6,6.7,8.1,9.7	8	14 days	7.5 ± 0.4
			IP	8.1,9.7,11.7,14.0,16.8	8	14 days	11.9 ± 0.8
		F	SC	5.6,6.7,8.1,9.7	8	14 days	7.0
			IP	8.1,9.7,11.7,14.0,13.8	8	14 days	12.2 ±0.7

All deaths in mice occurred within 24 hours after an intravenous dose or within 6 hours following an intraperitoneal dose. Toxic signs consisted of purplish colouration of the skin, immobility and bradypnea alternating with jumping and convulsions. Survivors exhibited no abnormal signs or symptoms at 24 hours following the test dose. Post-mortem examinations revealed meningorrhagia, especially in the cerebellum, and pulmonary congestion.

Death in rats occurred within 24 hours following subcutaneous injection and 6 hours following intraperitoneal dosing. Purplish colouration and reduction in elasticity of the skin, bradypnea, corneal opacity, piloerection, and immobility followed by jumping and convulsions were observed. All survivors appeared normal by 48 hours post-dose. Post-mortem examinations revealed meningorrhagia, pulmonary congestion, splenic cysts and spots, and, in rats who received IP dosing, dilation of the caecum with large amount of contents.

Groups of 6 rats of each sex were given a single intravenous or subcutaneous dose of ceftazidime (5 g/kg). One female died immediately after IV injection while the remaining animals survived in good condition. All animals were sacrificed 7 days post-dose. Post-mortem examinations revealed mild renal damage in the form of paling and slight dilation of some renal tubules containing cellular debris.

A single IV dose of ceftazidime (5 g/kg) was administered to 6-month-old Beagle dogs (2/sex), which survived in good condition except for intermittent emesis and transient tachycardia. The animals were sacrificed 7 days post-dose for extensive histological examinations, but no pathological findings were noted.

Sub chronic and Chronic Toxicity

TABLE 20

ANIMAL	AGES*	ROUTE	DOSES (g/kg/day)	ANIMALS/DOSE**	DURATION OF	
					TREATMENT	RECOVERY
rat	8 – 13 wk	IV	0.0,0.1,0.3,0.9,2.7,8.1	12	30 days	14 days
rat	8 – 13 wk	SC	0.0,0.1,0.3,0.9,2.7,8.1	12	30 days	14 days
rat	unavailable	IM	0.0,0.1,0.3,0.9	20	12 weeks	--
rat	6 – 7 wk	SC	0.0,0.1,0.3,0.9,2.7	20	28 weeks	59 days
rat	5 – 6 wk	SC	0.0,0.1,0.5,2.5	20	27 weeks	21 days
dog	5 – 18 mo	IM	0.00,0.06,0.18,0.54	2 or 4	30-32 days	22-23 days
dog	5 – 18 mo	IV	0.00,0.06,0.18,0.54	4 or 8	30-32 days	22-23 days
dog	5 – 18 mo	SC	0.00,0.06,0.18,0.54	2 or 4	30-32 days	22-23 days
dog	3 wk	IV	0.0,0.1,0.3,1.0	14	35 days	35 days
dog	8 – 10 mo	IM	0.000,0.125,0.250,0.500	6	13 weeks	--
dog	16 – 27 wk	IV	0.000, 0.085,0.255,0.595,0.85	8	28 weeks	3 weeks

* Ages at commencement of treatment.

** Each dosage group was composed of equal numbers of males and females.

- **Rats:**

Rat: 30-day study, intravenous and subcutaneous

All rats given 8.1 g/kg IV and 2 of 12 given 2.7 g/kg died within 10 minutes in convulsive shock and were found to have dilation of proximal and distal convoluted renal tubules.

The 8.1 g/kg dose given sc was tolerated by females for the entire 30-day treatment period; males, however, had to be sacrificed after their third dose, and were found to have coagulative necrosis of 50 to 85% of the proximal convoluted tubules, but no other organ pathology.

Toxicity in survivors was similar by either route of administration. The following biochemical and morphological changes were observed in survivors during or immediately following the treatment period: decreases in serum transaminases, protein (8.1 g/kg/day dose), alkaline phosphatase, calcium, and triglycerides; increases in serum sodium, potassium, inorganic phosphorus, protein (<8.1 g/kg/day doses), and cholesterol; increased weights of liver, kidney, spleen, ovaries, and adrenals; thymus involution; neutrophilia, lymphocytosis, and normocytic normochromic anemia; and increased urinary volume and output of epithelial cells, protein, and electrolytes. All of these abnormalities regressed during the recovery period.

Post-mortem examination of both treatment mortalities and sacrificed survivors of the 8.1 g/kg/day regimen revealed pulmonary edema, subpleural hemorrhages, fatty change in liver cells, and dilation and fluid content of renal tubules.

Rat: 12-week study, intramuscular
All animals survived treatment and no abnormal physical or behavioural symptoms were observed. The injections were well tolerated at the IM sites.

The following statistically significant changes in laboratory parameters which, nevertheless, still fell within the normal range occurred in the 0.9 g/kg/day group: erythrocyte counts increased in females and decreased in males; 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.

The following laboratory abnormalities were observed in the 0.3 and 0.9 g/kg/day groups: increases in serum cholesterol; inconsistent changes in serum proteins; and increases in urinary volume and pH and decreases in specific gravity.

Rat: 28-week study, subcutaneous
One male from the 2.7 g/kg/day group was killed on Day 95 for investigation of suspected hepatotoxicity. Post-mortem examination revealed splenomegaly and hepatic fibroplasia. A female from the 0.9 g/kg/day group died on Day 183 and was found to have congestion of the lung, thymus, liver and kidney. All other rats survived the entire treatment period. Adverse effects noted in the 2.7 g/kg/day group were local irritation, loose feces, lethargy, decreased weight gain, and a general loss of condition characterized by a rough sticky coat, dirty tail, irregular thickening of the skin, and increased aggressiveness.

Observed laboratory abnormalities in the 0.9 and 2.7 g/kg/day groups were decreases in serum hemoglobin, packed cell volume, and erythrocyte counts; increases in neutrophil, lymphocyte, and platelet counts; increases in prothrombin time; decreases in serum albumin, triglycerides, SGOT, SGPT, and alkaline phosphatase; increases in serum cholesterol and bilirubin; hematuria, bacteriuria, and increases in urinary volume and protein output. Post-mortem examinations revealed increased weights of liver, kidneys, spleen, and adrenals (in females), fibrosis around the central veins of the liver, hemorrhage and fibroplasia at the injection site, and salivary gland edema. Abnormalities which did not regress during the recovery period were increased weights of liver, spleen, adrenals (in females), and kidneys (in males).

Rat: 27-week study, subcutaneous
Environmental control failure resulted in the normal temperatures of 18 – 22°C being exceeded, and rats being exposed to temperatures as high as 29°C.

The toxicity of ceftazidime in heat-stressed animals was much higher in females than in males. All females in the 2.5 g/kg/day group died or had to be sacrificed after 8 to 12 weeks of treatment and were found to have extensive centrilobular liver necrosis, and in some, subendocardial fibrosis of the left ventricle. Although males survived the 2.5 g/kg/day dosage regimen, they also showed hepatic changes including fibrosis. Animals of both sexes in the high dose group were found to have dilation of renal tubules with casts and debris.

Changes in laboratory parameters in both sexes were decreased plasma enzyme activities and hypercholesterolemia at 0.1 g/kg/day or more, increased urinary protein at 0.5 g/kg/day or more, and increased BUN, hyperkalemia, hypoglycemia, hypochromic macrocytic anemia, leukocytosis, thrombocytosis, and increased diuresis at 2.5 g/kg/day.

- **Dogs:**

Dog: 30 to 32 days study, intravenous and subcutaneous/intramuscular
All beagles survived the treatment in good general condition apart from an erythematous skin condition which developed in six dogs, including one control. The IM and SC injections produced dose-related transient pain and irritation which varied from mild to severe. The IV injections caused no apparent local effects but were associated with a dose-related incidence of emesis.

Observed abnormalities consisted of increased total iron binding capacity in males at 0.18 g/kg/day, and increases in relative liver weight, hypoglycemia (in females), and hypertriglyceridemia at 0.54 g/kg/day. Post-mortem examinations revealed no abnormal pathology.

Infant Dog: 35-day study, intravenous
All beagles survived the treatment in good condition. Observed abnormalities consisted of salivation, emesis, and loose feces in the 0.3 and 1.0 g/kg/day groups. These symptoms regressed during the recovery period.

A tendency toward decreased SGOT levels was noted in the 1.0 kg/day group, but the mean change was not statistically significant. No other laboratory abnormalities were observed. Post-mortem findings were also negative.

Dog: 13-week study, intramuscular
All beagles survived the treatment in good condition. The injections were well tolerated at the IM site. No physical or behavioral abnormalities were observed.

The following hematological changes were noted in the 0.25 and 0.50 g/kg/day groups: decreased serum hemoglobin, hematocrit, lymphocytes, and platelets, and prolonged prothrombin time. These changes were statistically significant but the values remained within the normal range.

Other laboratory findings were increases in total serum cholesterol and BUN. Postmortem examinations revealed protein casts in the lumen of renal tubules in 6 males, including 2 out of the 3 male controls.

Dog: 28-week study, intravenous
Two beagles were sacrificed during the study and found to have, respectively, a cerebellar lesion and polyarteritis. All other dogs survived the study in satisfactory condition. Adverse effects of treatment were discomfort during injection, and a dose-related incidence of salivation and vomiting. Laboratory abnormalities were generally confined to the 0.595 and 0.850 g/kg/day groups and 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.

Genotoxicity
Ceftazidime was evaluated *in vivo* and *in vitro* in a series of standard mutagenicity assays.

In Vitro Assays
The mutagenic potential of ceftazidime was assessed using a modified Ames test, a modified fluctuation test (Harefield) and a yeast gene conversion test (Davis). The results of the Ames plate incorporation assay, in which six concentrations of antibiotic were tested in the presence and absence of microsomes, showed a significantly positive result with *Salmonella typhimurium* strain TA 1537 at 0.9 mcg of ceftazidime/plate but this was believed to have occurred by chance. Ceftazidime was negative in the modified Ames test in which it was pre-incubated with liver microsomes.

In the modified pre-incubation fluctuation test, no mutagenic effects were observed at ceftazidime concentrations up to 430 mcg/mL.

Similarly, ceftazidime did not induce detectable gene conversion in *Saccharomyces cerevisiae* JD1 cells at concentrations up to 860 mcg/mL.

In-vivo Micronucleus Test
In a micronucleus test, mice received single intraperitoneal injections of 0.56, 1.67 or 5.02 g/kg ceftazidime. No evidence of a clastogenic effect was noted.

In-vivo Cytogenicity Study
A micronucleus test was used to compare the clastogenic properties of freshly prepared solutions of ceftazidime with samples of ceftazidime stored for up to 24 hours at 25°C. Mice were injected with single IP doses of 1.0 or 2.5 g/kg. Neither fresh nor stored (which contains pyridine as a degradation product of the antibiotic during storage) solutions of ceftazidime induced a significant increase in detectable chromosomal damage. However, a significant ($p<0.05$) reduction in the ratio of immature to mature erythrocytes occurred in mice given 2.5 g/kg of ceftazidime (stored solution) 24 hours previously.

The effects of storage of ceftazidime (either as a dry powder at 37°C for 4 months or as a 25% w/v solution at 25°C for 72 hours) on its immunogenicity and elicitogenicity (i.e. the ability to

produce anaphylaxis in an immunized subject) were studied in rabbits and guinea pigs. Immunogenicity was unaffected but elicitogenicity was found to increase with storage.

Solutions of ceftazidime and its degradation products, formed on both wet and dry storage as above, did not cause the release of allergic mediators from human peripheral blood basophils or from fragments of human lung parenchyma *in vitro*.

Reproductive and Developmental Toxicology

Teratology:

- **Mouse:**

Four groups of pregnant female mice were administered sc injections of either saline (28 mice) or ceftazidime (1.5 g/kg/day - 21 mice, 3.25 g/kg/day - 20 mice, 6.5 g/kg/day - 29 mice) from day 6 to day 15 of pregnancy inclusive (period of organogenesis). Eight mice from the control group and eight from the group given 6.5 g/kg/day were allowed to give birth and rear their young to weaning. The remaining animals were sacrificed on day 18 of pregnancy and an examination made of their uterine contents.

The following external or soft tissue defects were found, each occurring in a single fetus only: control - left testis absent (1 mouse); 1.5 g/kg - small depression in palate (2 mice), right testis not found (1 mouse); cleft palate (1 mouse); 3.25 g/kg – small swelling at base of tail (1 mouse); 6.5 g/kg - enlarged space in thoracic cavity (1 mouse); cleft palate (1 mouse), enlarged thin walled bladder (1 mouse), small depression in palate (1 mouse).

The high incidence of skeletal variants seen in all groups (control: 39.51%, 1.5 g/kg: 53.98%, 3.25 g/kg: 50.70%, and 6.5 g/kg: 63.55%) was due to the large number of fetuses with supernumerary ribs. The incidence of rib variants was significantly higher ($p<0.05$) in the high-dose group (6.5 g/kg) than in the control group.

The overall incidence of skeletal abnormalities was 15% (controls), 20% (3.25 g/kg ceftazidime) and 24% (6.5 g/kg ceftazidime). These consisted mainly of obliquely fused sternebrae. In the group treated with the high dose (6.5 g/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 born to mice treated with the high-dose (6.5 g/kg) was significantly ($p<0.05$) lower (10) when compared to controls (13). Similarly the litter weights for the treated group were consistently and significantly ($p<0.05$) lower than those in the control group throughout lactation.

- **Rabbit:**

Female Dutch rabbits were given intramuscular injections of 0 (18 rabbits), 25 mg/kg (27), 50 mg/kg (18), 100 mg/kg (18) or 200 mg/kg (9) ceftazidime daily from day 6 to day 18 of pregnancy (organogenesis). 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 21.

TABLE 21

Observation	MEAN RESULTS				
	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) Within Litter Mean Live	191	153	136	141	138
Fetus Weight (g) Within Litter Mean	31.4	30.2	28.6	26.9	24.5
Placenta 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 AHA rats (approximately 10 wk of age, 200 g body weight) received a daily SC injection of either 0, 0.1, 0.5 or 2.5 g/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 (2.5 g/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 the control group and this effect was dose-related.

At termination (day 21 postpartum), pups in the high-dose group (2.5 g/kg) had gained significantly ($p<0.05$) less weight (47.95 g) than controls (52.23 g). This was observed throughout lactation. Two of the dams in the high-dose (2.5 g/kg) group were killed due to the death of their litters. Both animals had gastrointestinal disorders due to heavy growth of Gram-positive *Streptococcus*. One dam in the 0.5 g/kg group was killed due to ill health (diarrhea due to bacterial typhlitis).

Fertility and Reproduction

Groups of 20 male and 40 female mice received SC injections of either saline or 1.5, 3.25 or 6.5 g/kg of ceftazidime daily throughout 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. One 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 (control: 45.48%, 1.5 g/kg/day: 55.04%, 3.25 g/kg/day: 64.40%, 6.5 g/kg/day: 73.97%) was due to the large number of fetuses with supernumerary ribs.

The incidence of bone variants was significantly higher ($p<0.05$) in the high-dose group (6.5 g/kg/day) as compared to the controls. Throughout lactation, the mean pup weights (F1 generation) for the mid - (3.25 g/kg/day) and high - (6.5 g/kg/day) dose groups 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.

Special Toxicology

Tolerance Studies

An aqueous solution of ceftazidime 25% w/v was tested for intramuscular irritancy in both adult (1.0 mL) and infant (0.2 mL) rabbits. Lesions consisting of hemorrhage, inflammation, and

necrosis were produced which regressed and had almost completely healed by 14 days post-dose.

Intra-arterial injection of 0.5 mL ceftazidime 25% w/v into rabbit ears produced minimal local damage, being morphologically and histologically similar to that caused by intra-arterial injection of 0.5 mL normal saline.

The intracisternal injection of ceftazidime, ampicillin sodium, and gentamicin sulphate caused convulsions of dose-related severity in male rabbits. The minimum dosage levels at which convulsions were observed were 5 mg/kg for ceftazidime, 12 mg/kg for ampicillin sodium, 4.5 mg/kg for gentamicin sulphate.

Immunological Studies

Ceftazidime (25 mg/kg, IM) was administered as an aqueous solution to 10 rabbits (5M, 5F) once weekly for 6 weeks. Sera taken 7 days after the last dose were negative for ceftazidime antibody by both enzyme-linked immunosorbent assay (ELISA) and passive cutaneous anaphylaxis (PCA) test.

Four doses of ceftazidime (25 mg/kg) in an aqueous emulsion with Freund's adjuvant were given to 6 rabbits (3M, 3F) as a single inoculation followed by boosters on days 21, 56 and 95. Sera taken on day 102 were all negative for drug antibody by ELISA, but 1 out of 6 (female subject) was positive by PCA test. This antibody was skin fixing and heat labile.

Antisera prepared with cephaloridine, cephalexin, cephalothin, and cefotaxime showed cross-reactivity with a ceftazidime-cytochrome C antiserum, but did not cross-react with an antiserum prepared with a ceftazidime-human gamma globulin conjugate.

Nephrotoxicity Studies

TABLE 22

ANIMAL	SEX	ROUTE	CEFTAZIDIME DOSES (g/kg/day)	ANIMALS/ DOSE	CONCURRENT DRUG AND DOSE	COMPARATIVE DRUG AND DOSE	DURATION OF	
							TREATMENT	OBSERVATION
mouse	F	SC	0,4,6,8,10	10	--	cephaloridine 1.1 g/kg	1 dose	48 hr
	F	SC	0,10	10	furosemide 50 mg/kg	cephaloridine 1.1 g/kg	1 dose	48 hr
	F	SC	0,10	10	probenecid 100 g/kg	cephaloridine 1.1 g/kg	1 dose	48 hr
	F	SC	0,10	10	--	cephaloridine 1.1 g/kg	1 dose	1-7 days
rat	M	SC	0,4	5	--	cephaloridine 2 g/kg	1 dose	1-7 days
	M	SC	0,2,4,6,8,10	6	--	cephaloridine 2 g/kg	1 dose	48 hr

ANIMAL	SEX	ROUTE	CEFTAZIDIME DOSES (g/kg/day)	ANIMALS/ DOSE	CONCURRENT DRUG AND DOSE	COMPARATIVE DRUG AND DOSE	DURATION OF	
							TREATMENT	OBSERVATION
	M	SC	0,4	6	--	cefuroxime 4 g/kg	1 dose	48 hr
	M	SC	0,4	6	gentamicin 35 mg/kg	--	1 dose	48 hr
	M	SC	0,4	6	furosemide 100 mg/kg	cephaloridine 2 g/kg	1 dose	48 hr
	M	SC	0,4	6	probenecid 100 mg/kg	cephaloridine 2 g/kg	1 dose	48 hr
	M	SC	0,4	10	--	--	10 days	10 days
	M	SC	0,4	6	Gentamicin 35 mg/kg	--	10 days	24 hr
	M	SC	0,4	6	amikacin 250 mg/kg/day	--	10 days	24 hr
	M	SC	0,4	6	Tobramycin 60 mg/kg/day	--	10 days	24 hr
rabbit	M	IM	0.0,0.5	6	--	cephaloridine 0.14 g/kg	1 dose	48 hr
	F	SC	0.0,0.4,0.8	4	--	cephaloridine 0.2 g/kg	1 dose	48 hr
	F	SC	0.0,0.4,0.8	4	--	cefazolin 0.4 g/kg	1 dose	48 hr
	F	SC	0.0,0.4,0.8	4	--	cefazolin 0.8 g/kg	1 dose	48 hr

In female mice, a single sc dose of ceftazidime 6 g/kg resulted in no evidence of nephrotoxicity. Doses of 8 and 10 g/kg produced coagulative necrosis of inner cortical tubules. Cephaloridine (1.1 g/kg) was associated with more severe tubular necrosis than was ceftazidime (10 g/kg), the exerted its toxicity primarily on tubules of the outer cortex. The concurrent administration of furosemide 50 mg/kg potentiated the nephrotoxicity of cephaloridine but not that of ceftazidime. Pre-treatment with probenecid (100 mg/kg) prevented the nephrotoxicity of cephaloridine but not that of ceftazidime.

In male rats, single sc doses of ceftazidime, 4 g/kg or more, produced acute tubular necrosis (inner cortex) and elevations in serum urea nitrogen. This effect was not potentiated by concurrent administration of either gentamicin (35 mg/kg) or furosemide (100 mg/kg), nor was it prevented by pre-treatment with probenecid (100 mg/kg).

In both mice and rats (single dose studies), prolonged observation indicated that the tubular necrosis caused by a single dose of ceftazidime was maximal in severity 48 hours post-dose. Significant improvement was noted after 3 days, with nearly complete regeneration after 7 days.

Male rats given sc injections of ceftazidime 4 g/kg/day for 10 days exhibited increased urinary excretion of enzymes, protein and epithelial cells, which were maximal on day 2 but gradually returned to normal with continued treatment. Ten day treatment with either gentamicin (35 mg/kg/day), amikacin (250 mg/kg/day), or tobramycin (60 mg/kg/day) produced necrosis, mainly of outer cortical tubules. Combination of an aminoglycoside regimen with ceftazidime 4 g/kg/day

produced inner cortical tubular necrosis similar to that observed for ceftazidime alone, but with less outer cortical tubular necrosis than that caused by the aminoglycoside alone.

In the rabbit, single ceftazidime doses of 500 mg/kg IM, and 400 or 800 mg/kg SC were not nephrotoxic. Cephaloridine (140 mg/kg IM or 200 mg/kg SC), and cefazolin (800 mg/kg SC) caused marked abnormalities of plasma urea and creatinine, and of tubular ion transport, gluconeogenesis, and histology.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Fortaz® submission control number: 213619, Product Monograph. GlaxoSmithKline Inc., (AUG 16, 2018).

2. PrCEFTAZIDIME FOR INJECTION, USP (Sterile Powder for Solution, 1 g/vial, 2 g/vial, 6 g /vial) Submission Control Number: 254560, Product Monograph. Fresenius Kabi Canada Ltd., (FEB 17, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CEFTAZIDIME FOR INJECTION BP
(as ceftazidime pentahydrate)

Read this carefully before you start taking Ceftazidime for Injection BP. 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 BP.

Serious Warnings and Precautions

Seek medical help if you think you are experiencing any of the following serious side effects – you may need urgent medical treatment:

- **Hemolytic anemia (breakdown of red blood cells):** If you have a history of cephalosporin-associated hemolytic anemia, you should not take Ceftazidime for Injection BP. If you develop hemolytic anemia, you may have symptoms such as pale skin, weakness, tiredness, shortness of breath, yellowing of your skin and/or the whites of your eyes, fever.
- **Allergic reactions:** signs may include difficulty breathing, swelling of the face or throat, severe skin rash, sudden swelling.
- **Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs)**: signs may include 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 eye or face; flu-like feeling, fever, chills, body aches, swollen glands, cough, shortness of breath, chest pain or discomfort.

What is Ceftazidime for Injection BP used for?

Ceftazidime for Injection BP treats infections in different parts of the body:
- lungs and lower airways (lower respiratory tract)
- bladder (urinary tract)
- skin
- blood (sepsis)
- bone
- around the inner organs (peritonitis)
- around the brain (meningitis)

Ceftazidime for Injection BP may also be used to treat other infections caused by certain bacteria.

Antibacterial drugs like Ceftazidime for Injection BP treat only bacterial infections. They do not treat viral infections such as the common cold.

How does Ceftazidime for Injection BP work?

- Ceftazidime for Injection BP contains a medicine called ceftazidime. It is an antibiotic. Antibiotics kill the bacteria that cause some infections.

What are the ingredients in Ceftazidime for Injection BP?

Medicinal ingredient: ceftazidime (as pentahydrate)
Non-medicinal ingredient: sodium carbonate

Ceftazidime for Injection BP comes in the following dosage forms:

- powder for solution (1 g, 2 g, 3 g, 6 g vials)

Do not use Ceftazidime for Injection BP if:

- you or your child are allergic to ceftazidime, cephalosporin antibiotics, or any of the ingredients in Ceftazidime for Injection BP. See What are the ingredients in Ceftazidime for Injection BP.

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

- have had allergic reactions to other medicines (such as antibiotics)
- have had gastrointestinal disease; severe diarrhea or colitis
- have had anemia (low blood iron) after taking antibiotics like Ceftazidime for Injection BP
- have kidney disease or are elderly; your doctor may lower your dose of Ceftazidime for Injection BP
- need a low salt intake
- are pregnant, or think you could be, or if you are planning to become pregnant
- are breast-feeding; you must check with your doctor before you Ceftazidime for Injection BP, as the medicine can pass into breast milk

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

The following may interact with Ceftazidime for Injection BP:

- other antibiotics (such as chloramphenicol or aminoglycosides)
- a type of water pills (known as loop diuretics, for example furosemide)
- birth control pills (contraceptive pills) may be less effective. If you are taking "the pill" while you are being treated with Ceftazidime for Injection BP you also need to use a barrier method of contraception (like condoms). Ask your doctor for advice.

If you or your child need a blood or urine test tell the person taking the sample that you have been given Ceftazidime for Injection BP. Ceftazidime for Injection BP can change how some blood tests (Coombs), or urine tests for sugar (Benedict's or Fehling's) work.

How to take Ceftazidime for Injection BP

- Ceftazidime for Injection BP is given by a doctor or nurse as an injection or infusion (drip) into a vein or an injection into a muscle. Although you may feel better early in treatment your doctor will continue to treat you with Ceftazidime for Injection BP until the infection clears up.
- Misuse or overuse of Ceftazidime for Injection BP could lead to the growth of bacteria that will not be killed by Ceftazidime for Injection BP (resistance). This means that Ceftazidime for Injection BP may not work for you in the future.

If you have any questions about your dose of Ceftazidime for Injection BP or how Ceftazidime for Injection BP is given, **ask your doctor or nurse**.

Usual dose:

Your doctor will decide on the correct dose of Ceftazidime for Injection BP depending on:

- the severity and type of your infection
- your age
- how well your kidneys are working

Ceftazidime for Injection BP is usually given 2 – 4 times a day for 7 – 14 days.

Overdose:

If you think you have taken too much Ceftazidime for Injection BP, 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 BP?

Like all medicines, Ceftazidime for Injection BP can cause side effects. These are not all the possible side effects you may feel when taking Ceftazidime for Injection BP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- swelling, redness, or pain near the injection site
- diarrhea, nausea, vomiting, stomachache
- changes in blood or urine test results (noticed by your healthcare provider)
- white spots in the mouth or throat (yeast infection, thrush)
- vaginal yeast infection (in women)
- headache, dizziness
- blurred vision
- flushing (redness)
- bad taste in the mouth

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			
Blood problems: with symptoms like bleeding or bruising more easily than usual, or blood clotting too easily.	X		
Pseudomembranous colitis (digestive system problems): with symptoms like severe diarrhea, usually with blood and mucus, stomach pain and fever.			X
VERY RARE			
Allergic reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			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	
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
Erythema multiforme (severe skin reaction): skin rash which may blister and looks like small targets (central dark spots surrounded by a paler area with a dark ring around the edge).			X
Central Nervous System: problems such as tremors,			

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	
twitching, seeing things that are not there, tingling, convulsions (fits or seizures), or coma. Particularly in people with kidney disease.			X
Liver problems: with symptoms such as yellowing of the whites of the eyes or skin.	X		
Hemolytic anemia (breakdown of red blood cells): pale skin, weakness, tiredness, shortness of breath, yellowing of your skin and/or the whites of your eyes, fever.			X
Infection: fever, high heart rate, feeling unwell, or other signs of new or ongoing infection.			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, talk to 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:

Keep out of reach and sight of children.

Do not use Ceftazidime for Injection BP after the expiry date shown on the pack.

Protect from light.

If you want more information about Ceftazidime for Injection BP:

- 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 www.sterimaxinc.com, or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

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