PRODUCT MONOGRAPH

Pr CEFTAZIDIME FOR INJECTION, USP

1 g, 2 g, 6 g Vials

Antibiotic

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Pr CEFTAZIDIME for Injection, USP

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

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

INDICATIONS AND CLINICAL USES

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

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

Hypersensitivity

BEFORE THERAPY WITH CEFTAZIDIME FOR INJECTION, USP IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTAZIDIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. CEFTAZIDIME FOR INJECTION SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. THIS PRODUCT SHOULD BE GIVEN WITH CAUTION TO PATIENTS WITH TYPE I HYPERSENSITIVITY REACTIONS TO PENICILLIN. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFTAZIDIME FOR INJECTION OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Clostridium difficile-associated disease

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

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

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

Hemolytic Anemia

CEFTAZIDIME FOR INJECTION, USP SHOULD NOT BE USED IN PATIENTS WITH A HISTORY OF CEPHALOSPORIN-ASSOCIATED HEMOLYTIC ANEMIA SINCE THE RECURRENCE OF HEMOLYSIS IS MUCH MORE SEVERE.

An immune mediate hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials, including Ceftazidime for Injection, USP. Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2 - 3 weeks subsequent to the administration of Ceftazidime for Injection, USP, the diagnosis of a cephalosporin-associated anemia should be considered and the drug discontinued until the etiology is determined.

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

PRECAUTIONS

Ceftazidime for Injection, USP dosage should be reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**). High and prolonged serum antibiotic concentrations can occur from normal dosages in patients with transient or persistent reduction of urinary output because of renal insufficiency. The total daily dosage should be reduced when ceftazidime is administered to such patients to avoid the clinical consequences, e.g., seizures, encephalopathy, asterixis, and neuromuscular excitability due to elevated levels of antibiotics (see **DOSAGE AND ADMINISTRATION**). Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organism.

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

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

ceftazidime by *Staphylococcus aureus, Enterobacteriaceae, Acinetobacter* species, and *Pseudomonas* species.

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

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

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

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

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

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

Laboratory Test Changes
A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest tablets. As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine, hepatic enzymes [aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH) and alkaline phosphatases] were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis were very rarely seen.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

Hematologic: Cases of hemolytic anemia have been reported (see **WARNINGS**).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Signs and Symptoms

Overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, and neuromuscular excitability. Patients who receive an acute overdosage should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis or peritoneal dialysis may aid in the removal of ceftazidime from the body. It is reported that the administration of large doses of parenteral cephalosporins may cause dizziness, paresthesias, and headaches. Seizures may occur following overdosage with some cephalosporins, particularly in patients with renal impairment in whom accumulation is likely to occur.

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

Treatment

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

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

DOSAGE AND ADMINISTRATION

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

Dosage

Adults:

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

Table 1:

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

A normal course of treatment should continue until 48 - 72 hours after the patient defervesces or after bacterial eradication has been obtained, usually 10 - 14 days, except for bone infections where treatment can continue for 6 weeks. In the treatment of beta-hemolytic streptococcal infections, Ceftazidime for Injection, USP should be administered for at least 10 days.

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

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

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

$$\text{Females: } 0.85 \times \text{above value}$$

Table 2: MAINTENANCE DOSAGE GUIDE FOR PATIENTS WITH RENAL IMPAIRMENT

Creatinine Clearance (mL/min.)	Recommended Dose of Ceftazidime for Injection	Frequency
50 - 31	1 g	q12h
30 - 16	1 g	q24h
15 - 6	500 mg	q24h
≤ 5	500 mg	q48h

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

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

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

Children with Impaired Renal Function:
In children, as in adults, the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency should be reduced in cases of renal insufficiency.

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

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

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

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

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

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

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

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

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

NOTE: If therapy with Ceftazidime for Injection is carried out in combination with an aminoglycoside antibiotic, either, each of these antibiotics should be administered at different sites, or ceftazidime and aminoglycosides may be administered sequentially by intermittent intravenous infusion. After the administration of one of the two drugs, the tubing is carefully and thoroughly flushed with an approved solution for reconstitution and then the other drug solution is administered. An aminoglycoside should not be mixed with Ceftazidime for Injection in the same container.

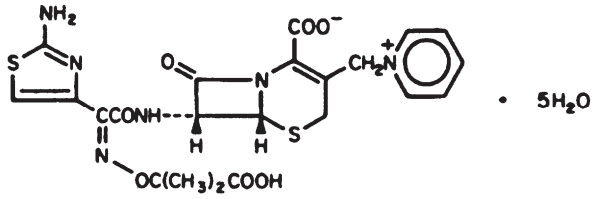
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Ceftazidime

Chemical Name: Pyridinium, 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, hydroxide, inner salt,pentahydrate, [6R-[6α,7ß(Z)]].

Structural Formula:



Molecular Formula: $C_{22}H_{22}N_6O_7S_2.5H_2O$

Molecular Weight: 636.65

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

Composition:
Ceftazidime for Injection, USP vials contain a mixture of ceftazidime and sodium carbonate.

The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq/g of ceftazidime activity).

Solutions of Ceftazidime for Injection 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.

RECONSTITUTION

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

For Intramuscular Use
Solutions for Reconstitution:
Sterile Water for Injection or, if required, Bacteriostatic Water for Injection, 0.5 to 1.0% Lidocaine Hydrochloride Injection.

Reconstitute as follows:

Reconstitution Table:

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

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

For Intravenous Use
Solutions for Reconstitution:
Sterile Water for Injection.

Reconstitute as follows:

Reconstitution Table:

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

Shake well until dissolved. The prepared solution may be further diluted to the desired volume with any of the solutions for i.v. infusion listed below. Refer to **STABILITY AND STORAGE**

RECOMMENDATIONS for recommended storage conditions for both dry state and reconstituted solutions.

For Direct Intravenous Injection: Reconstitute as directed above.

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

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

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

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

Reconstitution Table:

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

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

Solutions for IV Infusion:

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

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

Solutions of ceftazidime, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction. However, if concurrent therapy with ceftazidime and an aminoglycoside is indicated, each of these antibiotics should be administered in different sites.

Instructions for Reconstitution:

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

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

For 6 g Pharmacy Bulk Package

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

STABILITY AND STORAGE RECOMMENDATIONS

Dry Powder

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

Solutions

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

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

Incompatibility

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

AVAILABILITY OF DOSAGE FORMS

Vial stoppers do not contain natural rubber latex.

VL 7231:	Ceftazidime for Injection, USP 1 g, equivalent to 1 g ceftazidime and 118 mg sodium carbonate, 20 mL rubber-stoppered vial. (Dry Powder.)
VL 7234:	Ceftazidime for Injection, USP 2 g, equivalent to 2 g ceftazidime and 236 mg sodium carbonate, 50 mL rubber-stoppered vial. (Dry Powder.)
Pharmacy Bulk Vial VL 7241:	Ceftazidime for Injection, USP 6 g, equivalent to 6 g ceftazidime and 708 mg sodium carbonate, 100 mL rubber-stoppered vial. (Dry Powder.)

INSTRUCTIONS FOR USE – *ADD-Vantage*™ Vial

To Open:

Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container: USE ASEPTIC TECHNIQUE

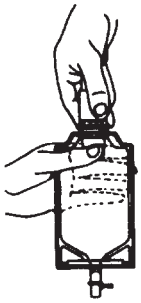
1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (SEE FIGURE 1.), then pull straight up to remove the cap. (SEE FIGURE 2.)
   NOTE: Once the breakaway cap has been removed, do not access vial with syringe.
   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately ½ turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.
   NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)
3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Fig. 1

Fig. 2

Fig. 3

Fig. 4



To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.
5. Immediately prior to administration, confirm that the contents of the vial have been dissolved by observing the inner cap/stopper in the flexible container.

Fig. 5

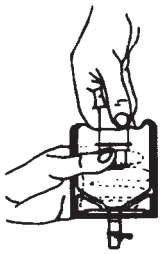


Fig. 6

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MICROBIOLOGY

The *in vitro* activity of ceftazidime against various Gram-positive and Gram-negative aerobic and anaerobic organisms is shown in Table 3.

Table 3

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

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

Table 3 (continued)

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

Inoculum Effect

The MIC's of ceftazidime against aerobic bacteria are not significantly affected by changes in inoculum size in the range 10^2 to 10^5 CFU/mL. However, increasing the inoculum size to 10^7 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 10^5 to 10^7 CFU/mL, MIC values increased 8- to 128-fold. The ratios of MBC to MIC are shown in Table 4.

Table 4: Ceftazidime MIC's and MBC's Tested against 110 Bacterial Isolates from 11 Genera

Organisms (No. Tested)	MIC (µg/mL)		MBC (µg/mL)		Ratio of Means
	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-*	0.15	0.06	0.20	0.12	1.33
Morganella spp. (20)					
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 5.

Table 5

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

Name	Source	CFZ	CFX	CAZ
PSE-2	*P. aeruginosa*	30	16	30
PSE-3	*P. aeruginosa*	41	<1	8
PSE-4	*P. aeruginosa*	10	1	2
S and A	*P. aeruginosa*	112	15	<1
PC-1	*S. aureus*	115	0	30

Abbreviations: CFZ, cefazolin; CFX, cefoxitin; CAZ, ceftazidime.

Development of Resistance

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

Susceptibility Testing

The standard single-disc susceptibility test (using the 30µg ceftazidime disc) and dilution susceptibility should be interpreted according to the criteria in Table 6.

Table 6

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

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

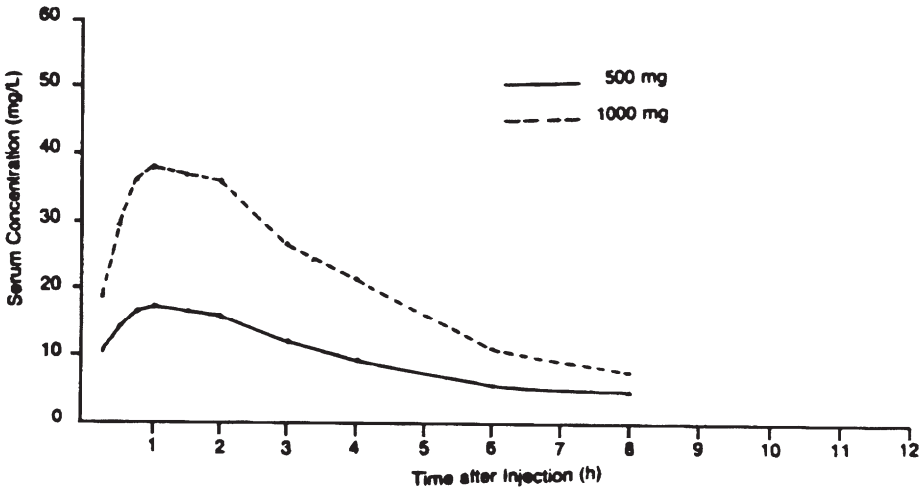
PHARMACOLOGY

Human

Intramuscular Injection:

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

Figure 1



The average urinary concentration, following 500 mg i.m. administration to 6 patients, was 2,100 mg/L. Mean urinary recovery over 24 hours ranged from 78.9% of a 1g i.m. dose to 84.6% of a 500 mg i.m. dose.

Figure 2

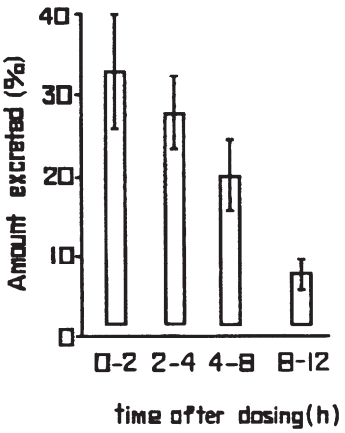


Table 7: Pharmacokinetic Profile of Ceftazidime after i.m. Injection

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

No drug accumulation was noted after repeated single intramuscular dosing over 10 days. Pharmacokinetic parameters remained unchanged. The addition of lidocaine did not alter the kinetics (see Table 7).

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

Figure 3

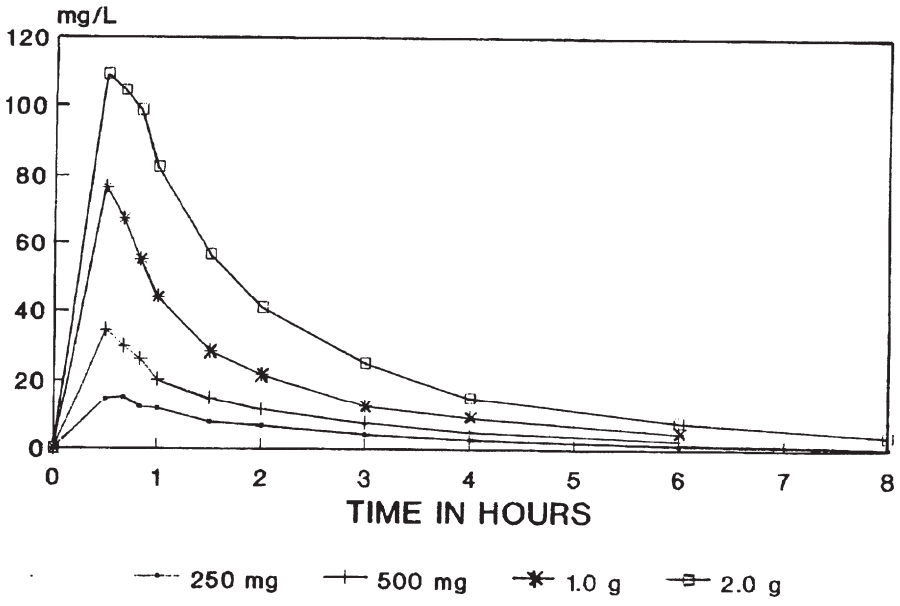
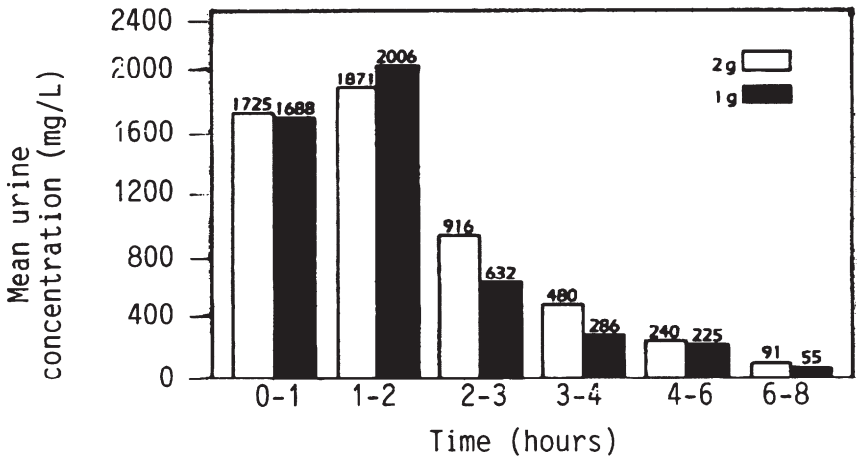


Figure 4



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

Table 8: Average pharmacokinetic parameters of ceftazidime after iv infusion

Dose/ Route (IV - Infusion)	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 24h (%)	Renal Clearance (mL/min)	Plasma Clearance (mL/min)
250 mg	15.2	16.2	33.5	1.5	77.5	100	126
500 mg	34.5	20.2	68.7	1.9	63.2	77	122
1 g	76.8	19.7	134.6	1.8	69.6	88	126
2 g	114.2	22.5	235.6	1.8	53.8	79	146

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

Excretion and Metabolism

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

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

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

Protein Binding

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

Tissue Concentrations

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

Table 9: Ceftazidime Concentration in Tissues and Body Fluids

Tissue or Fluid	Dose/ Route	No. of Patients	Time of Sample Post-Dose	Average Tissue or Fluid Level (µg/mL or µg/g)
Urine	500 mg IM	6	0 - 2 hr	2100
	2 g IV	6	0 - 2 hr	12000
Bile	2 g IV	3	90 min.	36.4
Synovial fluid	2 g IV	13	2 hr	25.6
Peritoneal fluid	2 g IV	8	2 hr	48.6
Sputum	1 g IV	8	1 hr	9
Cerebrospinal fluid (inflamed meninges)	2 g q 8h IV	5	120 min.	9.4
Aqueous humor	2 g IV	13	1 - 3 hr	11
Blister fluid	1 g IV	7	2 - 3 hr	19.7
Lymphatic fluid	1 g IV	7	2 - 3 hr	23.4
Bone	2 g IV	8	0.67 hr	31.1
Heart muscle	2 g IV	35	30 - 280 min.	12.7
Skin	2 g IV	22	30 - 180 min.	6.6
Skeletal muscle	2 g IV	35	30 - 280 min.	9.4
Myometrium	2 g IV	31	1 - 2 hr	18.7

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

Factors Influencing Pharmacokinetics

Sex:

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

Pregnancy:

Intramuscular injections to pregnant women scheduled for abortions resulted in serum levels of ceftazidime approximately 50% lower than similar doses given to non-pregnant females.

Age:

Neonates and Infants

Fifty-three neonates and infants (1 day to 12 months of age) were administered ceftazidime as a single intravenous bolus injection at a mean dose of 31 mg/kg (25.0 - 35.7 mg/kg) in addition to other antimicrobial therapy. Serum levels are presented in Table 10. The mean serum half-life for babies ages 2 months or younger was prolonged (4.2 ± 1.6 h). Those aged greater than 2 months had a half-life of 2.0 ± 0.6h.

Table 10

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

In another study pediatric patients (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 Serum Conc. (mg/L)	Serum half-life (h)	Vol. of Distri-bution (L/Kg)	Plasma Clearance (mL/min/Kg)
A	8	22.5	15	37.8	1.65	0.73	5.03
B	5	57.4	50	186.4	1.72	0.52	3.75

Elderly

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

Impaired Renal Function

The relationship between serum elimination half-life and glomerular filtration rate (GFR) is curvilinear. The half-life increases steeply at GFR's less-than 50mL/min/1.73m^2 (see Figure 5).

Figure 5

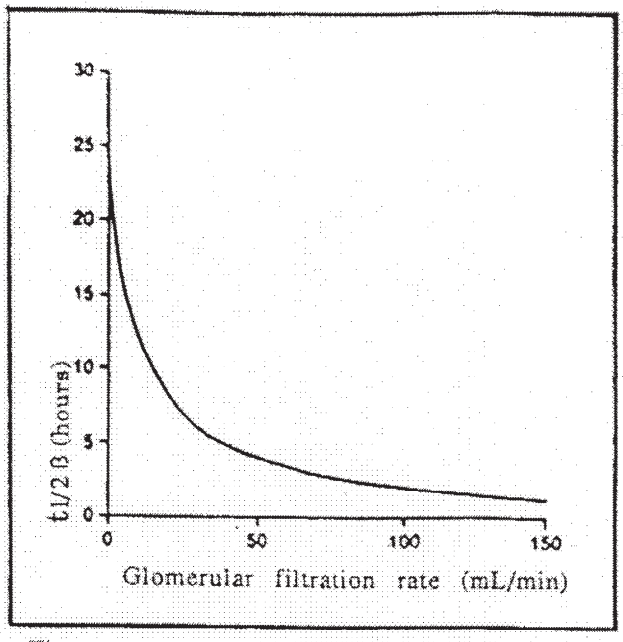


Fig. 5 Relationship between the ceftazidime half-life of elimination (t1/2ß) and glomerular filtration rate.

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

Table 12: Mean Pharmacokinetic Parameters after lg Ceftazidime iv

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

C_o = Fictive serum concentration at time zero
AUC_t = Area under the serum concentration/time curve to infinity
B = Serum elimination rate constant
$T_{1/2B}$ = Serum half-life
V_{dB} = Volume of distribution during the post-distributive phase
U_R = Urinary recovery over 24h

In another study, six normal volunteers and four end-stage renal disease (ESRD) patients on hemodialysis were administered a single lg 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 50mL/min, while the total body clearance in the normals ranged from 98 to 184 mL/min.

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

Cystic Fibrosis

The pharmacokinetics of an intravenous infusion (20 min) of 50 mg/kg ceftazidime were studied in 10 patients (20.8 ± 4.8 yr, 4 female, 6 males) with cystic fibrosis and 10 normal volunteers (21.6 ± 1.9 yr, 3 females, 7 males). Serum elimination half-lives were 1.76 ± 0.21h in controls and 1.50 ± 0.19h in cystic fibrotics. Total body clearance was 41.9% greater in the cystic fibrosis group (142.4 ±16.9mL/min/1.73m^2) compared to controls (100.5 ± 10.3mL/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 ± 11.6mL/min/1.73m^2 respectively).

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

TOXICOLOGY

Acute Toxicity

The effects produced by single doses of ceftazidime have been studied in mice, rats, dogs, and Rhesus monkeys using intravenous and subcutaneous administration. The results are shown in Table 13.

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

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

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

Subchronic Toxicity

Rats:

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

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

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

Table 13: Acute Toxicity Studies

Species	Animals M	Animals F	Duration of Study (Days)	Administration	Dose Levels (mg/kg)	Signs of Toxicity	Results (LD_{50} mg/kg)
Ceftazidime							
Mouse	50	50	14	Intravenous	516 - 5163	Leg weakness and tremors	> 5163
Rat	30	30	14	Intravenous	1033 or 2581	Leg weakness	> 2581
Rat	-	30	14	Subcutaneous	1033 or 2581	None	LD_O > 2581
Dog	1	1	14	Intravenous	1500	Vomiting and salivation	LD_O > 1500
Rhesus Monkey	1	1	14	Intravenous	1500	Soft stools and diarrhea	LD_O > 1500
Mouse	-	20	14	Intravenous	2000[a]	Leg weakness, poor grooming	> 2000
Mouse	-	20	14	Intravenous	2000[b]	Leg weakness, poor grooming, hypoactivity	> 2000

a Glaxo ceftazidime

b Lilly ceftazidime

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

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

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

Chronic Toxicity

Rats:

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

Dogs:

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

Mutagenicity Studies

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

Reproduction and Teratology Studies

Teratology:

Mouse:

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

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

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

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

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

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

Results of the examination of the uterine contents are presented in Table 14 (see below).

Table 14

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

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

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

No significant adverse reactions were seen during pregnancy with the exception of the high dose (2,500 mg/kg) group which produced large quantities of soft wet feces. During the second and third week of the lactation period the dams treated with ceftazidime gained weight more rapidly

than in the control group and this effect was dose-related. At termination (day 21 postpartum), pups in the high-dose group (2,500 mg/kg) had gained significantly ($p < 0.05$) less weight (47.95 g) than controls (52.23 g). This was observed through lactation.

Fertility and Reproduction

Groups of 20 male and 40 female mice received sc injections of either saline or ceftazidime daily through gametogenesis and mating and in the case of females through pregnancy. Males were treated for 60 days prior to mating and females for 14 days. Half of the pregnant mice were sacrificed on day 18 of pregnancy while the remainder were allowed to litter and rear their young for 21 days. Two pups from each litter were retained to study any effects on fertility of the F_1 generation.

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

A high incidence of skeletal variants seen in all of the groups was due to the large number of fetuses with supernumerary ribs. The incidence of bone variants was significantly higher in the high-dose group (6500 mg/kg/day) as compared to the controls. Throughout lactation, the mean pup weights (F_1 generation) for the mid- and high-dose groups (3250 and 6500 mg/kg/day) were lower than the corresponding control values but the differences did not achieve statistical significance.

There were no significant differences in pregnancy rates for any of the F_1 generation groups.

The mean pup weights (F_2 generation) during lactation in the high-dose group were consistently less than those of controls but the differences were not statistically significant and this was attributed to the lighter weights of the dams.

Miscellaneous Studies

Nephrotoxicity Studies in Rabbits:

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

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

In female mice single sc doses of 8,000 and 10,000 mg/kg ceftazidime produced coagulative necrosis of inner cortical tubules. Male rats given ≥ 4,000 mg/kg produced acute tubular necrosis (inner cortex) and elevations in serum urea nitrogen.

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

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

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

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

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

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