

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CEFTAZIDIME for Injection and DEXTROSE Injection safely and effectively. See full prescribing information for CEFTAZIDIME for Injection and DEXTROSE Injection.

CEFTAZIDIME for injection and DEXTROSE injection, for intravenous use

Initial U.S. Approval: 1985

RECENT MAJOR CHANGES

Warnings and Precautions, Neurologic Adverse Reactions (5.4) 10/2021

INDICATIONS AND USAGE

Ceftazidime for Injection and Dextrose Injection is a cephalosporin antibacterial indicated in the treatment of the following infections caused by susceptible isolates of the designated microorganisms: Lower respiratory tract infections (1.1); skin and skin-structure infections (1.2); bacterial septicemia (1.3); bone and joint infections (1.4); gynecologic infections (1.5); intra-abdominal infections (1.6); central nervous system infections (1.7).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftazidime for Injection and Dextrose Injection and other antibacterial drugs, Ceftazidime for Injection and Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.8)

DOSAGE AND ADMINISTRATION

For intravenous use only over approximately 30 minutes. (2)

Recommended Dosage Schedule for Creatinine Clearance greater than 50 mL/min		
Adults	Dose	Frequency
Bone and joint infections	2 grams IV	every 12hr
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg* 1 gram IV	every 8hr
Serious gynecologic and intra-abdominal infections	2 grams IV	every 8hr
Meningitis	2 grams IV	every 8hr
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	every 8hr

* Use this formulation of ceftazidime only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 1 g in 50 mL and 2 g in 50 mL in a DUPLEX® Container (3)

CONTRAINDICATIONS

- Hypersensitivity to ceftazidime or other cephalosporin class antibacterials, penicillins, or other beta-lactam antibacterials (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Include anaphylaxis and serious skin reactions. Cross-hypersensitivity may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug. (5.1)
- Clostridioides difficile*-associated diarrhea: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.3)
- Neurologic Adverse Reactions: Seizures and other neurological adverse reactions may occur, especially in patients with renal impairment. Adjust dosage in patients with renal impairment. (2.3, 5.4)

ADVERSE REACTIONS

- The most common adverse reactions occurring in less than 2% of patients include: hypersensitivity reactions, gastrointestinal symptoms, and central nervous system reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-854-6851 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Aminoglycosides: Increased potential of nephrotoxicity and ototoxicity. (7.1)
- Chloramphenicol: Has been shown to be antagonistic to beta-lactam antibacterials, including ceftazidime. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatric Use: To prevent unintentional overdose, this product should only be used in pediatric patients who require the full 1 g or 2 g dose of ceftazidime. (2.2, 8.4)

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Revised: 10/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Lower Respiratory Tract Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of lower respiratory tract infections, including pneumonia, caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp.; *Haemophilus influenzae*, including ampicillin-resistant isolates; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus mirabilis*; *Escherichia coli*; *Serratia* spp.; *Citrobacter* spp.; *Streptococcus pneumoniae*; and *Staphylococcus aureus* (methicillin-susceptible isolates).

1.2 Skin and Skin-structure Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of skin and skin-structure infections caused by *Pseudomonas aeruginosa*; *Klebsiella* spp.; *Escherichia coli*; *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus*; *Enterobacter* spp.; *Serratia* spp.; *Staphylococcus aureus* (methicillin-susceptible isolates); and *Streptococcus pyogenes* (group A beta-hemolytic streptococci).

1.3 Bacterial Septicemia

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of bacterial septicemia caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Haemophilus influenzae*, *Escherichia coli*, *Serratia* spp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible isolates).

1.4 Bone and Joint Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of bone and joint infections caused by *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., and *Staphylococcus aureus* (methicillin-susceptible isolates).

1.5 Gynecologic Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of gynecologic infections, including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli*.

1.6 Intra-abdominal Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of intra-abdominal infections, including peritonitis caused by *Escherichia coli*, *Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible isolates) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many isolates of *Bacteroides fragilis* are resistant).

1.7 Central Nervous System Infections

Ceftazidime for Injection and Dextrose Injection is indicated for the treatment of central nervous system infections, including meningitis, caused by *Haemophilus influenzae* and *Neisseria*

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

1.8 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftazidime for Injection and Dextrose Injection and other antibacterial drugs, Ceftazidime for Injection and Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Adult and Pediatric Patients (Who Require the Full Adult Dose)

Ceftazidime for Injection and Dextrose Injection in the DUPLEX® Container should be used only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. Ceftazidime for Injection and Dextrose Injection should be administered intravenously (IV) over approximately 30 minutes.

The guidelines for dosage of Ceftazidime for Injection and Dextrose Injection are listed in Table 1. The following dosage schedule is recommended.

Table 1: Recommended Dosage Schedule for Creatinine Clearance greater than 50 mL/min		
Adults	Dose	Frequency
Bone and joint infections	2 grams IV	every 12hr
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg*- 1 gram IV	every 8hr
Serious gynecologic and intra-abdominal infections	2 grams IV	every 8hr
Meningitis	2 grams IV	every 8hr
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	every 8hr

* Use this formulation of ceftazidime only in patients who require the entire 1 or 2 gram dose and not any fraction thereof.

2.2 Pediatric Patients

Ceftazidime for Injection and Dextrose Injection in the DUPLEX® Container is designed to deliver a 1 g or 2 g dose of ceftazidime. To prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of ceftazidime [see *Use in Specific Populations* (8.4)]

2.3 Patients with Renal Impairment

Ceftazidime for Injection and Dextrose Injection in the DUPLEX® Container is designed to deliver a 1 g or 2 g dose of ceftazidime. To prevent unintentional overdose, this product should not be used in patients with creatinine clearance less than or equal to 15 mL/min who require less than a 1 g dose of ceftazidime.

In patients with impaired renal function (creatinine clearance less than or equal to 50 mL/min), it is recommended that the dosage of ceftazidime be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 gram of Ceftazidime for Injection and Dextrose Injection may be given. An estimate of creatinine clearance should be made to determine the appropriate maintenance dosage. The recommended dosage is presented in Table 2.

Table 2: Recommended Maintenance Dosages of Ceftazidime for Injection and Dextrose Injection in Renal Insufficiency		
Creatinine Clearance (mL/min)	Recommended Unit Dose of Ceftazidime for Injection and Dextrose Injection	Frequency of Dosing
50-31	1 gram	every 12hr
30-16	1 gram	every 24hr

NOTE: IF THE DOSE RECOMMENDED IN TABLE 1 ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 2, THE LOWER DOSE SHOULD BE USED.

When only serum creatinine is available, the following formula (Cockcroft's equation)¹ may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

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

Females: 0.85 x above value

In patients with severe infections who would normally receive 2 grams IV every 8hr of Ceftazidime for Injection and Dextrose Injection were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency may be increased appropriately. Further dosing should be determined by therapeutic monitoring, severity of the infection, and susceptibility of the causative organism.

The creatinine clearance should be adjusted for body surface area or lean body mass, and the dosing frequency should be reduced in cases of renal insufficiency.

In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period.

2.4 Preparation for Use of Ceftazidime for Injection and Dextrose Injection in DUPLEX® Container

This reconstituted solution is for intravenous use only.

Do not use plastic containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

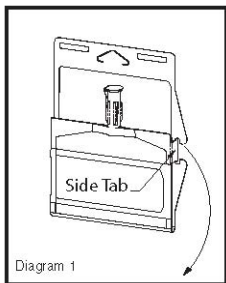
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use only if solution is clear and container and seals are intact.

DUPLEX® Container Storage

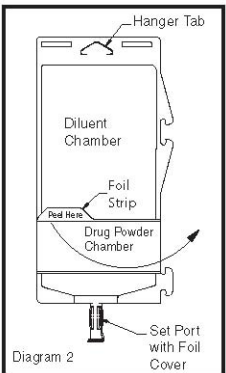
- To avoid inadvertent activation, the DUPLEX® Container should remain in the folded position until activation is intended.

Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. Use care to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX® Container (*see Diagram 1*).



- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber (*see Diagram 2*).

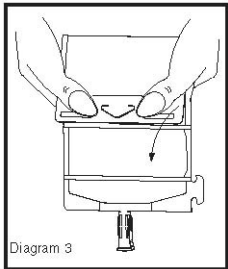


- Protect from light after removal of foil strip.

Note: If foil strip is removed, the container should be re-folded and the side tab latched until ready to activate. The product must then be used within 7 days, but not beyond the labeled expiration date.

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX® Container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber (see *Diagram 3*).

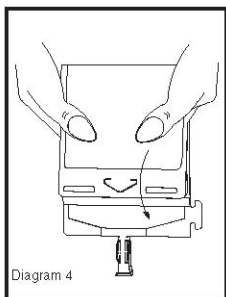


- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

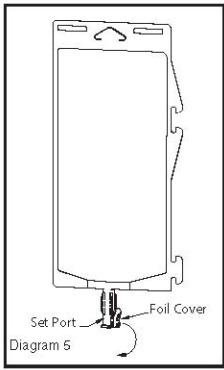
Note: Following reconstitution (activation), product must be used within 12 hours if stored at room temperature or within 3 days if stored under refrigeration.

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX® Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port (see *Diagram 4*).



- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be compromised.
- Using aseptic technique, peel foil cover from the set port and attach sterile administration set (see *Diagram 5*).



- Refer to directions for use accompanying the administration set.

Important Administration Instructions

- Do not use in series connections.
- Do not introduce additives into the DUPLEX® Container.
- Administer Ceftazidime for Injection USP and Dextrose Injection USP intravenously over approximately 30 minutes.
- Discard unused portions of solutions.
- Intermittent intravenous infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of Ceftazidime for Injection and Dextrose Injection, it is advisable to discontinue the other solution.
- Vancomycin solution exhibits a physical incompatibility when mixed with a number of drugs, including ceftazidime. The likelihood of precipitation with ceftazidime is dependent on the concentrations of vancomycin and ceftazidime present. It is therefore recommended, when both drugs are to be administered by intermittent IV infusion, that they be given separately, flushing the IV lines (with 1 of the compatible IV fluids) between the administration of these 2 agents.

Note: Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit. Solutions of Ceftazidime for Injection and Dextrose Injection should not be added to solutions of aminoglycoside antibacterials because of potential inactivation. If concurrent therapy with Ceftazidime for Injection and Dextrose Injection and an aminoglycoside is indicated, each of these antibacterials should be administered separately to the same patient.

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

3 DOSAGE FORMS AND STRENGTHS

Dual-chamber, single-dose container:

- 1 g ceftazidime for injection USP and 50 mL of 5% dextrose injection USP
- 2 g ceftazidime for injection USP and 50 mL of 5% dextrose injection USP

4 CONTRAINDICATIONS

Hypersensitivity Reactions to Ceftazidime or the Cephalosporin Class of Antibacterials, Penicillins, or Other Beta-lactam Antibacterials

Ceftazidime for Injection and Dextrose Injection is contraindicated in patients who have a history of immediate hypersensitivity reactions (e.g., anaphylaxis, serious skin reactions) to ceftazidime products or the cephalosporin class of antibacterial drugs, penicillins, or other beta-lactam antibacterial drugs. [see *Warnings and Precautions* (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions to Ceftazidime, Cephalosporins, Penicillins, or Other Drugs

Immediate hypersensitivity reactions to ceftazidime have been reported. Careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions with cephalosporins or penicillins. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterials 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 and Dextrose Injection occurs, discontinue the drug.

5.2 Hemolytic Anemia

An immune mediated hemolytic anemia has been observed in patients receiving cephalosporin class antibacterials including ceftazidime. Severe cases of hemolytic anemia, including fatalities, have been reported during treatment with cephalosporin class antibacterials in both adults and children. If a patient develops anemia while on ceftazidime, the diagnosis of a cephalosporin associated anemia should be considered and ceftazidime stopped until the etiology is determined.

5.3 *Clostridioides difficile*-associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ceftazidime products, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.4 Neurologic Adverse Reactions

Seizures, nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonus have been reported in patients treated with ceftazidime, including Ceftazidime for Injection and Dextrose Injection particularly in the setting of renal impairment. Adjust

dosing based on creatinine clearance in patients with renal impairment [see *Dosage and Administration* (2.3)].

5.5 Hypersensitivity to Dextrose-containing Products

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of dextrose containing products. These reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose). The reactions have also been reported when corn-derived dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products.

5.6 Risk of Development of Drug-resistant Bacteria

Prescribing Ceftazidime for Injection and Dextrose Injection in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of Ceftazidime for Injection and Dextrose Injection may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

5.7 Drug/Laboratory Test Interactions

Prothrombin Time

Many cephalosporins, including ceftazidime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Urinary Glucose

The administration of Ceftazidime for Injection and Dextrose Injection may result in a false-positive reaction with glucose in the urine when using glucose tests based on Benedict's copper reduction reaction that determine the amount of reducing substances like glucose in the urine. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

5.8 Inadvertent Intra-arterial Administration

Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.

6 ADVERSE REACTIONS

The following serious adverse reactions to ceftazidime are described below and elsewhere in the labeling:

- Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]
- Hemolytic Anemia [see *Warnings and Precautions* (5.2)]
- *Clostridioides difficile*-associated diarrhea [see *Warnings and Precautions* (5.3)]
- Neurological Adverse Reactions [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions were reported in less than or equal to 2% of patients from clinical trials:

- Local reactions including phlebitis and inflammation at the site of injection.
- Hypersensitivity reactions including pruritus, rash, fever and immediate reactions, generally manifested by rash and/or pruritus. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibacterial drugs, including ceftazidime. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported.
- Gastrointestinal reactions including diarrhea, nausea, vomiting, and abdominal pain. The onset of pseudomembranous colitis symptoms may occur during or after treatment. [see *Warnings and Precautions* (5.3)]
- Central nervous system adverse reactions included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including ceftazidime. In addition, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonus have been reported in patients with renal impairment treated with unadjusted dosing regimens of ceftazidime [see *Warnings and Precautions* (5.4)]
- Hematologic reactions including cases of hemolytic anemia have been reported. [see *Warnings and Precautions* (5.2)]
- Other adverse reactions include candidiasis (including oral thrush) and vaginitis.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of ceftazidime. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to readily estimate their frequency or establish a causal relationship to drug exposure.

- Anaphylaxis, allergic reactions, which, in rare instances, were severe (e.g., cardiopulmonary arrest), urticaria.
- Nephropathy, which may be severe (e.g., renal failure).
- Hyperbilirubinemia, jaundice.
- Pain at the injection site.

6.3 Cephalosporin-class Adverse Reactions

In addition to the adverse reactions listed above that have been observed in patients treated with ceftazidime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterials:

- Adverse Reactions: hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, and pancytopenia.
- Altered Laboratory Tests: Prolonged prothrombin time, false-positive test for urinary glucose. [see *Warnings and Precautions* (5.7)]

7 DRUG INTERACTIONS

7.1 Aminoglycosides

Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with Ceftazidime for Injection and Dextrose Injection because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterials. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

7.2 Chloramphenicol

Chloramphenicol has been shown to be antagonistic to beta-lactam antibacterials, including ceftazidime, based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. Due to the possibility of antagonism *in vivo*, particularly when bactericidal activity is desired, this drug combination should be avoided.

7.3 Drug/Laboratory Test Interactions

The administration of ceftazidime may result in a false-positive reaction for glucose in the urine with certain methods. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used [see *Warnings and Precautions* (5.7)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published prospective cohort studies, case series and case reports over several decades with cephalosporin use, including ceftazidime, in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Ceftazidime crosses the placenta. No adverse developmental effects were observed in pregnant rats and rabbits administered ceftazidime during organogenesis by subcutaneous or intramuscular injection, at approximately 5 and 0.6 times, respectively, the maximum recommended human dose (MRHD) (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from case-control studies and case reports over several decades have not identified an association with cephalosporin use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Published literature shows that ceftazidime crosses the placenta. There were no adverse effects on fetal development in pregnant mice or rabbits administered ceftazidime during organogenesis by subcutaneous or intramuscular injection at doses of 6.5 g/kg/day and 0.2 g/kg/day (approximately 5 and 0.6 times the MRHD based on body surface area comparison), respectively. The offspring of treated mice grew normally until weaning. Ceftazidime administered subcutaneously to pregnant and lactating mice during gestation and through lactation at 6500 mg/kg/day (approximately 5 times the MRHD) was not associated with any adverse fetal effects or impaired reproduction in first generation offspring.

8.2 Lactation

Risk Summary

Data from published literature report that ceftazidime is present in human milk, but is not expected to accumulate in a breastfed infant. There are no data on the effects of ceftazidime on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ceftazidime for Injection and Dextrose Injection and any potential adverse effects on the breastfed child from Ceftazidime for Injection and Dextrose Injection or from the mother's underlying condition.

8.3 Females and Males of Reproductive Potential

Infertility

Male

Limited animal data suggests that ceftazidime may impair sperm motility [see *Nonclinical Toxicology (13.1)*]. There are no reported effects of ceftazidime upon human male or female fertility.

8.4 Pediatric Use

Ceftazidime for injection and Dextrose injection is indicated for the treatment of lower respiratory tract infections, skin and skin structure infections, bacterial septicemia, bone and joint infections, gynecological infections, intra-abdominal infections and central nervous system infections in pediatric patients for whom appropriate dosing with this formulation can be achieved [see *Indications and Usage (1.1-1.7)*] and *Dosage and Administration (2.3)*].

Because of the limitations of the available strengths and administration requirements (i.e., administration of fractional doses is not recommended) of Ceftazidime for Injection and Dextrose Injection, and to avoid unintentional overdose, this is not recommended for use if a dose of Ceftazidime for Injection and Dextrose Injection that does not equal 1 gram or 2 grams is required and an alternative formulation of ceftazidime should be considered [see *Dosage and Administration (2)*].

8.5 Geriatric Use

Of the 2,221 subjects who received ceftazidime in 11 clinical studies, 824 (37%) were 65 and older while 391 (18%) were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater

susceptibility of some older individuals to drug effects cannot be ruled out. This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration*. (2.3)]

8.6 Patients with Renal Impairment

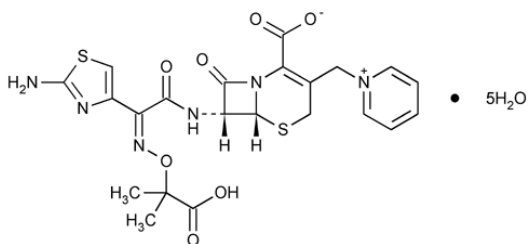
Ceftazidime is substantially eliminated by the kidneys, and the risk of adverse reactions to ceftazidime may be greater in patients with renal impairment due to slower elimination by the kidneys. Consequently, dosage adjustment of Ceftazidime for Injection and Dextrose Injection is required in patients with moderate (CrCl 30 to 50 mL/min) and severe (CrCl 16 to 29 mL/min) renal impairment [see *Dosage and Administration* (2.3) *Warnings and Precautions* (5.4) and *Clinical Pharmacology* (12.3)]

10 OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma [see *Warnings and Precautions* (5.4)]. 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.

11 DESCRIPTION

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibacterial for parenteral administration. The chemical name is 1-[[[(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide, inner salt, 7²-(*Z*)-[O-(1-carboxy-1-methylethyl)oxime]], pentahydrate. It has the following structure:



The molecular formula is $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$, representing a molecular weight of 636.6.

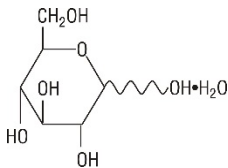
Ceftazidime for Injection USP is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/g of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/g of ceftazidime activity.

Ceftazidime for Injection USP in sterile crystalline form is supplied in the DUPLEX® Container equivalent to 1 g or 2 g of anhydrous ceftazidime. The pH of freshly constituted solutions usually ranges from 5 to 7.5.

The diluent chamber contains 50 mL of 5% Dextrose Injection USP.

Solutions of Ceftazidime for Injection USP and Dextrose Injection USP range in color from light yellow to amber. The solution is intended for intravenous (IV) use only. The pH of solutions ranges from 5 to 7.5. Dextrose Injection USP is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

Hydrous Dextrose USP has the following structural formula:



The molecular formula is C₆H₁₂O₆•H₂O, representing a molecular weight of 198.17.

After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use. When reconstituted, the osmolality of the reconstituted solution of Ceftazidime for Injection USP and Dextrose Injection USP is approximately 340 mOsmol/kg for the 1 g dose and approximately 400 mOsmol/kg for the 2 g dose.

The DUPLEX® dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ceftazidime is an antibacterial drug. [see *Clinical Pharmacology* (12.4)]

12.2 Pharmacodynamics

Similar to other beta-lactam antimicrobial agents, the time that the unbound plasma concentration of ceftazidime exceeds the MIC of the infecting organisms has been shown to best correlate with efficacy in animal models of infection. However, the pharmacokinetic/pharmacodynamic relationship for ceftazidime has not been evaluated in patients.

12.3 Pharmacokinetics

After IV administration of 500 mg and 1 g doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 and 90 mcg/mL, respectively, were achieved. After IV infusion of 500 mg, 1 g, and 2 g doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42, 69, and 170 mcg/mL, respectively, were achieved. The average serum concentrations following IV infusion of 500 mg, 1 g, and 2 g doses to these volunteers over an 8-hour interval are given in Table 3.

Ceftazidime IV Dose	Serum Concentrations (mcg/mL)				
	0.5 hr	1 hr	2 hr	4 hr	8 hr
500 mg	42	25	12	6	2
1 g	60	39	23	11	3
2 g	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following IV administration was approximately 1.9 hours. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple IV doses of 1 and 2 g every 8 hours for 10 days.

Distribution

Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. Therapeutic concentrations of ceftazidime are achieved in the following body tissues and fluids outlined in Table 4.

Tissue or Fluid	Dose/Route	No. of Patients	Time of Sample Postdose	Average Tissue or Fluid Level (mcg/mL or mcg/g)
Urine	2 g IV	6	0-2 hr	12,000.0
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	9.0
Cerebrospinal fluid	2 g every 8hr IV	5	120 min	9.8
(inflamed meninges)	2 g every 8hr IV	6	180 min	9.4
Aqueous humor	2 g IV	13	1-3 hr	11.0
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

Metabolism

Excretion

After the IV administration of single 500 mg or 1 g doses, approximately 50% of the dose appeared in the urine in the first 2 hours. An additional 20% was excreted between 2 and 4 hours after dosing, and approximately another 12% of the dose appeared in the urine between 4 and 8 hours later. The elimination of ceftazidime by the kidneys resulted in high therapeutic concentrations in the urine (Table 4).

The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route. Administration of probenecid before dosing had no effect on the elimination kinetics of ceftazidime. This suggested that ceftazidime is eliminated by glomerular filtration and is not actively secreted by renal tubular mechanisms.

Specific Populations

Hepatic Impairment

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days. Therefore, a dosage adjustment from the normal recommended dosage is not required for patients with hepatic dysfunction, provided renal function is not impaired.

Renal Impairment

Since ceftazidime is eliminated almost solely by the kidneys, its serum half-life is significantly prolonged in patients with impaired renal function. Consequently, dosage adjustments in such patients are suggested. [see *Dosage and Administration* (2.3)]

12.4 Microbiology

Mechanism of Action

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

Mechanism of Resistance

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

Interaction with Other Antimicrobials

In an *in vitro* study, antagonistic effects have been observed with the combination of chloramphenicol and ceftazidime.

Ceftazidime has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section (1):

- Gram-negative bacteria

Citrobacter species
Enterobacter species
Escherichia coli
Haemophilus influenzae
Klebsiella species
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Serratia species

- Gram-positive bacteria
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus agalactiae
- **Anaerobic bacteria**
Bacteroides species (Note: many isolates of *Bacteroides* species are resistant)

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

- Gram-negative bacteria
Acinetobacter species
Citrobacter diversus
Citrobacter freundii
Providencia species (including *Providencia rettgeri*)
Salmonella species
Shigella species
Haemophilus parainfluenzae
Morganella morganii
Neisseria gonorrhoeae
Yersinia enterocolitica
- Gram-positive bacteria
Staphylococcus epidermidis
- Anaerobic bacteria
Clostridium species (Not including *Clostridium difficile*)
Peptostreptococcus species

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: <http://www.fda.gov/STIC>.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis

A mouse micronucleus test and an Ames test were both negative for mutagenic effects.

Impairment of Fertility

Adult male rats administered ceftazidime for 11 consecutive days by intraperitoneal injection at 50 or 250 mg/kg/day (approximately 8 and 40 times the MRHD based on body surface area comparison) resulted in a similar reduction in sperm motility of > 80% compared to controls.

15 REFERENCES

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ceftazidime for Injection USP and Dextrose Injection USP in the DUPLEX® Container is a flexible dual chamber container supplied in two concentrations. The diluent chamber contains approximately 50 mL of 5% Dextrose Injection. After reconstitution, the concentrations are equivalent to 1 g and 2 g of anhydrous ceftazidime.

Ceftazidime for Injection USP and Dextrose Injection USP is supplied sterile and nonpyrogenic in the DUPLEX® Container packaged 24 units per case.

<u>NDC</u>	<u>REF</u>	<u>Dose</u>	<u>Volume</u>
0264-3143-11	3143-11	1 g	50 mL
0264-3145-11	3145-11	2 g	50 mL

Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature.] Protect from light. Freezing solutions of Ceftazidime for Injection USP and Dextrose Injection USP is not recommended.

Not made with natural rubber latex, PVC, or DEHP.

As with other cephalosporins, Ceftazidime for Injection USP and Dextrose Injection USP powder, as well as solutions, tend to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Use only if prepared solution is clear and free from particulate matter.

17 PATIENT COUNSELING INFORMATION

Allergic reactions

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment and discontinuation of Ceftazidime for Injection and Dextrose Injection. Patients should report to their health care provider any previous allergic reactions to ceftazidime, cephalosporins, penicillins, or other similar antibacterials.

Neurologic Adverse Reactions

Advise patients of central nervous system reactions including neurological adverse reactions that could occur with Ceftazidime for Injection and Dextrose Injection use. Instruct patients to inform a healthcare provider at once of any neurological signs and symptoms, including encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures, for immediate treatment, dosage adjustment, or discontinuation of Ceftazidime for Injection and Dextrose Injection.

Diarrhea

Patients should be advised that diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs, including Ceftazidime for Injection and Dextrose Injection, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Ceftazidime for Injection and Dextrose Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ceftazidime for Injection and Dextrose Injection or other antibacterial drugs in the future.

Rx only

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B. Braun Medical Inc.

Bethlehem, PA 18018-3524 USA

1-800-227-2862

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