Fortez™
(Ceftazidime)

Highnoon

COMPOSITION

Fortez 250mg IM/IV Injection: Each pack contains:
Vial: Ceftazidime Pentahydrate equivalent to Ceftazidime 250mg (with Sodium Carbonate)
Ampoule: Sterile water for injection USP 5mL

Fortez 500mg IM/IV Injection: Each pack contains:
Vial: Ceftazidime Pentahydrate equivalent to Ceftazidime 500mg (with Sodium Carbonate)
Ampoule: Sterile water for injection USP 5mL

Fortez 1g IM/IV Injection: Each pack contains:
Vial: Ceftazidime Pentahydrate equivalent to Ceftazidime 1g (with Sodium Carbonate)
Ampoule: Sterile water for injection USP 10mL

Fortez 2g IV Injection: Each pack contains:
Vial: Ceftazidime Pentahydrate equivalent to Ceftazidime 2g (with Sodium Carbonate)
Ampoule: Sterile water for injection USP 10mL

DESCRIPTION

Powder of Injection/Infusion
Ceftazidime is a semisynthetic, third generation, broad-spectrum, beta-lactam antibacterial drug for parenteral administration. Fortez is a sterile, dry-powdered mixture of ceftazidime pentahydrate and sodium carbonate. When reconstituted, mixture provide solution of ceftazidime sodium.

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

Gram-negative Bacteria
Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella species, Haemophilus influenzae, 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)

Efficacy of ceftazidime in treating clinical infections due to these microorganisms has not been established:

- 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), Pepto streptococcus species.

PHARMACOKINETICS

Ceftazidime is given by injection as the sodium salt or in solution with arginine. Mean peak plasma concentration of 17 and 39 micrograms/mL have been reported about 1 hour after intramuscular doses of 0.5 and 1 gram of ceftazidime respectively. Five minutes after intravenous bolus injections of 0.5, 1 and 2 grams of ceftazidime mean plasma concentration of 45, 90 and 170 micrograms/mL respectively, have been reported. The plasma half-life of ceftazidime is about 2 hours, but this prolongs in patients with renal impairment and neonates. Clearance may be enhanced in patients with cystic fibrosis. It is about 10% bound to plasma proteins.
Ceftazidime is widely distributed in body tissues and fluids; therapeutic concentration occurs in the CSF when the meninges are inflamed. It crosses the placenta and distributed into breast milk.
Ceftazidime is passively excreted in bile, although only a small proportion is eliminated by this route. It is mainly excreted by the kidneys, almost exclusively by glomerular filtration; probenecid has little effect on the excretion. About 80% to 90% of a dose appears unchanged in the urine within 24 hours. It is removed by hemodialysis and peritoneal dialysis.

INDICATIONS AND USAGE

It is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Pseudomonas aeruginosa* and other *Pseudomonas spp.; Haemophilus influenzae, including ampicillin-resistant strains; Klebsiella spp.; Enterobacter spp.; Proteus mirabilis; Escherichia coli; Serratia spp.; Citrobacter spp.; Streptococcus pneumonia and Staphylococcus aureus* (methicillin-susceptible strains).
2. **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 strains); and Streptococcus pyogenes* (group A beta-hemolytic streptococci).
3. **Urinary Tract Infections,** both complicated and uncomplicated, caused by *Pseudomonas aeruginosa; Enterobacter spp.; Proteus spp., including Proteus mirabilis and indole-positive Proteus; Klebsiella spp.; and Escherichia coli.*
4. **Bacterial Septicemia** caused by *Pseudomonas aeruginosa, Klebsiella spp., Haemophilus influenzae, Escherichia coli, Serratia spp., Streptococcus pneumoniae, and Staphylococcus aureus* (methicillin-susceptible strains).
5. **Bone and Joint Infections** caused by *Pseudomonas aeruginosa, Klebsiella spp., Enterobacter spp., and Staphylococcus aureus* (methicillin-susceptible strains).
6. **Gynecologic Infections,** including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *Escherichia coli.*
7. **Intra-abdominal Infections,** including peritonitis caused by *Escherichia coli, Klebsiella spp.,* and *Staphylococcus aureus* (methicillin susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides spp.* (many strains of *Bacteroides fragilis* are resistant).
8. **Central Nervous System Infections,** including meningitis, caused by *Haemophilus influenzae, Neisseria meningitides, Pseudomonas aeruginosa, and Streptococcus pneumoniae.*
9. **Prophylaxis for transurethral resection of prostate**
10. **Febrile neutropenia**
11. **Susceptible infections due to sensitive Gram-positive and Gram-negative bacteria,** *caused by Pseudomonas species.*

It may be used alone in cases of confirmed or suspected sepsis. It may also be used concomitantly with other antibacterial drugs, such as aminoglycosides, vancomycin, and clindamycin; in severe and life-threatening infections; and in the immunocompromised patient. When such concomitant treatment is appropriate, prescribing information in the labeling for the other antibacterial drugs should be followed. The dose depends on the severity of the infection and the patient's condition.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftazidime and other antibacterial drugs, it 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.

DOSAGE AND ADMINISTRATION

The usual adult dosage is 1 gram administered intravenously or intramuscularly every 8 to 12 hours. The dosage and route should be determined by the susceptibility of the causative organisms, the severity of infection, and the condition and renal function of the patient.
The following dosage schedule is recommended

Adults	Dose	Frequency
Usual recommended dosage	**1 gram intravenous or intramuscular**	**every 8 to 12 hours**
Uncomplicated urinary tract infections	250 mg intravenous or intramuscular	every 12 hours
Bone and joint infections	2 grams intravenous	every 12 hours
Complicated urinary tract infections	500 mg intravenous or intramuscular	every 8 to12 hours
Uncomplicated pneumonia: mild skin and skin- structure infections	500 mg to 1 gram intravenous or intramuscular	every 8 hours
Serious gynecologic and intra-abdominal infections	2 grams intravenous	every 8 hours
Meningitis	2 grams intravenous	every 8 hours
Very severe life-threatening infections, especially in immunocompromised patients	2 grams intravenous	every 8 hours
Lung infections caused by Pseudomonas spp, in patients with cystic fibrosis with normal renal function	30 to 50 mg/kg intravenous to a maximum of 6 grams per day	every 8 hours
Febrile neutropenia	2 grams intravenous	every 8 hours
Susceptible infection due to gram positive and gram-negative bacteria	1-2 grams intravenous	every 8 hours
Prophylaxis for transurethral resection of prostate	1 gram single dose (intramuscular or intravenous) to be administered up to 30 minutes before procedure and may be repeated if necessary, when catheter removed	
Neonates (aged 8 to 28 days) and weighing ≤ 2 kg	50 mg/kg intravenous	every 8 to 12 hours
Neonates (aged 8 to 28 days) and weighing > 2 kg	50 mg/kg intravenous	every 8 hours
Neonates aged ≤ 7 days (irrespective of body weight)	50 mg/kg intravenous	every 12 hours
Infants and children (1 month-12 years)	30 to 50 mg/kg intravenous to a maximum of 6 grams per day	every 8 hours

Impaired Hepatic Function
No adjustment in dosage is required for patients with hepatic dysfunction.
Impaired Renal Function
Ceftazidime is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] <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 may be given. An estimate of GFR should be made to determine the appropriate maintenance dosage. The recommended dosage is:

Patients with renal insufficiency, the lower dose should be used		
Creatinine Clearance (mL/min)	**Recommended Unit Dose of Ceftazidime**	**Frequency of Dosing**
31 – 50	1 gram	every 12 hours
16 – 30	1 gram	every 24 hours
6 – 15	500 mg	every 24 hours
less than 5	500 mg	every 48 hours

In patients with severe infections who would normally receive 6 grams of Ceftazidime daily 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.
In pediatric patients as for 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. In patients undergoing hemodialysis, a loading dose of 1 gram is recommended, followed by 1 gram after each hemodialysis period. It can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of Ceftazidime may be given, followed by 500 mg every 24 hours. In addition to intravenous use, it can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 L of dialysis fluid.

Administration
Intramuscular Administration
For direct intramuscular injection reconstitute with sterile water for injection. Use 1.0mL, 1.5mL and 3.0mL for 250mg, 500mg and 1g respectively.

Intravenous Administration
The intravenous 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.

For direct intermittent IV administration, constitute Fortez (Ceftazidime), with sterile water for injection. For intravenous injection use sterile water for injection 2.5mL, 5mL and 10mL for 250mg, 500mg and 1g respectively. Slowly inject directly into the vein over a period of 3 to 5 minutes or give through the tubing of an administration set while the patient is also receiving one of the compatible IV fluids.

For IV infusion, constitute the 500mg, 1gram, vial, and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids.

Intermittent IV infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing ceftazidime, it is desirable to discontinue the other solution.

Directions for Proper Use
Not for direct infusion. Using aseptic technique, the container closure may be penetrated only one time using a suitable sterile dispensing set or transfer device that allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage. The withdrawal of container contents should be accomplished without delay. When constituted as directed with sterile water for injection and after constitution, add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids. Solutions of Ceftazidime, like those of most beta-lactam antibacterial drugs, should not be added to solutions of aminoglycoside antibacterial drugs because of potential interaction. However, if concurrent therapy with Ceftazidime and an aminoglycoside is indicated, each of these antibacterial drugs can be administered separately to the same patient.

COMPATIBILITY AND STABILITY

Fortez (Ceftazidime), when constituted as directed with sterile water for injection maintains satisfactory potency for 12 hours at room temperature or for 3 days under refrigeration. It is compatible with the more commonly used IV infusion fluids. Solutions at concentrations between 1 and 40 mg/mL in 0.9% Sodium Chloride Injection; 1/6 M Sodium Lactate Injection; 5% Dextrose Injection; 5% Dextrose and 0.225% Sodium Chloride Injection; 5% Dextrose and 0.45% Sodium Chloride Injection; 5% Dextrose and 0.9% Sodium Chloride Injection; 10% Dextrose Injection; Ringer's Injection, USP; Lactated Ringer's Injection, USP; and 10% Invert Sugar in Water for Injection may be stored for up to 12 hours at room temperature or for 3 days if refrigerated. It is less stable in Sodium Bicarbonate Injection than in other IV fluids. It is not recommended as a diluent. 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. Parenteral drug products should be inspected visually for particulate matter before administration whenever solution and container permit. As with other cephalosporins, Fortez (Ceftazidime) powder, as well as solutions, tend to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

CONTRAINDICATIONS

It is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibacterial drugs.

DRUG INTERACTIONS

- Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibacterial drugs or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs.
- Chloramphenicol has been shown to be antagonistic to beta-lactam antibacterial drugs, including ceftazidime. Due to the possibility of antagonism in vivo, particularly when bactericidal activity is desired, this drug combination should be avoided.
- In common with other antibacterial drugs, ceftazidime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

WARNINGS AND PRECAUTIONS

- Before therapy with Ceftazidime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to ceftazidime, cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in patients with a history of penicillin allergy. If an allergic reaction to Ceftazidime occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.
- Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftazidime, and may range in severity from mild diarrhoea 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 diarrhoea following antibacterial drug 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 drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- Elevated levels of ceftazidime in patients with renal insufficiency can lead to seizures, nonconvulsive status epilepticus encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia.
- High and prolonged serum ceftazidime concentrations can occur from usual 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 patients with renal insufficiency. Elevated levels of ceftazidime in these patients can lead to, seizures, nonconvulsive status epilepticus encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.
- As with other antibacterial drugs, prolonged use of Ceftazidime may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
- Inducible type I beta-lactamase resistance has been noted with some organisms (e.g., Enterobacter spp., Pseudomonas spp., and Serratia spp.). As with other extended-spectrum beta-lactam antibacterial drugs, resistance can develop during therapy, leading to clinical failure in some cases. When treating infections caused by these organisms, periodic susceptibility testing should be performed when clinically appropriate. If patients fail to respond to monotherapy, an aminoglycoside or similar agent should be considered.
- Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal and 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.
- It should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Distal necrosis can occur after inadvertent intra-arterial administration of ceftazidime.
- Prescribing Ceftazidime in the absence of a 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.
- Patients should be counseled that antibacterial drugs, including Ceftazidime, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).
- Diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, 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 drug. If this occurs, patients should contact their physician as soon as possible.
- The administration of ceftazidime may result in a false-positive reaction for glucose in the urine. It is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

ADVERSE REACTIONS

The following are the reported adverse events of Ceftazidime; phlebitis, inflammation at the site of injection, hypersensitivity reactions (pruritus, rash, fever, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, and anaphylaxis), diarrhea, nausea, vomiting, abdominal pain, pseudomembranous colitis, headache, dizziness, paresthesia, seizures, encephalopathy, coma, asterixis, neuromuscular excitability, myoclonia, candidiasis (including oral thrush), vaginitis, hemolytic anemia, eosinophilia, positive Coombs test without hemolysis, thrombocytosis, slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), LDH, GGT, alkaline phosphatase, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine, leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis.
The other additional reported adverse events are; anaphylaxis, allergic reactions, urticaria, pain at injection site, hyperbilirubinemia, jaundice, renal impairment, colitis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage, prolonged prothrombin time, false-positive test for urinary glucose and pancytopenia.

OVERDOSAGE

Ceftazidime overdosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, neuromuscular excitability, and coma. 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.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

Note: Effervescence occurs on addition of water for injection.

PRESENTATION

Fortez 250mg IM/IV Injection
1 vial of 250mg Ceftazidime and 1 ampoule of 5mL sterile water for injection.

Fortez 500mg IM/IV Injection
1 vial of 500mg Ceftazidime and 1 ampoule of 5mL sterile water for injection.

Fortez 1g IM/IV Injection
1 vial of 1g Ceftazidime and 1 ampoule of 10mL sterile water for injection.

Fortez 2g IV Injection
1 vial of 2g Ceftazidime and 1 ampoule of 10mL sterile water for injection.

فورٹیز™
(سیفٹازیڈیم)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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