PROFORT

Vial

Composition

Each vial contains Ceftazidime 1000 mg

Action

Profort is bactericidal in action, exerting its effect by inhibition of enzymes responsible for cell-wall synthesis. A wide range of gram-negative organisms is susceptible to Ceftazidime in *vitro*, including strains resistant to Gentamicin and other aminoglycosides. In addition, Profort has been shown to be active against gram-positive organisms. It is highly stable to most clinically important beta-lactamases, plasmid or chromosomal, which are produced by both gram-negative and gram-positive organisms and, consequently, is active against many strains resistant to ampicillin and other cephalosporins. Profort has been shown to be active against the following organisms both *in vitro* and in clinical infections:

Gram-negative

Pseudomonas aeruginosa.
Pseudomonas spp (including Ps. pseudomallei).
Escherichia coli.
Klebsiella spp (including Klebsiella pneumoniae).
Proteus mirabilis.
Proteus vulgaris.
Morganella morganii (formerly Proteus morganii).
Proteus rettgeri.
Providencia spp.
Enterobacter spp.
Citrobacter spp.
Serratia spp.
Salmonella spp.
Shigella spp.
Yersinia enterocolitica.
Pasteurella multocida.
Acinetobacter spp.
Neisseria gonorrhoeae.
Neisseria meningitidis.
Haemophilus influenzae (including ampicillin resistant strains)
Haemophilus parainfluenzae (including ampicillin resistant strains).

Gram-positive

Staphylococcus aureus (methicillin-sensitive strains)
Staphylococcus epidermidis (methicillin-sensitive strains)
Micrococcus spp.
Streptococcus pyogenes (Group A β-haemolytic streptococci)
Streptococcus Group B (Strept agalactiae).
Streptococcus pneumoniae.
Streptococcus mitis.
Streptococcus spp (excluding Enterococcus (Streptococcus) faecalis).

Anaerobic strains

Peptococcus spp.
Peptostreptococcus spp.
Streptococcus spp.
Propionibacterium spp.
Clostridium perfringens.
Fusobacterium spp.
Bacteroides spp (many strains of Bacteroides fragilis resistant)

Ceftazidime is not active *in vitro* against the following organisms:-
Methicillin-resistant staphylococci.
Enterococcus (Streptococcus) faecalis and many other Enterococci.
Clostridium difficile.
Listeria monocytogenes.
Campylobacter spp.

Pharmacokinetics
Absorption
After intramuscular administration of 500 mg and 1 g of ceftazidime, peak plasma levels of 18 and 37 mg/l respectively are achieved rapidly. Five minutes after intravenous bolus injection of 500 mg, 1 g or 2 g, plasma levels are 46, 87 and 170mg/l, respectively. The kinetics of ceftazidime is linear within the single dose range of 0.5 to 2 g following intravenous or intramuscular dosing.

Distribution
The serum protein binding of ceftazidime is low at about 10%. Concentrations in excess of the MIC for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily, and is excreted in the breast milk. Penetration of the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, concentrations of 4 to 20 mg/l or more are achieved in the CSF when the meninges are inflamed.

Biotransformation
Ceftazidime is not metabolised.

Elimination
After parenteral administration plasma levels decrease with a half-life of about 2 h. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 to 90 % of the dose is recovered in the urine within 24 h. Less than 1 % is excreted via the bile.

<u>Special patient populations</u>
Renal impairment
Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced.

Hepatic impairment
The presence of mild to moderate hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously every 8 hours for 5 days, provided renal function was not impaired.

Elderly
The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeat BID dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Paediatric population
The half-life of ceftazidime is prolonged in preterm and term neonates by 4.5 to 7.5 hours after doses of 25 to 30 mg/kg. However, by the age of 2 months the half-life is within the range for adults.

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

Lower Respiratory Tract Infections

Including pneumonia, caused by Pseudomonas aeruginosa and other Pseudomonas spp.; Haemophilus influenza, including ampicillin-resistant strains; Klebsiella spp.; Enterobacter spp.; *Proteus mirabilis*; *Escherichia coli*; Serratia spp.; Citrobacter spp.;Streptococcus pneumoniae; and *Staphylococcus aureus* (methicillin-susceptible strains).

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).

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.*

Bacterial Septicemia
Caused by *Pseudomonas aeruginosa*; Klebsiella spp., *Haemophilus influenza*, *Escherichia coli*, Serratia spp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible strains).

Bone and Joint Infections
Caused by *Pseudomonas aeruginosa*; Klebsiella spp.; Enterobacter spp.; and *Staphylococcus aureus* (methicillin-susceptible strains).

Gynecologic Infections
Including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by Escherichia coli.

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).

Central Nervous System Infections
Including meningitis caused by *Haemophilus influenza* and *Neisseria meningitidis*. Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae.*

Profort may be used alone in cases of confirmed or suspected sepsis. Profort has been used successfully in clinical trials as empiric therapy in cases where various concomitant therapies with other antibiotics have been used.

Profort may also be used concomitantly with other antibiotics, 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 antibiotics should be followed. The dose depends on the severity of the infection and the patient's condition

Contraindications
Ceftazidime is contraindicated in patients who have shown hypersensitivity to ceftazidime or the cephalosporin group of antibiotics.

Warnings
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 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

occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Ceftazidime, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."
After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile.
Elevated levels of Ceftazidime in patients with renal insufficiency can lead to seizures, encephalopathy, asterixis, and neuromuscular excitability.

Adverse Reactions

Ceftazidime is generally well tolerated. The incidence of adverse reactions associated with the administration of Ceftazidime was low in clinical trials. The most common were local reactions following IV injection and allergic and gastrointestinal reactions. Other adverse reactions were encountered infrequently. No disulfiram like reactions were reported.

The following adverse effects from clinical trials were considered to be either related to Ceftazidime therapy or were of uncertain etiology:

Local Effects

Reported in fewer than 2% of patients, were phlebitis and inflammation at the site of injection.

Hypersensitivity Reactions

Reported in 2% of patients, were pruritus, rash, and fever. Immediate reactions, generally manifested by rash and/or pruritus, occurred in 1 in 285 patients. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporin antibiotics, including Ceftazidime. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastrointestinal Symptoms

Reported in fewer than 2% of patients, were diarrhea, nausea, vomiting, and abdominal pain. The onset of pseudomembranous colitis symptoms may occur during or after treatment.

Central Nervous System Reactions

(less than 1%) included headache, dizziness, and paresthesia. Seizures have been reported with several cephalosporins, including Ceftazidime. In addition, encephalopathy, asterixis, and neuromuscular excitability have been reported in renally impaired patients treated with unadjusted dosing regimens of Ceftazidime.

Less Frequent Adverse Events

(Less than 1%) were candidiasis (including oral thrush) and vaginitis. Hematologic: Rare cases of hemolytic anemia have been reported.

Laboratory Test Changes

Noted during Ceftazidime clinical trials were transient and included: eosinophilia, positive Coombs' test without hemolysis, thrombocytosis, and slight elevations in one or more of the hepatic enzymes, aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), LDH, GGT, and

alkaline phosphatase. As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally. Transient leukopenia, neutropenia, agranulocytosis, thrombocytopenia, and lymphocytosis were seen very rarely.

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 antibiotics:

Adverse Reactions

Urticaria, colitis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemorrhage.

Altered Laboratory Tests

Prolonged prothrombin time, false-positive test for urinary glucose, elevated bilirubin, pancytopenia.

Precautions

General

Ceftazidime has not been shown to be nephrotoxic; however, high and prolonged serum antibiotic 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, encephalopathy, asterixis, and neuromuscular excitability. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms.

As with other antibiotics, prolonged use of Ceftazidime may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If super infection 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 antibiotics, 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.
Ceftazidime 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.

Pregnancy

Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nursing Mothers

Ceftazidime is excreted in human milk in low concentrations. Caution should be exercised when Ceftazidime is administered to a nursing woman.

Drug Interactions

Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics 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 aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when Ceftazidime was given alone in clinical trials.

Chloramphenicol has been shown to be antagonistic to beta-lactam antibiotics, 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.

Drug/Laboratory Test Interactions
The administration of Ceftazidime may result in a false-positive reaction for glucose in the urine when using Clinitest tablets, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Testape) be used.

Dosage and Administrations

Dosage
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 guidelines for dosage of Profort and recommended dosage schedule listed in the table below.

Recommended Dosage Schedule		
Adults	**Dose**	**Frequency**
Usual recommended dosage	**1 gram IV or IM**	**q8-12h**
Uncomplicated urinary tract infections	250 mg IV or IM	q12h
Bone and joint infections	2 grams IV	q12h
Complicated urinary tract infections	500 mg IV or IM	q8-12h
Uncomplicated pneumonia; mild skin and skin-structure infections	500 mg-1 gram IV or IM	q8h
Serious gynecologic and intra-abdominal infections	2 grams IV	q8h
Meningitis	2 grams IV	q8h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams IV	q8h
Lung infections caused by *Pseudomonas* spp. in patients with cystic fibrosis with normal renal function*	30-50 mg/kg IV to a maximum of 6 grams per day	q8h
Neonates (0-4 weeks)	30 mg/kg IV	q12h
Infants and children (1 month-12 years)	30-50 mg/kg IV to a maximum of 6 grams per day†	q8h
***** Although clinical improvement has been shown, bacteriologic cures cannot be expected in patients with chronic respiratory disease and cystic fibrosis.		
† The higher dose should be reserved for immunocompromised pediatric patients or pediatric patients with cystic fibrosis or meningitis.		

Impaired Hepatic Function
No adjustment in dosage is required for patients with hepatic dysfunction.

Impaired Renal Function

Profort is excreted by the kidneys, almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function (glomerular filtration rate [GFR] <50 ml per minute), it is recommended that the dosage of Profort be reduced to compensate for its slower excretion. In patients with suspected renal insufficiency, an initial loading dose of 1 gram of Profort may be given. An estimate of GFR should be made to determine the appropriate maintenance dose. The recommended dosage is presented in the table below

Recommended Maintenance Dosages of Profort in Renal Insufficiency		
NOTE: IF THE DOSE RECOMMENDED IN THE TABLE ABOVE IS LOWER THAN THAT RECOMMENDED FOR PATIENTS WITH RENAL INSUFFICIENCY AS OUTLINED IN TABLE 4, THE LOWER DOSE SHOULD BE USED.		
Creatinine Clearance (ml/min)	**Recommended Profort Unit Dose**	**Frequency of Dosing**
50-31	1 gram	q12h
30-16	1 gram	q24h
15-6	500 mg	q24h
<5	500 mg	q48h

When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function.
Males: Creatinine clearance (ml/min) = [Weight (kg) X (140 - age)] / [72 X serum creatinine (mg/dl)]
Females: 0.85 X male value

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 above table 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.

Profort can also be used in patients undergoing intraperitoneal dialysis and continuous ambulatory peritoneal dialysis. In such patients, a loading dose of 1 gram of Profort may be given, followed by 500 mg every 24 hours. In addition to IV use, Profort can be incorporated in the dialysis fluid at a concentration of 250 mg for 2 l of dialysis fluid.
Note: Generally Profort should be continued for 2 days after the signs and symptoms of infection have disappeared, but in complicated infections longer therapy may be required.

Administration
Profort may be given intravenously or by deep IM injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. Intra-arterial administration should be avoided.

Intramuscular Administration
For IM administration, Profort should be constituted with one of the following diluents: sterile water for injection, bacteriostatic water for injection, or 0.5% or 1% lidocaine hydrochloride injection.

Intravenous Administration
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.

Over Dosage

Ceftazidime over dosage has occurred in patients with renal failure. Reactions have included seizure activity, encephalopathy, asterixis, and neuromuscular excitability. Patients who receive an acute over dosage 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.

Storage

Ceftazidime in the dry state should be stored between 15° and 30 °C (59° and 86 °F) and protected from light.

Presentation

Box of 5 vials