PACKAGE INSERT TEMPLATE FOR CEFTAZIDIME POWDER FOR SOLUTION FOR INJECTION/INFUSION

Brand or Product Name
[Product name] Powder for Solution For Injection/Infusion 250mg, 500mg, 1g, 2g, 3g

Name and Strength of Active Substance(s)
Ceftazidime…….. mg
Ceftazidime Pentahydrate…mg equivalent to …mg Ceftazidime

Product Description
[Visual description of the appearance of the product (eg colour, odour etc)
eg White to off-white caked powder. Upon reconstitution, ceftazidime powder yields a white to off white solution]

Pharmacodynamics
Ceftazidime is a third-generation cephalosporin agent with a broad range of antimicrobial activity, including greater activity than other third-generation agents against Pseudomonas aeruginosa, Serratia marcescens and Acinetobacter.

Ceftazidime possesses the basic beta-propiolactam ring, which is essential for inhibition of bacterial cell wall synthesis.

It is bactericidal against a wide range of gram-negative and gram-positive organisms but is highly stable to clinically important plasmid and chromosomal beta-lactamases produced by these organisms.

It is also active against many strains resistant to ampicillin and other cephalosporins.

Ceftazidime is active *in vitro* against the following organisms:

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 beta-haemolytic streptococci)
Streptococcus Group B (*S. 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

One hour after i.m. administration of 500 mg and 1 g, mean peak serum levels of 18 and 37 mg/1, are achieved respectively. Five minutes after intravenous bolus injection of 500 mg, 1 g or 2 g, mean plasma concentrations are, respectively, 46, 87 and 170 mg/l.
Bioavailability, intramuscular injection: 91%.

Distribution

Therapeutically effective concentrations are still present in the serum 8 to 12 h after either i.v. or i.m. administration. It is about 10% bound to plasma proteins.

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. Therapeutic concentrations occur in the CSF when the meninges are inflamed.

It crosses the placenta and is distributed into breast milk.

Volume of Distribution: 0.28 to 0.4 L/kg.

Metabolism

Ceftazidime is not metabolised in the body.

Elimination

The plasma half-life of ceftazidime is about 2 hours, but this is prolonged in patients with renal impairment and in neonates. Clearance may be enhanced in patients with cystic fibrosis.

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 haemodialysis and peritoneal dialysis.

Special Patient Populations

Elimination of ceftazidime is decreased in patients with impaired renal function and the dose should be reduced.

Indication

Treatment of single or multiple infections caused by susceptible organisms.

May be used alone as first choice drug before the results of sensitivity tests are available.

May be used in combination with an aminoglycoside or most other beta-lactam antibiotics.

May be used with an antibiotic against anaerobes when the presence of Bacteroides fragilis is suspected.

Indications include:

- severe infections e.g.
    - septicaemia, bacteraemia, peritonitis, meningitis
    - infections in immunosuppressed patients
    - infections in patients in intensive care, e.g. infected burns
- respiratory tract infections including lung infections in cystic fibrosis
- ear, nose and throat infections
- urinary tract infections
- skin and soft tissue infections
- gastrointestinal, biliary and abdominal infections
- bone and joint infections
- infections associated with haemo- and peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD).

Recommended Dosage

Dosage depends upon the severity, sensitivity, site and type of infection and upon the age, and renal function of the patient.

Adults
1 to 6 g/day in two or three divided doses by i.v. or i.m. injection.
Urinary tract and less severe infections:

- 500 mg or 1 g every 12 h.

Most infections:

- 1 g every 8 h or 2 g every 12 h.

Very severe infections particularly in immunocompromised patients including those with neutropenia:

- 2 g every eight or 12 h, or 3 g every 12 h.

Fibrocystic adults with pseudomonal lung infections:

- 100 to 150 mg/kg/day in three divided doses.

In adults with normal renal function 9 g/day has been used without ill effect.

Infants and children (greater than 2 months)
30 to 100 mg/kg/day in two or three divided doses.
Doses up to 150 mg/kg/day (maximum 6 g/day) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

Neonates (0 to 2 months)
25 to 60 mg/kg/day in two divided doses.
In neonates, the serum half life of ceftazidime can be three to four times that in adults.

Elderly
In view of the reduced clearance of ceftazidime in acutely ill elderly patients, the daily dosage should not normally exceed 3 g, especially in those over 80 years of age.

Renal Impairment
Ceftazidime is excreted unchanged by the kidneys. Therefore, in patients with impaired renal function, the dosage should be reduced. An initial loading dose of 1 g should be given. Maintenance doses should be based on creatinine clearance:

Recommended maintenance doses of *ceftazidime* in renal insufficiency:

Creatinine Clearance (ml / min)	Approx. Serum creatinine (micromoles / l) (mg / dl)	Recommended unit dose of *ceftazidime* (g)	Frequency of dosing (hourly)
50	150 (<1.7)	Normal dosage	
50 – 31	150–200 (1.7 - 2.3)	1.0	12
30 – 16	200–350 (2.3 - 4.0)	1.0	24
15 – 6	350–500 (4.0 - 5.6)	0.5	24
5	500(5.6)	0.5	48

In patients with severe infections the unit dose should be increased by 50% or the dosing frequency increased. In such patients the ceftazidime serum levels should be monitored and trough levels should not exceed 40 mg/l.

In children the creatinine clearance should be adjusted for body surface area or lean body mass.

Haemodialysis

The serum half-life during haemodialysis ranges from 3 to 5 h.

Following each haemodialysis period, the maintenance dose of *ceftazidime* recommended in the above table should be repeated.

Peritoneal dialysis

Ceftazidime may be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD).

In addition to i.v. use, *ceftazidime* can be incorporated into the dialysis fluid (usually 125 to 250 mg for 2 litres of dialysis solution).

For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units; 1 g daily either as a single dose or in divided doses. For low-flux haemofiltration, follow the dosage recommended under impaired renal function.

For patients on venovenous haemofiltration and venovenous haemodialysis, follow the dosage recommendations in the tables below.

Continuous venovenous haemofiltration dosage guidelines for *ceftazidime*

Residual renal function (creatinine clearance in ml/min)	Maintenance dose (mg) for a ultrafiltration rate (ml/min) of [a]:			
	5	16.7	33.3	50
0	250	250	500	500
5	250	250	500	500
10	250	500	500	750
15	250	500	500	750
20	500	500	500	750

[a-] Maintenance dose to be administered every 12 h.

***Ceftazidime* dosage guidelines during continuous venovenous haemodialysis**

Residual renal function (creatinine clearance in ml/min)	Maintenance dose (mg) for a dialysate in flow rate of [a]:					
	1.0 litre/h			2.0 litres/h		
	Ultrafiltration rate (litre/h)			Ultrafiltration rate (litres/h)		
	0.5	1.0	2.0	0.5	1.0	2.0
0	500	500	500	500	500	750
5	500	500	750	500	500	750
10	500	500	750	500	750	1000
15	500	750	750	750	750	1000
20	750	750	1000	750	750	1000

a- Maintenance dose to be administered every 12 h.

Mode of Administration

Use ceftazidime injection i.v. or by deep i.m. injection. Recommended i.m. injection sites are the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Ceftazidime solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

Contraindications

- Patients with known hypersensitivity to cephalosporin antibiotics.
- Hypersensitivity to ceftazidime or to any of the excipients of the injection.

Warnings and Precautions

Before initiating therapy with ceftazidime, careful inquiry should be made concerning history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other drugs. If an allergic reaction to ceftazidime occurs discontinue the drug. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactams.

As with other broad spectrum antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms (e.g. Candida, enterococci) which may require interruption of treatment or appropriate measures. Hence, continuous monitoring of each patient is necessary.

As with other extended-spectrum cephalosporins and penicillins, some initially susceptible strains of *Enterobacter* spp. and *Serratia* spp. may develop resistance during ceftazidime therapy. When clinically appropriate during therapy of such infections, periodic susceptibility testing should be considered.

Ceftazidime is eliminated via the kidneys, therefore the dosage should be reduced according to the degree of renal impairment. There is a risk for seizures and encephalopathy for patients with renal impairment.

Patients with history of gastrointestinal disease, particularly colitis.

Patients with risk factors for altered prothrombin time; renal or hepatic impairment, poor nutritional status, prolonged course of antibiotic therapy.

Effects on Ability to Drive and Use Machines
None reported.

Interactions with Other Medicaments
Concurrent use of high doses with nephrotoxic drugs may adversely affect renal function.
Unlike that of many other cephalosporins, the renal clearance of ceftazidime is not much affected by probenecid.

Concurrent use of ceftazidime and chloramphenicol may result in decreased ceftazidime effectiveness.

Concurrent use of ceftazidime and combined oral contraceptives may result in decreased contraceptive effectiveness.

Concurrent use of ceftazidime and live typhoid vaccine may result in a decreased immunological response to the typhoid vaccine.

Concurrent use of ceftazidime and warfarin may result in an increased risk of bleeding.

Ceftazidime does not interfere with enzyme-based tests for glycosuria but slight interference may occur with copper reduction methods (Benedict"s, Fehling"s, Clinitest).
Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Statement on Usage During Pregnancy and Lactation
Pregnancy
There are no well-controlled studies of ceftazidime use in pregnant women. The effects, if any, on the developing fetus are unknown; but as with all drugs, ceftazidime should be administered with caution during the early months of pregnancy and early infancy.

Lactation
Ceftazidime is excreted in breast milk in small quantities (in concentrations generally higher than other cephalosporins.) and should be used with caution in breast feeding

Adverse Effects / Undesirable Effects
Blood and lymphatic system disorders
Common: Eosinophilia and thrombocytosis
Uncommon: Leucopenia, thrombocytopenia, neutropenia, prothrombin time increased
Very rare: Lymphocytosis, agranulocytosis, haemolytic anaemia

Gastrointestinal disorders
Common: Diarrhoea
Uncommon: Nausea, vomiting, abdominal pain, and colitis
Very rare: Bad taste

As with other cephalosporins, colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.

General disorders and administration site conditions

Common: Pain and/or inflammation after i.m. injection
Uncommon: Fever

Hepatobiliary disorders

Common: Transient elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SOGT), LDH, GGT and alkaline phosphatase.
Very rare: Jaundice
Not known: Hyperbilirubinemia

Investigations

Common: Positive Coombs test
Uncommon: As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen and/or serum creatinine have been observed.

A positive Coombs test develops in about 5% of patients and may interfere with blood cross matching.

Immune system disorders

Very rare: Anaphylaxis (including bronchospasm and/or hypotension)
Unknown immune hypersensitivity reaction

Infections and infestations

Common: superinfection
Uncommon: Candidiasis (including vaginitis and oral thrush)

Nervous system disorders

Uncommon: Headache and dizziness
Very rare: Paraesthesia
Unknown: Seizure, asterixis

There have been reports of neurological sequelae including tremor, myoclonia, convulsions, encephalopathy, and coma in patients with renal impairment in whom the dose of *ceftazidime* has not been appropriately reduced.

Renal Effect

Uncommon: Serum blood urea nitrogen raised, serum creatinine raised
Unknown: Azotemia**,** glomerular filtration abnormal, glomerular filtration decreased

Skin and subcutaneous tissue disorders

Common: Maculopapular or urticarial rash, injection site pain
Uncommon: Pruritus
Very rare: Angioedema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis
Unknown: pemphigus erythematosus, phototoxicity, rash

Vascular disorders

Common: Phlebitis or thrombophlebitis with i.v. administration

Overdose and Treatment

Symptoms

Acute ingestion of large doses of cephalosporins may result in nausea, vomiting, diarrhea, and abdominal pain. Seizures have developed after parenteral overdose.

Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma.

Treatment

Treatment is symptomatic and supportive.

Activated charcoal may be necessary for patients with underlying renal insufficiency.

Haemodialysis or peritoneal dialysis may reduce the serum levels of ceftazidime.

Incompatibilities

[To add appropriate information based on formulation]

Instructions for Use

[To add appropriate information and graphic]

Storage Conditions

[Store below …. ℃]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]