Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ceftazidime 250 mg Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 291 mg of ceftazidime pentahydrate, equivalent to 250mg of ceftazidime

Excipient: each 250 mg vial of powder contains 30 mg of sodium carbonate

This medicinal product contains 0.57 mmol (or 13 mg) of sodium per vial

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection

The powder is white or off-white

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ceftazidime is indicated for treatment of the following bacterial infections when they are caused by ceftazidime-sensitive bacteria, and only if beta-lactam-antibiotics with a narrower spectrum cannot be used:

- Nosocomial pneumonia
- Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa
- Meningitis caused by aerobic gram-negative microorganisms

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose depends on the degree of severity of the infection, sensitivity and type of infection, and on the age, weight and renal function of the patient.

With normal renal function

Age group	**Infection**	**Normal dose**
Adults	Most indications	1 g every 8 hours (3 g/day) or 2 g every 12 hours (4 g/day)
	Nosocomial pneumonia and infections in patients with neutropaenia	2 g every 8 hours (6 g/day)
	Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa	100-150 mg/kg/day, divided into 3 doses; 9 g/day must not be exceeded

Infants and children aged over two months	Most indications	30-100 mg/kg/day, divided into 2 or 3 doses
	Infected neutropenic paediatric patients, paediatric patients with cystic fibrosis or paediatric patients with meningitis	Up to 150 mg/kg/day (a maximum of 6 g total per day) divided into 3 doses
Neonates and children up to 2 months of age	Most indications	25-60 mg/kg/day divided into 2 doses*

* The plasma half-life of ceftazidime may be 3-4 times the half life in adults

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

The duration of treatment depends on patient response. Generally treatment must continue for at least 48 hours after clinical convalescence.

Impaired renal function

Ceftazidime is not metabolised and only eliminated by glomerular filtration. In patients with impaired renal function (i.e. creatinine clearance ≤ 50 ml/min) the dose should be reduced according to the following table to compensate for the extended elimination. A loading dose of 1000 mg of ceftazidime may be given, followed by a suitable maintenance dose as indicated in the table.

Creatinine clearance ml/min	**Approximate serum creatinine* µmol/l (mg/dl)**	**Recommended single dose of ceftazidime (g)**	**Dosing frequency, indicated in hours**
50-31	150-200 (1.7-2.3)	1	12
30-16	200-350 (2.3-4.0)	1	24
15-6	350-500 (4.0-5.6)	0.5	24
< 5	> 500 (> 5.6)	0.5	48

* These values are for guidance only and cannot accurately predict the renal function of all the patients, particularly in elderly patients where the serum creatinine concentration may be due to an overestimated renal function

In patient with a combination of renal insufficiency and serious infections, particularly in patients with neutropaenia, a single dose, as indicated in the above table, can be increased by 50% or the dosing frequency can be suitably increased. In these patients the plasma concentration of ceftazidime should be monitored, if possible, and the minimum concentration (blood sample taken immediately before the next dose) should not exceed 40 mg/l.

In children with renal insufficiency the creatinine clearance should be adjusted on the basis of body area or mean body weight (without fat) and the dosing frequency should be reduced as for adults.

Patients in haemodialysis

The plasma half-life of ceftazidime under haemodialysis varies from 3-5 hours. The appropriate maintenance dose of ceftazidime should be repeated after each haemodialysis period. In patients with kidney failure, who are undergoing continuous atrio-venous haemodialysis or high-flux haemofiltration in the intensive care department, a dose of 1 g per day is recommended, divided into several doses. In the case of low-flux haemofiltration a dose specified for impaired function is recommended.

In patients who are undergoing venous haemofiltration and venous haemodialysis the dosing recommendations in the tables below must be followed.

Ceftazidime dosing guideline during continuous venous haemofiltration:

Residual renal function (creatinine clearance ml/min)	**Maintenance dose (mg) at an 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] The maintenance dose is administered every 12 hours

Ceftazidime dosing guideline during continuous venous haemodialysis:

Residual renal function (creatinine clearance ml/min)	**Maintenance dose (mg) at a dialysate in-flow rate of[a]**					
	1.0 litre/hour			2.0 litres/hour		
	Ultrafiltration rate (litres/hour)			**Ultrafiltration rate (litres/hour)**		
	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] The maintenance dose is administered every 12 hours

Posology in the case of hepatic insufficiency

No dose adjustment is required unless renal function is also impaired.

Routes of administration

Ceftazidime should be administered intravenously (by bolus injection) or by deep intramuscular injection into a large muscle mass, such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.
For preparation of solution for injection (see section 6.6).

4.3 Contraindications

Hypersensitivity to Ceftazidime or to any other cephalosporin antibiotics.
Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.

4.4 Special warnings and precautions for use

It is recommended that results from bacteria cultures and sensitivity tests are obtained before treatment is initiated. This is particularly important if ceftazidime is used as a monotherapy.

Ceftazidime should be used in combination with another antibiotic when treating infections that are probably due to a mixture of sensitive and resistant strains of bacteria. For example, combination treatment with an antibacterial substance that is active against anaerobic bacteria should be considered if the infection is assumed to be due to aerobic and anaerobic bacteria.

Special care is indicated in patients who have experienced any allergic reaction to penicillins or any other beta-lactam-antibiotics as cross-reactions may occur (for contraindications due to known hypersensitivity reactions see section 4.3).

Sensitive bacterial strains of *Enterobacter* spp. and *Serratia* spp. may develop a resistance during ceftazidime treatment. If it is clinically appropriate during the treatment of such infections, a periodic sensitivity test should be considered.

Antibiotic-associated diarrhoea, colitis and pseudomembranous colitis associated with *Clostridium difficile* have been reported during the use of ceftazidime. These diagnoses should be considered in any patient who develops diarrhoea during or immediately after treatment. Ceftazidime should be discontinued if severe and/or bloody diarrhoea occurs during treatment, or a suitable treatment should be initiated. Peristaltic inhibitors are contraindicated.
Ceftazidime should be used with caution in patients with gastrointestinal diseases, particularly colitis.

Ceftazidime has not been shown to be nephrotoxic. However, the total daily dose should be reduced when ceftazidime is administered to patients with acute or chronic renal insufficiency to avoid possible clinical consequences such as convulsive attacks (see point 4.2).

Cephalosporin antibiotics should be given with caution to patients being treated concomitantly with nephrotoxic drugs, e.g. aminoglycoside antibiotics or strong diuretics (e.g. furosemide), since these combinations may have a negative influence on renal function and have been associated with ototoxicity (see points 4.5 and 4.8).

Ceftazidime and aminoglycosides should not be mixed in the solution for injection because of the risk for precipitation (see section 6.2).

The use of ceftazidime may result in the proliferation of resistant microorganisms such as *Enterococci* and *Candida* spp.
During long-term treatment with ceftazidime it is recommended that the blood composition of the patient be regularly monitored and that regular blood samples are taken to monitor hepatic and renal function.

If copper reduction methods are employed (Benedict’s test, Fehling’s test, Clinitest), minor interference may be seen when ceftazidime is administered. Enzyme-based tests for glucosuria are not influenced, nor is the alkaline picrate assay of creatinine.

The development of a positive Coombs’ test in 5% of patients when using ceftazidime may interfere with blood cross-matching.

Sodium content

This product contains sodium (see section 2).
Patients on a controlled sodium diet must allow for the sodium content.

4.5 Interaction with other medicinal products and other forms of interaction

Chloramphenicol, macrolides and tetracyclines have been shown, *in vitro*¸ to have an antagonistic effect on ceftazidime and other cephalosporins. The clinical relevance of this is not known, but if concomitant administration of ceftazidime and chloramphenicol (or other bacteriostatic substances: e.g. tetracycline, macrolides or sulphonamides) is proposed, the possibility of antagonism should be considered.

Concomitant treatment with nephrotoxic drugs should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amounts of data from the use of ceftazidime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.

Lactation

Ceftazidime is excreted in human milk in small quantities but at therapeutic doses of ceftazidime no effects on the breast-fed infant are anticipated. Ceftazidime can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Consideration should be given to the fact that dizziness and convulsions may occur when driving or use machines.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Approx. 5% of the patients treated suffer from undesirable effects.

Organ system class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Blood and lymphatic system disorders	Eosinophilia, thrombocytosis	Thrombocytopaenia, leucopaenia, neutropaenia, lymphocytosis. Positive Coomb's test	Agranulocytosis, haemolytic anaemia	
Immune system disorders				Angioneurotic oedema, anaphylactic reactions
Nervous system disorders		Headache, dizziness, consciousness disorders, paraesthesias and dysgeusia, convulsions		
Hepatobiliary disorders			Increased serum activity of liver derived enzymes, e.g. gamma glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, alanine transminase, aspartate transaminase	Jaundice
Gastrointestinal disorders		Nausea, vomiting, diarrhoea, stomach pains	Thrush, pseudomembranous colitis	
Skin and subcutaneous	Urticaria rash, pruritus, redness,		Erythema multiforme, Stevens-	

tissue disorders	maculopapulous rash (exanthema)		Johnson syndrome, toxic epidermal necrolysis	
Renal and urinary disorders			Reduction of glomerular filtration rate and increase in serum concentration of urea and creatinine	
Pregnancy, puerperium and perinatal conditions			Vaginal candidiasis, vaginitis	
General disorders and administration site conditions	Phlebitis or thrombophlebitis, pains, inflammation of the point of injection or intravenous administration	Fever		

There have been reports of neurological after-effects, including tremor, myoclonus, convulsions, encephalopathy and coma in patients with impaired renal function whose ceftazidime dose has not been suitably reduced.

There is a risk of superinfections with *Enterococcus* and *Candida* strains, for example.

Nephrotoxicity has been reported after concomitant administration of cephalosporins and aminoglycoside antibiotics or strong diuretics, e.g. furosemide. Renal function should be closely monitored, particularly if higher doses of aminoglycoside are given or if the treatment is extended because of the potential nephro- and ototoxicity of aminoglycoside antibiotics (see points 4.4 and 4.5).

4.9 Overdose

An overdose of ceftazidime may be associated with pain, inflammation and phlebitis at the point of injection.

Overdose or administration of unsuitably high doses combined with renal insufficiency may result in neurological after-effects, including dizziness, paraesthesias, headache, encephalopathy, convulsions and coma.

Abnormal laboratory values which may occur after an overdose include an increase in serum concentrations of bilirubin, creatinine, urea, increase in the serum activity of liver-derived enzymes, e.g. ASAT and ALAT, positive Coombs' test, thrombocytosis, thrombocytopaenia, eosinophilia, leucopaenia and an extension of prothrombin time.

General symptomatic and supportive procedures should be instituted together with specific procedures aimed at monitoring convulsive attacks. In case of a serious overdose, particularly in patients with renal failure, combined haemodialysis and haemoperfusion may be considered if there is no response to more conservative treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **OTHER BETA-LACTAM ANTIBACTERIALS, third generation cephalosporins**

ATC code: J01DD02

Mechanism of action

Ceftazidime is a semi-synthetic bactericidal antibacterial substance belonging to the cephalosporin class. Like other

beta-lactam drugs, ceftazidime displays antibacterial activity by binding itself to and inhibiting the action of certain synthesis enzymes (transpeptidases) in the cell wall of the bacteria. Inhibition of one or more of these essential penicillin-binding proteins results in an interruption in cell wall biosynthesis in the final stage of peptidoglycane production, which gives rise to dissolution of the cell of the bacterium and its death.

PK/PD relationship
The antibacterial is dependent on the time the free concentration in serum/urine exceeds their MIC-value.

Resistance mechanism

Bacterial resistance to ceftazidime may be due to one or more of the following mechanisms:

- hydrolysis by means of betalactamases. Ceftazidime can be effectively hydrolysed by some of the broad spectrum beta-lactamases (ESBLs) and by chromosome decoded (AmpC) enzymes which can be induced or undergo stable de-repression in certain aerobic gram-negative strains of bacteria
- reduced affinity of penicillin-binding proteins to ceftazidime
- exterior membrane impermeability which limits the access of ceftazidime to penicillin-binding proteins in gram-negative bacteria
- drug efflux pumps

More than one of these resistance mechanisms may occur simultaneously in one single bacterial cell. Depending on the existing mechanism(s) bacteria may display cross-resistance to several or all other beta-lactams and/or antibacterial substances belonging to another class.

Breakpoints (according to EUCAST)

Clinical MIC breakpoints for separating sensitive (S) pathogens from resistant (R) pathogens according to EUCAST (27.04.2010) are:

- *Enterobacteriaceae:* S≤1.0 mg/l; R>4 mg/l
- *Pseudomonas* spp.: S≤8*mg/l; R>8 mg/l
- Non-species related breakpoints: S≤4 mg/l; R>8 mg/l

* The breakpoints relate to high dose therapy (2g x 3)

Sensitivity

The prevalence of acquired resistance may very geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Gram-positive microorganisms *Streptococcus agalactiae* (group B) *Streptococcus pyogenes* *Gram-negative* microorganisms: *Haemophilus influenzae* *Moraxella catarrhalis* *Proteus mirabilis*$^{++}$ *Proteus vulgaris* *Serratia liquefaciens*
Species for which acquired resistance may be a problem
Gram-positive microorganisms: *Staphylococcus aureus MSSA* *Streptococcus pneumoniae#* Gram-negative microorganisms: *Escherichia coli*$^{++}$

Acinetobacter spp. *Burkholderia cepacia* *Citrobacter freundii* *Enterobacter aerogenes* and *Enterobacter cloacae* *Klebsiella pneumoniae*$^{++}$ *Klebsiella oxytoca*$^{++}$ *Morganella morganii* *Pseudomonas aeruginosa* *Serratia marcescens* *Stenotrophomonas maltophilia*$^{+++}$
Inherently resistant organisms
Gram-positive microorganisms: *Enterococcus* spp. *Staphylococcus aureus,* methicillin resistant (MRSA) *Staphylococcus* – coagulase negative, methicillin resistant. Anaerobes: *Bacteroides fragilis* *Clostridium difficile* Other: *Chlamydia* spp. *Chlamydophila* spp. *Legionella* spp. *Mycoplasma* spp. *Treponema pallidum*

++ ESBL producing strains are always resistant
+++ In at least one region the resistance is over 50%
# Exhibits some in-vitro activity to penicillin-sensitive strains, but this should not be relied on in the treatment of pneumococcal infections

5.2 Pharmacokinetic properties

Mean maximum serum concentrations after different doses were as follows in persons with normal renal function.

	Intramuscular injection (after 1 hour)	**Intravenous bolus injection (after 5 minutes)**
250 mg	---	26 mg/l
500 mg	18 mg/l	45 mg/l
1 g	39 mg/l	90 mg/l
2 g	---	170 mg/l
3 g	---	200 – 300 mg/l*

* measured in patients with cystic fibrosis whose distribution volume may be increased

Generally the plasma concentration of ceftazidime exceeds 2 mg/l 8 hours after intramuscular administration of 500 mg or more.

After repeated intravenous doses of 1 and 2 g every 8 hours for 10 days, no signs of accumulation of ceftazidime were seen in the serum in persons with normal renal function.

Distribution

Less than 10% of ceftazidime is protein bound, and the degree of protein binding is independent of the concentration.

Ceftazidime concentrations which are higher than the minimum inhibition concentration for general pathogens can be obtained in tissues such as bones, heart and gall bladder, sputum, chamber wall, synovial, pleural and peritoneal fluids. Ceftazidime quickly passes through the placenta.

Ceftazidime only passes through the blood-brain barrier to a small extent and low concentrations are obtained in the cerebrospinal fluid in the absence of inflammation. Therapeutic levels of 4-20 mg/ml or more are obtained in the cerebrospinal fluid in the case of meningeal inflammation.

Elimination

Approx. 80-90% of a ceftazidime dose is eliminated unconverted via the kidneys over a period of 24 hours, which gives to high concentrations in the urine.
In persons with normal renal function the half life of ceftazidime is approx. 2 hours after intramuscular administration.

Impaired liver function had no effect on the pharmacokinetics of ceftazidime in persons who received 2 g intravenously every 8 hours for 5 days. Dose adjustment is not therefore necessary in patients with impaired hepatic function unless the renal function is also impaired.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, toxicity to reproduction. Carcinogenicity studies have not been performed with ceftazidime.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Sodium Carbonate

6.2 Incompatibilities

Ceftazidime and aminoglycosides must not be mixed in the same infusion solution due to the risk of precipitation.

Cannulae and catheters for intravenous application must be rinsed with isotonic salt water between the administration of ceftazidime and vancomycin to avoid precipitation.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before breaking open:

1 year

Vial after breaking open:

The product should be used immediately

After reconstitution:

The product should be used immediately

From the microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability has been demonstrated for:

- 6 hours at 2ºC - 8ºC when prepared in Sterile Water for Injection
- 12 hours at 2ºC - 8ºC when prepared in 1% Lidocaine Hydrochloride Injection

6.4 Special precautions for storage

Unopened:
Store below 25°C
Keep the vial in the outer carton in order to protect from light

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

250 mg powder for injection
Clear, colourless type I glass vial (10 ml) with bromobutyl rubber stopper and polypropylene flip-off aluminium seal, 20 mm orange coloured, both sides lacquered. The vials are placed in cartons. Pack sizes: boxes of one, five or ten vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal

For single use only. Discard any unused solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Instructions for reconstitution:

Ceftazidime should be reconstituted with Sterile Water for Injection or 1% Lidocaine Hydrochloride Injection (intramuscular use only) (see the following table).

Preparation of solutions of Ceftazidime

-	**Amount of diluent to be added (ml)**	**Approximate ceftazidime concentration (mg/ml)**
Intramuscular		
250 mg	1.0	210
Intravenous-Injection		
250 mg	2.5	90

All vials as supplied are under reduced pressure.

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

Preparation for direct administration for 250 mg
The following reconstitution guidelines should be followed:
1. Insert the syringe needle through the original vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent.
2. Remove the syringe needle.

3. Shake the original vial to dissolve the content. Carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
4. Invert the original vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the head space.
5. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

For intravenous injection, the solution must be administered directly into the vein.

Please refer to section 6.3 for in use stability of the reconstituted product.

Extemporaneous solutions for paediatric single doses are to be reconstituted with the most adequate strength in order to reduce as far as possible volumes to be discarded. Multiple use of the single dose containers is not appropriate. The reconstituted product should be used immediately (see section 6.3).

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used. Within the stated recommendations, product potency is not adversely affected by such colour variations.

Before administration, the reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration. Only clear, and colourless solution free from particles should be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 361/33/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd June 2011

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