Public Assessment Report

Decentralised Procedure

CEFTAZIDIME 250MG, 500MG & 1G POWDER FOR SOLUTION FOR INJECTION

CEFTAZIDIME 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION

Ceftazidime pentahydrate

UK/H/1402/001-4/DC
UK licence no: PL 25975/0046-9

Cardinal Health UK 434 Ltd
CEFTAZIDIME 250MG, 500MG & 1G POWDER FOR SOLUTION FOR INJECTION

CEFTAZIDIME 2G POWDER FOR SOLUTION FOR INJECTION/INFUSION

LAY SUMMARY

On 13th September 2010, Denmark, Germany, Finland, Ireland, Norway, Sweden and the UK agreed to grant marketing authorisations to Cardinal Health UK 434 Ltd for the medicinal products Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion. The marketing authorisations were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 18th October 2010.

Ceftazidime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or “germs” that cause infections.

Ceftazidime is used to treat specific types of infections which are sensitive to the drug which include:

- Pneumonia acquired at hospitals (nosocomial pneumonia)
- Lung infections in patients with cystic fibrosis
- Infections of the tissues covering the brain

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

| **Product Name** | Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection  
|                  | Ceftazidime 2g Powder for Solution for Injection/Infusion |
| **Type of Application** | Generic application, Article 10.1 |
| **Active Substance** | Ceftazidime pentahydrate |
| **Form** | 250mg, 500mg & 1g - Powder for Solution for Injection  
|           | 2g - Powder for Solution for Injection/Infusion |
| **Strength** | 250mg, 500mg, 1g and 2g |
| **MA Holder** | Cardinal Health UK 434 Limited  
|               | Bampton Road  
|               | Harold Hill  
|               | Romford  
|               | RM3 8UG |
| **RMS** | UK |
| **CMS** | UK/H/1402/01/DC - Denmark and Germany  
|           | UK/H/1402/02-4/DC – Denmark, Germany, Finland, Ireland, Norway and Sweden |
| **Procedure Number** | UK/H/1402/001-4/DC |
| **Timetable** | Day 210 – 13th September 2010 |
Module 2
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 250 mg 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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Infection</th>
<th>Normal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Most indications</td>
<td>1 g every 8 hours (3 g/day) or 2 g every 12 hours (4 g/day)</td>
</tr>
<tr>
<td></td>
<td>Nosocomial pneumonia and infections in patients with neutropaenia</td>
<td>2 g every 8 hours (6 g/day)</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa</td>
<td>100-150 mg/kg/day, divided into 3 doses; 9 g/day must not be exceeded</td>
</tr>
<tr>
<td>Infants and children aged over two months</td>
<td>Most indications</td>
<td>30-100 mg/kg/day, divided into 2 or 3 doses</td>
</tr>
<tr>
<td></td>
<td>Infected neutropenic paediatric patients, paediatric patients with cystic fibrosis or paediatric patients with meningitis</td>
<td>Up to 150 mg/kg/day (a maximum of 6 g total per day) divided into 3 doses</td>
</tr>
<tr>
<td>Neonates and children up to 2 months of age</td>
<td>Most indications</td>
<td>25-60 mg/kg/day divided into 2 doses*</td>
</tr>
</tbody>
</table>

* 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 3 g, 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.

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

* 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:**

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at an ultrafiltration rate (ml/min) of a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>20</td>
<td>500</td>
</tr>
</tbody>
</table>

a The maintenance dose is administered every 12 hours

**Ceftazidime dosing guideline during continuous venous haemodialysis:**

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at a dialysate in-flow rate of b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 litre/hour</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
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 diarrhea during or immediately after treatment. Ceftazidime should be discontinued if severe and/or bloody diarrhea 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, Clinistest), minor interference may be seen when ceftazidime is administered. Enzyme-based tests for glucosuria are not influenced, nor is the alkaline picoate 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 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.

<table>
<thead>
<tr>
<th>Organ system class</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, thrombocytosis</td>
<td>Thrombocytopaenia, leucopaenia, neutropaenia, lymphocytosis. Positive Coomb’s test</td>
<td>Agranulocytosis, haemolytic anaemia</td>
<td>Angioneurotic oedema, anaphylactic reactions</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness, consciousness disorders, paraesthesias and dysgeusia, convulsions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increased serum activity of liver derived enzymes, e.g. gamma glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, alanine transaminase, aspartate transaminase</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Nausea, vomiting, diarrhoea, stomach pains</td>
<td>Thrush, pseudomembranous colitis</td>
<td></td>
</tr>
</tbody>
</table>
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, thrombocytopenia, eosinophilia, leucopenia 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.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive microorganisms</td>
</tr>
<tr>
<td>Streptococcus agalactiae (group B)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Gram-negative microorganisms:</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Proteus mirabilis++</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
</tr>
<tr>
<td>Serratia liquefaciens</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive microorganisms:</td>
</tr>
<tr>
<td>Staphylococcus aureus MSSA</td>
</tr>
<tr>
<td>Streptococcus pneumoniae#</td>
</tr>
<tr>
<td>Gram-negative microorganisms:</td>
</tr>
<tr>
<td>Escherichia coli++</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>Enterobacter aerogenes and Enterobacter cloacae</td>
</tr>
<tr>
<td>Klebsiella pneumoniae++</td>
</tr>
<tr>
<td>Klebsiella oxytoca++</td>
</tr>
<tr>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia+++</td>
</tr>
</tbody>
</table>
Inherently resistant organisms

<table>
<thead>
<tr>
<th>Gram-positive microorganisms:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus spp.</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus, methicillin resistant (MRSA)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus – coagulase negative, methicillin resistant.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaerobes:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides fragilis</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia spp.</td>
<td></td>
</tr>
<tr>
<td>Chlamydophila spp.</td>
<td></td>
</tr>
<tr>
<td>Legionella spp.</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
</tr>
</tbody>
</table>

++ 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.

<table>
<thead>
<tr>
<th></th>
<th>Intramuscular injection (after 1 hour)</th>
<th>Intravenous bolus injection (after 5 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>---</td>
<td>26 mg/l</td>
</tr>
<tr>
<td>500 mg</td>
<td>18 mg/l</td>
<td>45 mg/l</td>
</tr>
<tr>
<td>1 g</td>
<td>39 mg/l</td>
<td>90 mg/l</td>
</tr>
<tr>
<td>2 g</td>
<td>---</td>
<td>170 mg/l</td>
</tr>
<tr>
<td>3 g</td>
<td>---</td>
<td>200 – 300 mg/l*</td>
</tr>
</tbody>
</table>

* 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 2°C - 8°C when prepared in Sterile Water for Injection
12 hours at 2°C - 8°C 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

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

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td></td>
</tr>
<tr>
<td>250 mg</td>
<td>1.0</td>
</tr>
<tr>
<td>Intravenous-Injection</td>
<td></td>
</tr>
<tr>
<td>250 mg</td>
<td>2.5</td>
</tr>
</tbody>
</table>

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.
1 NAME OF THE MEDICINAL PRODUCT
Ceftazidime 500 mg Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 582 mg of ceftazidime pentahydrate, equivalent to 500 mg of ceftazidime
Excipient: each 500 mg vial of powder contains 60 mg of sodium carbonate
This medicinal product contains 1.13 mmol (or 26 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.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Infection</th>
<th>Normal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Most indications</td>
<td>1 g every 8 hours (3 g/day) or 2 g every 12 hours (4 g/day)</td>
</tr>
<tr>
<td></td>
<td>Nosocomial pneumonia and infections in patients with neutropaenia</td>
<td>2 g every 8 hours (6 g/day)</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa</td>
<td>100-150 mg/kg/day, divided into 3 doses; 9 g/day must not be exceeded</td>
</tr>
<tr>
<td>Infants and children aged over two months</td>
<td>Most indications</td>
<td>30-100 mg/kg/day, divided into 2 or 3 doses</td>
</tr>
<tr>
<td></td>
<td>Infected neutropenic paediatric patients, paediatric patients with cystic fibrosis or paediatric patients with meningitis</td>
<td>Up to 150 mg/kg/day (a maximum of 6 g total per day) divided into 3 doses</td>
</tr>
<tr>
<td>Neonates and children up to 2 months of age</td>
<td>Most indications</td>
<td>25-60 mg/kg/day divided into 2 doses*</td>
</tr>
</tbody>
</table>

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 1 g of ceftazidime may
be given, followed by a suitable maintenance dose as indicated in the table.
### Approximate Serum Creatinine and Recommended Dose Table

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

* 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 patients 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 arterio-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:**

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at an ultrafiltration rate (ml/min) of*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>20</td>
<td>500</td>
</tr>
</tbody>
</table>

* The maintenance dose is administered every 12 hours.

**Ceftazidime dosing guideline during continuous venous haemodialysis:**

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at a dialysate in-flow rate of*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 litre/hour</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration rate (litres/hour)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>10</td>
<td>500</td>
</tr>
<tr>
<td>15</td>
<td>500</td>
</tr>
<tr>
<td>20</td>
<td>750</td>
</tr>
</tbody>
</table>

* 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.
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and
2g Powder for Solution for Injection/Infusion

**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 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.

<table>
<thead>
<tr>
<th>Organ system class</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, thrombocytosis</td>
<td>Thrombocytopenia, neutropenia, lymphocytosis. Positive Coomb’s test</td>
<td>Agranulocytosis, haemolytic anaemia</td>
<td>Angioneurotic oedema, anaphylactic reactions</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Increased serum activity of liver derived enzymes, e.g. gamma glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, alanine transaminase, aspartate transaminase</td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Nausea, vomiting, diarrhoea, stomach pains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria rash, pruritus, redness, maculopapular rash (exanthema)</td>
<td></td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td></td>
</tr>
<tr>
<td>Renal and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction of</td>
<td></td>
</tr>
</tbody>
</table>
urinary disorders | 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, thrombocytopenia, 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
extracellular 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 vary 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*<sup>++</sup>
  - *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*<sup>+++</sup>
  - *Acinetobacter* spp.
  - *Burkholderia cepacia*
  - *Citrobacter freundii*
  - *Enterobacter aerogenes* and *Enterobacter cloacae*
  - *Klebsiella pneumoniae*<sup>++</sup>
  - *Klebsiella oxytoca*<sup>++</sup>
  - *Morganella morganii*
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*
  - *Stenotrophomonas maltophilia*<sup>+++</sup>

### 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 and with different methods of administration were as follows in persons with normal renal function.

<table>
<thead>
<tr>
<th></th>
<th>Intramuscular injection (after 1 hour)</th>
<th>Intravenous bolus injection (after 5 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>---</td>
<td>26 mg/l</td>
</tr>
<tr>
<td>500 mg</td>
<td>18 mg/l</td>
<td>45 mg/l</td>
</tr>
<tr>
<td>1 g</td>
<td>39 mg/l</td>
<td>90 mg/l</td>
</tr>
<tr>
<td>2 g</td>
<td>---</td>
<td>170 mg/l</td>
</tr>
<tr>
<td>3 g</td>
<td>---</td>
<td>200 – 300 mg/l*</td>
</tr>
</tbody>
</table>

* 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 intravenous or 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 intravenous or 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 hours at 2ºC - 8ºC when prepared in Metronidazole Hydrochloride Injection (500 mg in 100 ml)

6.4 Special precautions for storage
Unopened:
Store below 25ºC
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
500 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
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).
Ceftazidime at a concentration of 5mg/ml can be admixedtured with Metronidazole Hydrochloride Injection (500 mg in 100 ml).

<table>
<thead>
<tr>
<th>Preparation of solutions of Ceftazidime</th>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>1.5</td>
<td>260</td>
</tr>
<tr>
<td>Intravenous-Injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>5.0</td>
<td>90</td>
</tr>
</tbody>
</table>

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 500 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.
1 NAME OF THE MEDICINAL PRODUCT
Ceftazidime 1 g Powder for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1165 mg of ceftazidime pentahydrate, equivalent to 1 g of ceftazidime
Excipient: each 1 g vial of powder contains 121 mg of sodium carbonate
This medicinal product contains 2.28 mmol (or 52.5 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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Infection</th>
<th>Normal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Most indications</td>
<td>1 g every 8 hours (3 g/day) or 2 g every 12 hours (4 g/day)</td>
</tr>
<tr>
<td></td>
<td>Nosocomial pneumonia and infections in patients with neutropaenia</td>
<td>2 g every 8 hours (6 g/day)</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa</td>
<td>100-150 mg/kg/day, divided into 3 doses; 9 g/day must not be exceeded</td>
</tr>
<tr>
<td>Infants and children aged over two months</td>
<td>Most indications</td>
<td>30-100 mg/kg/day, divided into 2 or 3 doses</td>
</tr>
<tr>
<td></td>
<td>Infected neutropenic paediatric patients, paediatric patients with cystic fibrosis or paediatric patients with meningitis</td>
<td>Up to 150 mg/kg/day (a maximum of 6 g total per day) divided into 3 doses</td>
</tr>
<tr>
<td>Neonates and children up to 2 months of age</td>
<td>Most indications</td>
<td>25-60 mg/kg/day divided into 2 doses*</td>
</tr>
</tbody>
</table>

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 1 g 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 neutropenia, 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 arterio-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) ofa |
|---|---|---|---|
| | 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 ofa |
|---|---|---|---|---|---|
| | 1.0 litre/hour | 2.0 litre/hour | 1.0 litre/hour | 2.0 litre/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 picate 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 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/fetal 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.

<table>
<thead>
<tr>
<th>Organ system class</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, thrombocytosis</td>
<td>Thrombocytopenia, leucopenia, neutropaenia, lymphocytosis. Positive Coomb’s test</td>
<td>Agranulocytosis, haemolytic anaemia</td>
<td>Angioneurotic oedema, anaphylactic reactions</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness, consciousness disorders, paraesthesias and dysgeusia, convulsions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increased serum activity of liver derived enzymes, e.g. gamma glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, alanine transaminase, aspartate transaminase</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Nausea, vomiting, diarrhoea, stomach pains</td>
<td>Thrush, pseudomembranous colitis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria rash, pruritus, redness, maculopapulosity rash (exanthema)</td>
<td></td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td></td>
</tr>
<tr>
<td>Renal and</td>
<td></td>
<td></td>
<td>Reduction of</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>urinary disorders</th>
<th>glomerular filtration rate and increase in serum concentration of urea and creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>Vaginal candidiasis, vaginitis</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Phlebitis or thrombophlebitis, pains, inflammation of the point of injection or intravenous administration</td>
</tr>
<tr>
<td>overall</td>
<td>Fever</td>
</tr>
</tbody>
</table>

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, thrombocytopenia, 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 vary 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.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive microorganisms</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (group B)</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
</tbody>
</table>
| *Gram-negative microorganisms:*
| *Haemophilus influenzae* |
| *Moraxella catarrhalis* |
| *Proteus mirabilis*** |
| *Proteus vulgaris* |
| *Serratia liquefaciens* |

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive microorganisms:</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> MSSA</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>#</td>
</tr>
<tr>
<td>Gram-negative microorganisms:</td>
</tr>
<tr>
<td><em>Escherichia coli</em>**</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em> and <em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em>**</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em>**</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em>**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive microorganisms:</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin resistant (MRSA)</td>
</tr>
<tr>
<td><em>Staphylococcus</em> – coagulase negative, methicillin resistant.</td>
</tr>
</tbody>
</table>

Anaerobes:
*Bacteroides fragilis*
5.2 Pharmacokinetic properties

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

<table>
<thead>
<tr>
<th></th>
<th>Intramuscular injection (after 1 hour)</th>
<th>Intravenous bolus injection (after 5 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>26 mg/l</td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>18 mg/l</td>
<td>45 mg/l</td>
</tr>
<tr>
<td>1 g</td>
<td>39 mg/l</td>
<td>90 mg/l</td>
</tr>
<tr>
<td>2 g</td>
<td>170 mg/l</td>
<td></td>
</tr>
<tr>
<td>3 g</td>
<td>200 – 300 mg/l*</td>
<td></td>
</tr>
</tbody>
</table>

* 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 intravenous or 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 intravenous or 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 12 hours at 2°C - 8°C when prepared in Sterile Water for Injection or 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

1 g powder for injection

Clear, colourless type I glass vial (15 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

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

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td></td>
</tr>
<tr>
<td>1 g</td>
<td>3.0 *</td>
</tr>
<tr>
<td></td>
<td>260</td>
</tr>
<tr>
<td>1 g</td>
<td>3.0 **</td>
</tr>
<tr>
<td></td>
<td>260</td>
</tr>
<tr>
<td>Intravenous-Injection</td>
<td></td>
</tr>
<tr>
<td>1 g</td>
<td>10.0 *</td>
</tr>
<tr>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>

* Sterile Water for Injection
** 1% Lidocaine Hydrochloride Injection (intramuscular use only)

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 1 g

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
Cardinal Health UK 434 Ltd.
Bampton Road, Harold Hill
Romford, Essex
RM3 8UK
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 25975/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/10/2010

10 DATE OF REVISION OF THE TEXT
18/10/2010
1 NAME OF THE MEDICINAL PRODUCT
Ceftazidime 2 g Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 2330 mg of ceftazidime pentahydrate, equivalent to 2 g of ceftazidime
Excipient: each 2 g vial of powder contains 242 mg of sodium carbonate
This medicinal product contains 4.57 mmol (or 105 mg) of sodium per vial
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
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

<table>
<thead>
<tr>
<th>Age group</th>
<th>Infection</th>
<th>Normal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Most indications</td>
<td>1 g every 8 hours (3 g/day) or 2 g every 12 hours (4 g/day)</td>
</tr>
<tr>
<td></td>
<td>Nosocomial pneumonia and infections in patients with neutropaenia</td>
<td>2 g every 8 hours (6 g/day)</td>
</tr>
<tr>
<td></td>
<td>Bronchopulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa</td>
<td>100-150 mg/kg/day, divided into 3 doses; 9 g/day must not be exceeded</td>
</tr>
<tr>
<td>Infants and children aged over two months</td>
<td>Most indications</td>
<td>30-100 mg/kg/day, divided into 2 or 3 doses</td>
</tr>
<tr>
<td></td>
<td>Infected neutropenic paediatric patients, paediatric patients with cystic fibrosis or paediatric patients with meningitis</td>
<td>Up to 150 mg/kg/day (a maximum of 6 g total per day) divided into 3 doses</td>
</tr>
<tr>
<td>Neonates and children up to 2 months of age</td>
<td>Most indications</td>
<td>25-60 mg/kg/day divided into 2 doses*</td>
</tr>
</tbody>
</table>

* 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 1 g of ceftazidime may be given, followed by a suitable maintenance dose as indicated in the table.

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>Approximate serum creatinine* µmol/l (mg/dl)</th>
<th>Recommended single dose of ceftazidime (g)</th>
<th>Dosing frequency, indicated in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-31</td>
<td>150-200 (1.7-2.3)</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at an ultrafiltration rate (ml/min) ofa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>250</td>
</tr>
<tr>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>20</td>
<td>500</td>
</tr>
</tbody>
</table>

*a The maintenance dose is administered every 12 hours

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 arterio-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:

<table>
<thead>
<tr>
<th>Residual renal function (creatinine clearance ml/min)</th>
<th>Maintenance dose (mg) at a dialysate in-flow rate ofa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 litre/hour</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration rate (litres/hour)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
</tr>
<tr>
<td>10</td>
<td>500</td>
</tr>
<tr>
<td>15</td>
<td>500</td>
</tr>
<tr>
<td>20</td>
<td>750</td>
</tr>
</tbody>
</table>

*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 (either by bolus injection or by infusion).

For preparation of solution for injection or infusion (see section 6.6 and 6.2).

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 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.

<table>
<thead>
<tr>
<th>Organ system class</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, thrombocytosis</td>
<td>Thrombocytopenia, leucopenia, neutropenia, lymphocytosis. Positive Coomb’s test</td>
<td>Agranulocytosis, haemolytic anaemia</td>
<td>Angioneurotic oedema, anaphylactic reactions</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness, consciousness disorders, paraesthesias and dysgeusia, convulsions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increased serum activity of liver derived enzymes, e.g. gamma glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, alanine transminase, aspartate transaminase</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Nausea, vomiting, diarrhoea, stomach pains</td>
<td>Thrus, pseudomembranous colitis</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria rash, pruritus, redness, maculopapulous rash (exanthema)</td>
<td></td>
<td>Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Reduction of glomerular filtration rate and increase in serum concentration of urea and creatinine</td>
<td></td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal</td>
<td></td>
<td></td>
<td>Vaginal candidiasis, vaginitis</td>
<td></td>
</tr>
</tbody>
</table>
### 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.*
  - *Chlamydia phila 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 and with different methods of administration were as follows in persons with normal renal function.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Intravenous bolus injection (after 5 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>26 mg/l</td>
</tr>
<tr>
<td>500 mg</td>
<td>45 mg/l</td>
</tr>
<tr>
<td>1 g</td>
<td>90 mg/l</td>
</tr>
<tr>
<td>2 g</td>
<td>170 mg/l</td>
</tr>
<tr>
<td>3 g</td>
<td>200 – 300 mg/l*</td>
</tr>
</tbody>
</table>

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

Serum concentrations after intravenous infusion.

<table>
<thead>
<tr>
<th>Ceftazidime Intraavenous infusion dose</th>
<th>Serum concentrations (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 hour</td>
</tr>
<tr>
<td>500 mg</td>
<td>42</td>
</tr>
<tr>
<td>1 g</td>
<td>60</td>
</tr>
<tr>
<td>2 g</td>
<td>129</td>
</tr>
</tbody>
</table>

Generally the plasma concentration of ceftazidime exceeds 2 mg/l 8 hours after intravenous 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 meningal 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 intravenous or 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 a microbiological point of view, the product should 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 2°C - 8°C when prepared in 0.9% (9mg/ml) Sodium Chloride Injection and 5% (50mg/ml) Dextrose Injection
12 hours at 2°C - 8°C when prepared in Sterile Water for Injection
12 hours at 2°C - 8°C when prepared in 5% (50mg/ml) Dextrose Injection, Compound Sodium Lactate Injection, Dextran 40 Injection 10% in 0.9% (9mg/ml) Sodium Chloride Injection and Dextran 40 Injection in 10% in 5% (50mg/ml) Dextrose Injection
12 hours at 2°C - 8°C when Ceftazidime for Injection 2g (4mg/mL) is prepared with Cefuroxime Sodium (3mg/ml), Heparin (10µ/mL), Potassium Chloride (10mEq/L) and Cloxacillin Sodium (4mg/mL) in 0.9% (9mg/ml) Sodium Chloride Injection.
24 hours at 2°C - 8°C when prepared in 0.9% (9mg/ml) Sodium Chloride 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
2 g powder for injection or infusion
Clear, colourless type I glass vial (50 ml) with bromobutyl rubber stopper and polypropylene flip-off aluminium seal, 32 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
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
Preparation of solutions of Ceftazidime

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous-Injection</td>
<td></td>
</tr>
<tr>
<td>2 g</td>
<td>10.0*</td>
</tr>
<tr>
<td></td>
<td>170</td>
</tr>
<tr>
<td>Intravenous-Infusion</td>
<td></td>
</tr>
<tr>
<td>2 g</td>
<td>50.0**</td>
</tr>
<tr>
<td></td>
<td>40†</td>
</tr>
</tbody>
</table>

6.7 Others
* Sterile Water for Injection  
** Note: Addition should be in two stages  
† Note: Use 0.9% (9mg/ml) Sodium Chloride Injection, 5% (50mg/ml) Dextrose Injection, 5% (50mg/ml) Dextrose and 0.9% (9mg/ml) Sodium Chloride Injection, Dextran 40 Injection BP 10% in 0.9% (9mg/ml) Sodium Chloride Injection, Dextran 40 Injection BP 10% in 5% (50mg/ml) Dextrose Injection and Compound Sodium Lactate Injection as Sterile Water for Injection produces hypotonic solutions at this concentration.

Compatibility of Ceftazidime for Injection 2g (4mg/mL) has been demonstrated with Cefuroxime Sodium (3mg/mL), Heparin (10µ/mL), Potassium Chloride (10mEq/L) and Cloxacillin Sodium (4mg/mL) in 0.9% (9mg/ml) Sodium Chloride Injection. 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 2 g
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 or introduced into the tubing of the giving set if the patient is receiving parenteral fluid (see above for compatible fluids).

Preparation for administration of 2 g vials by infusion
This vial may be constituted for short intravenous infusion (e.g. up to 30 minutes).

Prepare using a total of 50ml of compatible diluent, added in TWO stages as below:
1. Insert the syringe needle through the vial closure and add 10 ml 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. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relive the internal pressure.
5. Transfer the reconstituted solution to the final delivery vehicle, making up to a total volume of at least 50 ml, and administer by intravenous infusion over 15-30 minutes.

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.

MARKETING AUTHORISATION HOLDER
Cardinal Health UK 434 Ltd.
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Romford, Essex
RM3 8UK
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 25975/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   18/10/2010

10 DATE OF REVISION OF THE TEXT
    18/10/2010
Module 3
PACKAGE LEAFLET: INFORMATION FOR THE USER

Ceftazidime 250 mg Powder for Solution for Injection

Ceftazidime (as pentahydrate)

Read all this leaflet carefully before you have been given Ceftazidime injection

- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or pharmacist
- If any of the side effects become serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist
- This medicine has been prescribed for you personally and should not be passed on to others. It may harm them even if their symptoms are the same as yours

In this leaflet:
1. What Ceftazidime for injection is and what it is used for
2. Before you are given Ceftazidime for injection
3. How Ceftazidime for injection is given
4. Possible side-effects
5. Storing Ceftazidime for injection
6. Further information

1. What Ceftazidime for injection is and what it is used for
Ceftazidime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or “germs” that cause infections.

Ceftazidime is used to treat specific types of infections which are sensitive to the drug which include:
- Pneumonia acquired at hospitals (nosocomial pneumonia)
- Lung infections in patients with cystic fibrosis
- Infections of the tissues covering the brain

2. Before you are given Ceftazidime for injection:

You should not be given Ceftazidime for injection if:
- You are allergic to Cephalosporins including Ceftazidime or any of the ingredients in this injection (e.g sodium carbonate)
- You have had a previous, immediate and/or severe allergic reaction to penicillin or any beta-lactam antibiotic (if you are unsure what a beta-lactam antibiotic is, please ask your doctor or pharmacist)

Take special care with Ceftazidime for injection if:
- You are taking a diuretic (water tablet) such as furosemide
- You are taking any other antibiotics e.g. chloramphenicol or aminoglycoside antibiotics
- You are on a low sodium diet
- You have any diseases of the stomach and/or intestine (gastrointestinal diseases e.g. colitis)
- If you experience bloody diarrhoea, you must stop treatment and contact your doctor immediately
- You have kidney problems. You may still receive Ceftazidime but you may need a lower dose.

If you are unsure, ask your doctor or the other health care personnel for advice. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are having Ceftazidime, as it may affect your results. If your urine is being tested for sugar, Ceftazidime may cause a false positive result.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Medicines which may interact with Ceftazidime include:
- chloramphenicol
- macrolides
- tetracyclines
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

- drugs known to cause diseases or damage to the kidney as a side effect (e.g. cisplatin), aminoglycoside antibiotics such as gentamicin or amikacin, diuretics (e.g. furosemide or cyclosporine)

**Pregnancy and Breastfeeding**
Please inform your doctor if you are pregnant, planning on becoming pregnant or breastfeeding before taking this medicine. This medicine should not be used during pregnancy or breastfeeding unless advised by your doctor.

**Driving and using machines**
Ceftazidime can cause dizziness and convulsions. If affected you should not drive or operate machinery.

**Important information about some of the ingredients of Ceftazidime**
This medicinal product contains 13 mg (0.57mmol) of sodium per dose.

To be taken into consideration by patients on a controlled sodium diet.

3. **How Ceftazidime for injection is given**
The dose depends on the severity and type of infection you have, as well as on your age, weight and function of your kidney. Tell your doctor if you have any kidney problems.

**Adults**
The usual adult dose is 1 g three times a day or 2 g twice a day. For severe infections, or for patients who have a special risk of infections due to a low white blood cell count, the usual dose is 2 g three times a day.

**Adults with moderate to severe kidney problems**
For patients with moderate to severe kidney problems the dose of Ceftazidime will be reduced.

For patients with renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration the dose is 1 g daily in divided doses.

For patients who have haemodialysis courses, the appropriate dose should be repeated after each haemodialysis period. This is because some of the Ceftazidime may be removed from the body during this type of dialysis and so needs to be topped up.

**Elderly**
For elderly patients the total daily dose should normally not be more than 3 g, especially in those over 80 years of age.

**Children aged over 2 months**
For children aged over 2 months the usual dose is 30 mg to 100 mg per kg of body weight daily divided into 2 or 3 separate doses. Severely ill children may receive up to 150 mg per kg of body weight daily (to a maximum of 6 g daily), divided into 3 separate doses.

**Newborn and children aged under 2 months**
For new-borns and children less than 2 months old, the usual dose is 25 mg to 60 mg per kg of body weight daily divided into 2 or doses.

**If you are given too much, or too little, Ceftazidime**
Your medication will usually be given to you by the health professional – if you think you may have missed a dose or have received too much or too little of the medicine please tell your doctor or nurse immediately. Signs of overdose include pain and swelling of injection site, dizziness, pins and needles, headaches, and fits, inflammation of the brain and loss of consciousness. As with all antibiotics it is important that you are given Ceftazidime regularly and the full course is completed.

**If you have any further questions on the use of this product, ask your doctor or the other health personnel.**

4. **Possible side effects**
Like all medicines, Ceftazidime can cause side effects, although not everybody gets them. As with some other antibiotics, some people find they have an allergy to Ceftazidime.
If any of the following serious side effects happens tell your doctor or nurse immediately:
- allergic reactions, such as sudden wheezing and tightness of the chest, swelling of the eyelids, face, throat or lip, severe skin rashes that can blister and may involve the eyes, mouth and throat and genital, fainting.
- diarrhoea that is serious lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of serious bowel inflammation that can happen during or after taking antibiotics.

Common side effects: affects 1 to 10 users in 100
- Blood: blood abnormalities causing changes in blood test results of the numbers of some blood cells including an increase in red blood cells and platelets, which may cause blood clots.
- Skin: itching, flushing, eruption on the skin (maculopapulous rash or exanthema)
- General: local skin reactions, inflammation of a blood vessel, inflammation at the site of injection after intravenous administration.

Uncommon side effects: affects 1 to 10 users in 1,000
- Blood: blood abnormalities causing bleeding tendency, easy bruising, increased risk of infections. Changes in blood test results of the number of some blood cells
- Nervous system: “pins and needles”, bad taste in the mouth, headache, dizziness, numbness, tingling, burning sensations, cramps, confusion, sleepiness, convulsions
- Gastrointestinal: nausea, vomiting, diarrhoea and pain in the gut
- General: fever

Rare side effects: affects 1 to 10 users in 10,000
- Skin: severe skin reactions with blistering of the skin, mouth or eyes (e.g. Stevens-Johnson’s syndrome) or with peeling of the skin (e.g. Lyell’s syndrome)
- Blood: anaemia with symptoms such as fatigue, pale skin colouration and shortness of breath, big fall in the number of circulating white blood cells (agranulocytosis) leading to an increase in the risk of infection
- Liver: changes in the result of the blood tests that check the liver function
- Genitals: itching or pain in the vagina (symptoms of fungal or bacterial vaginal infections)
- Gastrointestinal: fungal infection in the mouth, a particular infection of the large gut following treatment with antibiotics causing severe and persistent diarrhoea (pseudomembranous colitis)
- Kidney: impaired kidney function, changes in the results of the blood tests that check the kidney function

Very rare side effects: affects less than 1 user in 10,000
- Liver: yellowing of the skin and eyes (jaundice)
- Immune system: severe allergic reaction causing sudden swelling of the throat, wheezing, shortness of breath and sudden drop in blood pressure.
- Nervous system: trembling, uncontrolled stiffness of the muscle, fits, unconsciousness and a general inflammation of the brain can also happen, but usually only in people with poor kidneys.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. Storing Ceftazidime for injection:
Keep out of the reach and sight of children
Store below 25°C
Keep the vial in the outer carton in order to protect from light.
Discard any unused solution

This product should not be used after the expiry date printed on the carton and ampoule label after EXP. The doctor or nurse will check that the product has not passed this date. Any product that has passed this date must be returned to a pharmacist or doctor for safe disposal.

6. Further Information

What Ceftazidime for injection contains
Each vial contains the active ingredient, Ceftazidime pentahydrate, equivalent to 250 mg of Ceftazidime, as a powder for solution for injection. It also contains the inactive ingredient, sodium carbonate. This medicinal
product contains 13 mg (0.57mmol) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

**What Ceftazidime for injection looks like and contents of the pack**
Ceftazidime is available powder for solution for injection. The powder is white or off-white. The vials are placed in cartons. Pack sizes: Boxes of one, five or ten vials.

**Marketing Authorisation Holder**
Cardinal Health, Bampton Road,
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This medicinal product is authorised in the Member States of the EEA under the following names:
<To be completed nationally>

**Product Licence Nos.:**
<To be completed nationally>

**TECHNICAL PRESCRIBING INFORMATION**

**NAME OF THE MEDICINAL PRODUCT**
Ceftazidime 250 mg Powder for Solution for Injection

**PHARMACEUTICAL FORM**
Powder for solution for injection

**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 ‘Special precautions for use and handling’.

**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 2°C - 8°C when prepared in Sterile Water for Injection
- 12 hours at 2°C - 8°C when prepared in 1% Lidocaine Hydrochloride Injection

**Special precautions for use and 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 discolouration 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

<table>
<thead>
<tr>
<th></th>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate Ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg</td>
<td>1.0</td>
<td>210</td>
</tr>
<tr>
<td>Intravenous-Injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg</td>
<td>2.5</td>
<td>90</td>
</tr>
</tbody>
</table>

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 discolouration. Only clear, and colourless solution free from particles should be used.

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**Manufacturer**
Cardinal Health UK 434 Ltd.
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

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United Kingdom

Product Licence Nos.:
<To be completed nationally>
Ceftazidime 500 mg Powder for Solution for Injection

Ceftazidime (as pentahydrate)

Read all this leaflet carefully before you have been given Ceftazidime injection

- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or pharmacist
- If any of the side effects become serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist
- This medicine has been prescribed for you personally and should not be passed on to others. It may harm them even if their symptoms are the same as yours

In this leaflet:
1. What Ceftazidime for Injection is and what it is used for
2. Before you are given Ceftazidime for Injection
3. How Ceftazidime for Injection is given
4. Possible side-effects
5. Storing Ceftazidime for Injection
6. Further information

1. What Ceftazidime for Injection is and what it is used for
Ceftazidime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or “germs” that cause infections.

Ceftazidime is used to treat specific types of infections which are sensitive to the drug which include:
- Pneumonia acquired at hospitals (nosocomial pneumonia)
- Lung infections in patients with cystic fibrosis
- Infections of the tissues covering the brain

2. Before you are given Ceftazidime for injection:
You should not be given Ceftazidime for injection if:
- You are allergic to Cephalosporins including Ceftazidime or any of the ingredients in this injection (e.g. sodium carbonate)
- You have had a previous, immediate and/or severe allergic reaction to penicillin or any beta-lactam antibiotic (if you are unsure what a beta-lactam antibiotic is, please ask your doctor or pharmacist)

Take special care with Ceftazidime for injection if:
- You are taking a diuretic (water tablet) such as furosemide
- You are taking any other antibiotics e.g. chloramphenicol or aminoglycoside antibiotics
- You are on a low sodium diet
- You have any diseases of the stomach and/or intestine (gastrointestinal diseases e.g. colitis)
- If you experience bloody diarrhoea, you must stop treatment and contact your doctor immediately
- You have kidney problems. You may still receive Ceftazidime but you may need a lower dose

If you are unsure, ask your doctor or the other health care personnel for advice. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are having Ceftazidime, as it may affect your results. If your urine is being tested for sugar, Ceftazidime may cause a false positive result.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Medicines which may interact with Ceftazidime include:
- chloramphenicol
- macrolides
- tetracyclines
- drugs known to cause diseases or damage to the kidney as a side effect (e.g. cisplatin), aminoglycoside antibiotics such as gentamicin or amikacin, diuretics (e.g. furosemide or cyclosporine)
3. How Ceftazidime for injection is given
The dose depends on the severity and type of infection you have, as well as on your age, weight and function of your kidney. Tell your doctor if you have any kidney problems.

Adults
The usual adult dose is 1 g three times a day or 2 g twice a day. For severe infections, or for patients who have a special risk of infections due to a low white blood cell count, the usual dose is 2 g three times a day.

Adults with moderate to severe kidney problems
For patients with moderate to severe kidney problems the dose of Ceftazidime will be reduced.

For patients with renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration the dose is 1 g daily in divided doses.

For patients who have haemodialysis courses, the appropriate dose should be repeated after each haemodialysis period. This is because some of the Ceftazidime may be removed from the body during this type of dialysis and so needs to be topped up.

Elderly
For elderly patients the total daily dose should normally not be more than 3 g, especially in those over 80 years of age.

Children aged over 2 months
For children aged over 2 months the usual dose is 30 mg to 100 mg per kg of body weight daily divided into 2 or 3 separate doses. Severely ill children may receive up to 150 mg per kg of body weight daily (to a maximum of 6 g daily), divided into 3 separate doses.

Newborn and children aged under 2 months
For new-borns and children less than 2 months old, the usual dose is 25 mg to 60 mg per kg of body weight daily divided into 2 or doses.

If you are given too much, or too little, Ceftazidime
Your medication will usually be given to you by the health professional – if you think you may have missed a dose or have received too much or too little of the medicine please tell your doctor or nurse immediately. Signs of overdose include pain and swelling of injection site, dizziness, pins and needles, headaches, and fits, inflammation of the brain and loss of consciousness.
As with all antibiotics it is important that you are given Ceftazidime regularly and the full course is completed.

If you have any further questions on the use of this product, ask your doctor or the other health personnel.

4. Possible side effects
Like all medicines, Ceftazidime can cause side effects, although not everybody gets them. As with some other antibiotics, some people find they have an allergy to Ceftazidime.

If any of the following serious side effects happens tell your doctor or nurse immediately:
- allergic reactions, such as sudden wheezing and tightness of the chest, swelling of the eyelids, face, throat or lip, severe skin rashes that can blister and may involve the eyes, mouth and throat and genital, fainting.
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

- diarrhoea that is serious lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of serious bowel inflammation that can happen during or after taking antibiotics.

Common side effects: affects 1 to 10 users in 100
- Blood: blood abnormalities causing changes in blood test results of the numbers of some blood cells including an increase in red blood cells and platelets, which may cause blood clots.
- Skin: itching, flushing, eruption on the skin (maculopapulous rash or exanthema)
- General: local skin reactions, inflammation of a blood vessel, inflammation at the site of injection after intravenous administration.

Uncommon side effects: affects 1 to 10 users in 1,000
- Blood: blood abnormalities causing bleeding tendency, easy bruising, increased risk of infections. Changes in blood test results of the numbers of some blood cells
- Nervous system: “pins and needles”, bad taste in the mouth, headache, dizziness, numbness, tingling, burning sensations, cramps, confusion, sleepiness, convulsions
- Gastrointestinal: nausea, vomiting, diarrhoea and pain in the gut.
- General: fever

Rare side effects: affects 1 to 10 users in 10,000
- Skin: severe skin reactions with blistering of the skin, mouth or eyes (e.g. Stevens Johnson’s syndrome) or with peeling of the skin (e.g. Lyell’s syndrome)
- Blood: anaemia with symptoms such as fatigue, pale skin colouration and shortness of breath, big fall in the number of circulating white blood cells (agranulocytosis) leading to an increase in the risk of infection
- Liver: changes in the result of the blood tests that check the liver function
- Genitals: itching or pain in the vagina (symptoms of fungal or bacterial vaginal infections)
- Gastrointestinal: fungal infection in the mouth, a particular infection of the large gut following treatment with antibiotics causing severe and persistent diarrhoea (pseudomembranous colitis)
- Kidney: impaired kidney function, changes in the results of the blood tests that check the kidney function.

Very rare side effects: affects less than 1 user in 10,000
- Liver: yellowing of the skin and eyes (jaundice)
- Immune system: severe allergic reaction causing sudden swelling of the throat, wheezing, shortness of breath and sudden drop in blood pressure.
- Nervous system: trembling, uncontrolled stiffness of the muscle, fits, unconsciousness and a general inflammation of the brain can also happen, but usually only in people with poor kidneys.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. Storing Ceftazidime for injection:
Keep out of the reach and sight of children
Store below 25°C
Keep the vial in the outer carton in order to protect from light.
Discard any unused solution

This product should not be used after the expiry date printed on the carton and ampoule label after EXP. The doctor or nurse will check that the product has not passed this date. Any product that has passed this date must be returned to a pharmacist or doctor for safe disposal.

6. Further Information

What Ceftazidime for injection contains
Each vial contains the active ingredient, Ceftazidime pentahydrate, equivalent to 500 mg of Ceftazidime, as a powder for solution for injection. It also contains the inactive ingredient, sodium carbonate. This medicinal product contains 26 mg (1.13 mmol) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet

What Ceftazidime for injection looks like and contents of the pack
Ceftazidime is available powder for solution for injection. The powder is white or off-white. The vials are placed in cartons. Pack sizes: Boxes of one, five or ten vials.

**Marketing Authorisation Holder**
Cardinal Health, Bampton Road, Romford, United Kingdom.
RM3 8UG

**Manufacturer**
Cardinal Health, Bampton Road, Romford, United Kingdom.
RM3 8UG

This medicinal product is authorised in the Member States of the EEA under the following names:
<To be completed nationally>

**Product Licence Nos.:**
<To be completed nationally>

**TECHNICAL PRESCRIBING INFORMATION**

**NAME OF THE MEDICINAL PRODUCT**
Ceftazidime 500 mg Powder for Solution for Injection

**PHARMACEUTICAL FORM**
Powder for solution for injection

**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 ‘Special precautions for use and handling’.

**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 2°C - 8°C when prepared in Sterile Water for Injection
- 12 hours at 2°C - 8°C when prepared in 1% Lidocaine Hydrochloride Injection
- 6 hours at 2°C - 8°C when prepared in Metronidazole Hydrochloride Injection (500 mg in 100 ml)

**Special precautions for use and 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 discolouration 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).

Ceftazidime at a concentration of 5mg/ml can be admixed with Metronidazole Hydrochloride Injection (500 mg in 100 ml).

**Preparation of solutions of Ceftazidime**

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate Ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>1.5</td>
</tr>
<tr>
<td>Intravenous-Injection</td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>5.0</td>
</tr>
</tbody>
</table>

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 500 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.

**Marketing Authorisation Holder**

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United Kingdom

Product Licence Nos.:
<To be completed nationally>
Ceftazidime 1 g Powder for Solution for Injection

Ceftazidime (as pentahydrate)

Read all this leaflet carefully before you have been given Ceftazidime injection

- Keep this leaflet. You may need to read it again
- If you have any further questions, please ask your doctor or pharmacist
- If any of the side effects become serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist
- This medicine has been prescribed for you personally and should not be passed on to others. It may harm them even if their symptoms are the same as yours

In this leaflet:
1. What Ceftazidime for injection is and what it is used for
2. Before you are given Ceftazidime for injection
3. How Ceftazidime for injection is given
4. Possible side-effects
5. Storing Ceftazidime for injection
6. Further information

1. What Ceftazidime for injection is and what it is used for
Ceftazidime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or “germs” that cause infections.

Ceftazidime is used to treat specific types of infections which are sensitive to the drug which include:
- Pneumonia acquired at hospitals (nosocomial pneumonia)
- Lung infections in patients with cystic fibrosis
- Infections of the tissues covering the brain

2. Before you are given Ceftazidime for injection:
You should not be given Ceftazidime for injection if:
- You are allergic to Cephalosporins including Ceftazidime or any of the ingredients in this injection (e.g. sodium carbonate)
- You have had a previous, immediate and/or severe allergic reaction to penicillin or any beta-lactam antibiotic (if you are unsure what a beta-lactam antibiotic is, please ask your doctor or pharmacist)

Take special care with Ceftazidime for injection if:
- You are taking a diuretic (water tablet) such as furosemide
- You are taking any other antibiotics e.g. chloramphenicol or aminoglycoside antibiotics
- You are on a low sodium diet
- You have any diseases of the stomach and/or intestine (gastrointestinal diseases e.g. colitis)
- If you experience bloody diarrhoea, you must stop treatment and contact your doctor immediately
- You have kidney problems. You may still receive Ceftazidime but you may need a lower dose.

If you are unsure, ask your doctor or the other health care personnel for advice. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are having Ceftazidime, as it may affect your results. If your urine is being tested for sugar, Ceftazidime may cause a false positive result.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Medicines which may interact with Ceftazidime include:
- chloramphenicol
- macrolides
- tetracyclines
- drugs known to cause diseases or damage to the kidney as a side effect (e.g. cisplatin), aminoglycoside antibiotics such as gentamicin or amikacin, diuretics (e.g. furosemide or cyclosporine)

Pregnancy and Breastfeeding
Please inform your doctor if you are pregnant, planning on becoming pregnant or breastfeeding before taking this medicine. This medicine should not be used during pregnancy or breastfeeding unless advised by your doctor.

Driving and using machines
Ceftazidime can cause dizziness and convulsions. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Ceftazidime
This medicinal product contains 52.5 mg (2.28 mmol) of sodium per dose.

3. How Ceftazidime for injection is given
The dose depends on the severity and type of infection you have, as well as on your age, weight and function of your kidney. Tell your doctor if you have any kidney problems.

Adults
The usual adult dose is 1 g three times a day or 2 g twice a day. For severe infections, or for patients who have a special risk of infections due to a low white blood cell count, the usual dose is 2 g three times a day.

Adults with moderate to severe kidney problems
For patients with moderate to severe kidney problems the dose of Ceftazidime will be reduced.

For patients with renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration the dose is 1 g daily in divided doses.

For patients who have haemodialysis courses, the appropriate dose should be repeated after each haemodialysis period. This is because some of the Ceftazidime may be removed from the body during this type of dialysis and so needs to be topped up.

Elderly
For elderly patients the total daily dose should normally not be more than 3 g, especially in those over 80 years of age.

Children aged over 2 months
For children aged over 2 months the usual dose is 30 mg to 100 mg per kg of body weight daily divided into 2 or 3 separate doses. Severely ill children may receive up to 150 mg per kg of body weight daily (to a maximum of 6 g daily), divided into 3 separate doses.

Newborn and children aged under 2 months
For new-borns and children less than 2 months old, the usual dose is 25 mg to 60 mg per kg of body weight daily divided into 2 or doses.

If you are given too much, or too little, Ceftazidime
Your medication will usually be given to you by the health professional – if you think you may have missed a dose or have received too much or too little of the medicine please tell your doctor or nurse immediately. Signs of overdose include pain and swelling of injection site, dizziness, pins and needles, headaches, and fits, inflammation of the brain and loss of consciousness.

As with all antibiotics it is important that you are given Ceftazidime regularly and the full course is completed.

If you have any further questions on the use of this product, ask your doctor or the other health personnel.

4. Possible side effects
Like all medicines, Ceftazidime can cause side effects, although not everybody gets them. As with some other antibiotics, some people find they have an allergy to Ceftazidime.

If any of the following serious side effects happens tell your doctor or nurse immediately:
- allergic reactions, such as sudden wheezing and tightness of the chest, swelling of the eyelids, face, throat or lip, severe skin rash that can blister and may involve the eyes, mouth and throat and genital, fainting.
- diarrhoea that is serious lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of serious bowel inflammation that can happen during or after taking antibiotics.

Common side effects: affects 1 to 10 users in 100
PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

- Blood: blood abnormalities causing changes in blood test results of the numbers of some blood cells including an increase in red blood cells and platelets, which may cause blood clots.
- Skin: itching, flushing, eruption on the skin (maculopapulous rash or exanthema)
- General: local skin reactions, inflammation of a blood vessel, inflammation at the site of injection after intravenous administration.

Uncommon side effects: affects 1 to 10 users in 1,000
- Blood: blood abnormalities causing bleeding tendency, easy bruising, increased risk of infections. Changes in blood test results of the number of some blood cells
- Nervous system: “pins and needles”, bad taste in the mouth, headache, dizziness, numbness, tingling, burning sensations, cramps, confusion, sleepiness, convulsions
- Gastrointestinal: nausea, vomiting, diarrhoea and pain in the gut
- General: fever

Rare side effects: affects 1 to 10 users in 10,000
- Skin: severe skin reactions with blistering of the skin, mouth or eyes (e.g. Stevens Johnson’s syndrome) or with peeling of the skin (e.g. Lyell’s syndrome)
- Blood: anaemia with symptoms such as fatigue, pale skin colouration and shortness of breath, big fall in the number of circulating white blood cells (agranulocytosis) leading to an increase in the risk of infection
- Liver: changes in the result of the blood tests that check the liver function
- Genitals: itching or pain in the vagina (symptoms of fungal or bacterial vaginal infections)
- Gastrointestinal: fungal infection in the mouth, a particular infection of the large gut following treatment with antibiotics causing severe and persistent diarrhoea (pseudomembranous colitis)
- Kidney: impaired kidney function, changes in the results of the blood tests that check the kidney function

Very rare side effects: affects less than 1 user in 10,000
- Liver: yellowing of the skin and eyes (jaundice)
- Immune system: severe allergic reaction causing sudden swelling of the throat, wheezing, shortness of breath and sudden drop in blood pressure
- Nervous system: trembling, uncontrolled stiffness of the muscle, fits, unconsciousness and a general inflammation of the brain can also happen, but usually only in people with poor kidneys.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. Storing Ceftazidime for Injection:
Keep out of the reach and sight of children
Store below 25°C
Keep the vial in the outer carton in order to protect from light
Discard any unused solution

This product should not be used after the expiry date printed on the carton and ampoule label after EXP. The doctor or nurse will check that the product has not passed this date. Any product that has passed this date must be returned to a pharmacist or doctor for safe disposal.

6. Further Information

What Ceftazidime for injection contains
Each vial contains the active ingredient, Ceftazidime pentahydrate, equivalent to 1 g of Ceftazidime, as a powder for solution for injection. It also contains the inactive ingredient, sodium carbonate. This medicinal product contains 52.5 mg (2.28 mmol) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

What Ceftazidime for injection looks like and contents of the pack
Ceftazidime is available powder for solution for injection. The powder is white or off-white. The vials are placed in cartons. Pack sizes: Boxes of one, five or ten vials.

Marketing Authorisation Holder
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Romford
United Kingdom
RM3 8UG

Manufacturer
Cardinal Health, Bampton Road,
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United Kingdom.
RM3 8UG

This medicinal product is authorised in the Member States of the EEA under the following names:
<To be completed nationally>

Product Licence Nos.:
<To be completed nationally>

TECHNICAL PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT
Ceftazidime 1 g Powder for Solution for Injection

PHARMACEUTICAL FORM
Powder for solution for injection

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 ‘Special precautions for use and handling’.

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 12 hours at 2°C - 8°C when prepared in Sterile Water for Injection or 1% Lidocaine Hydrochloride Injection.

Special precautions for use and 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 discolouration 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**

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intramuscular</strong></td>
<td></td>
</tr>
<tr>
<td>1 g</td>
<td>3.0 *</td>
</tr>
<tr>
<td>1 g</td>
<td>3.0 **</td>
</tr>
<tr>
<td><strong>Intravenous-Injection</strong></td>
<td></td>
</tr>
<tr>
<td>1 g</td>
<td>10.0 *</td>
</tr>
</tbody>
</table>

* Sterile Water for Injection
** 1% Lidocaine Hydrochloride Injection (intramuscular use only)

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 1 g**

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 discolouration. Only clear and colourless solution free from particles should be used.

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PAR Ceftazidime 250mg, 500mg and 1g Powder for Solution for Injection and 2g Powder for Solution for Injection/Infusion

Product Licence Nos.:  
<To be completed nationally>
Ceftazidime 2 g Powder for Solution for Injection or Infusion

Ceftazidime (as pentahydrate)

Read all this leaflet carefully before you have been given Ceftazidime injection or infusion

- Keep this leaflet. You may need to read it again
- If you any have further questions, please ask your doctor or pharmacist
- If any of the side effects become serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- This medicine has been prescribed for you personally and should not be passed on to others. It may harm them even if their symptoms are the same as yours

In this leaflet:
1. What Ceftazidime for injection or infusion is and what it is used for
2. Before you are given Ceftazidime for injection or infusion
3. How Ceftazidime for injection or infusion is given
4. Possible side-effects
5. Storing Ceftazidime for injection or infusion
6. Further information

1. What Ceftazidime for injection or infusion is and what it is used for
Ceftazidime belongs to a group of antibiotics called cephalosporins. Antibiotics are used to kill the bacteria or “germs” that cause infections.

Ceftazidime is used to treat specific types of infections which are sensitive to the drug which include:
- Pneumonia acquired at hospitals (nosocomial pneumonia)
- Lung infections in patients with cystic fibrosis
- Infections of the tissues covering the brain

2. Before you are given Ceftazidime for injection or infusion:

You should not be given Ceftazidime for injection or infusion if:
- You are allergic to Cephalosporins including Ceftazidime or any of the ingredients in this injection or infusion (e.g. sodium carbonate)
- You have had a previous, immediate and/or severe allergic reaction to penicillin or any beta-lactam antibiotic (if you are unsure what a beta-lactam antibiotic is, please ask your doctor or pharmacist)

Take special care with Ceftazidime for injection or infusion if:
- You are taking a diuretic (water tablet) such as furosemide
- You are taking any other antibiotics e.g. chloramphenicol or aminoglycoside antibiotics
- You are on a low sodium diet
- You have any diseases of the stomach and/or intestine (gastrointestinal diseases e.g. colitis)
- If you experience bloody diarrhoea, you must stop treatment and contact your doctor immediately
- You have kidney problems. You may still receive Ceftazidime but you may need a lower dose.

If you are unsure, ask your doctor or the other health care personnel for advice. If you are having a blood test for any reason, tell the person who is taking your blood sample that you are having Ceftazidime, as it may affect your results. If your urine is being tested for sugar, **Ceftazidime may cause a false positive result.**

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Medicines which may interact with Ceftazidime include:
- chloramphenicol
- macrolides
- tetracyclines
- drugs known to cause diseases or damage to the kidney as a side effect (e.g. cisplatin), aminoglycoside antibiotics such as gentamicin or amikacin, diuretics (e.g. furosemide or cyclosporine)
Pregnancy and Breastfeeding
Please inform your doctor if you are pregnant, planning on becoming pregnant or breastfeeding before taking this medicine. This medicine should not be used during pregnancy or breastfeeding unless advised by your doctor.

Driving and using machines
Ceftazidime can cause dizziness and convulsions. If affected you should not drive or operate machinery.

Important information about some of the ingredients of Ceftazidime
This medicinal product contains 105 mg (4.57 mmol) of sodium per dose.
To be taken into consideration by patients on a controlled sodium diet.

3. How Ceftazidime for injection or infusion is given
The dose depends on the severity and type of infection/infusion you have, as well as on your age, weight and function of your kidney. Tell your doctor if you have any kidney problems.

Adults
The usual adult dose is 1 g three times a day or 2 g twice a day. For severe infections, or for patients who have a special risk of infections due to a low white blood cell count, the usual dose is 2 g three times a day.

Adults with moderate to severe kidney problems
For patients with moderate to severe kidney problems the dose of Ceftazidime will be reduced.

For patients with renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration the dose is 1 g daily in divided doses.

For patients who have haemodialysis courses, the appropriate dose should be repeated after each haemodialysis period. This is because some of the Ceftazidime may be removed from the body during this type of dialysis and so needs to be topped up.

Elderly
For elderly patients the total daily dose should normally not be more than 3 g, especially in those over 80 years of age.

Children aged over 2 months
For children aged over 2 months the usual dose is 30 mg to 100 mg per kg of body weight daily divided into 2 or 3 separate doses. Severely ill children may receive up to 150 mg per kg of body weight daily (to a maximum of 6 g daily), divided into 3 separate doses.

Newborn and children aged under 2 months
For new-borns and children less than 2 months old, the usual dose is 25 mg to 60 mg per kg of body weight daily divided into 2 or doses.

If you are given too much, or too little, Ceftazidime
Your medication will usually be given to you by the health professional – if you think you may have missed a dose or have received too much or too little of the medicine please tell your doctor or nurse immediately. Signs of overdose include pain and swelling of injection site, dizziness, pins and needles, headaches, and fits, inflammation of the brain and loss of consciousness.
As with all antibiotics it is important that you are given Ceftazidime regularly and the full course is completed.

If you have any further questions on the use of this product, ask your doctor or the other health personnel.

4. Possible side effects
Like all medicines, Ceftazidime can cause side effects, although not everybody gets them. As with some other antibiotics, some people find they have an allergy to Ceftazidime.

If any of the following serious side effects happens tell your doctor or nurse immediately
- allergic reactions, such as sudden wheezing and tightness of the chest, swelling of the eyelids, face, throat or lip, severe skin rashes that can blister and may involve the eyes, mouth and throat and genital, fainting.
- diarrhoea that is serious lasts a long time or has blood in it, with stomach pain or fever. This can be a sign of serious bowel inflammation that can happen during or after taking antibiotics.
Common side effects: affects 1 to 10 users in 100
- Blood: blood abnormalities causing changes in blood test results of the numbers of some blood cells including an increase in red blood cells and platelets, which may cause blood clots.
- Skin: itching, flushing, eruption on the skin (maculopapuluous rash or exanthema)
- General: local skin reactions, inflammation of a blood vessel, inflammation at the site of injection after intravenous administration.

Uncommon side effects: affects 1 to 10 users in 1,000
- Blood: blood abnormalities causing bleeding tendency, easy bruising, increased risk of infections. Changes in blood test results of the number of some blood cells
- Nervous system: “pins and needles”, bad taste in the mouth, headache, dizziness, numbness, tingling, burning sensations, cramps, confusion, sleepiness, convulsions
- Gastrointestinal: nausea, vomiting, diarrhoea and pain in the gut.
- General: fever

Rare side effects: affects 1 to 10 users in 10,000
- Skin: severe skin reactions with blistering of the skin, mouth or eyes (e.g. Stevens Johnson’s syndrome) or with peeling of the skin (e.g. Lyell’s syndrome)
- Blood: anaemia with symptoms such as fatigue, pale skin colouration and shortness of breath, big fall in the number of circulating white blood cells (agranulocytosis) leading to an increase in the risk of infection
- Liver: changes in the result of the blood tests that check the liver function
- Genitals: itching or pain in the vagina (symptoms of fungal or bacterial vaginal infections)
- Gastrointestinal: fungal infection in the mouth, a particular infection of the large gut following treatment with antibiotics causing severe and persistent diarrhoea (pseudomembranous colitis)
- Kidney: impaired kidney function, changes in the results of the blood tests that check the kidney function.

Very rare side effects: affects less than 1 user in 10,000
- Liver: yellowing of the skin and eyes (jaundice)
- Immune system: severe allergic reaction causing sudden swelling of the throat, wheezing, shortness of breath and sudden drop in blood pressure.
- Nervous system: trembling, uncontrolled stiffness of the muscle, fits, unconsciousness and a general inflammation of the brain can also happen, but usually only in people with poor kidneys.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. Storing Ceftazidime for injection or infusion:
Keep out of the reach and sight of children
Store below 25°C
Keep the vial in the outer carton in order to protect from light
Discard any unused solution

This product should not be used after the expiry date printed on the carton and ampoule label after EXP. The doctor or nurse will check that the product has not passed this date. Any product that has passed this date must be returned to a pharmacist or doctor for safe disposal.

6. Further Information

What Ceftazidime for injection or infusion contains
Each vial contains the active ingredient, Ceftazidime pentahydrate, equivalent to 2 g of Ceftazidime, as a powder for solution for injection or infusion. It also contains the inactive ingredient, sodium carbonate. This medicinal product contains 105 mg (4.57 mmol) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet

What Ceftazidime for injection or infusion looks like and contents of the pack
Ceftazidime is available powder for solution for injection or infusion. The powder is white or off-white. The vials are placed in cartons. Pack sizes: Boxes of one, five or ten vials.
**Marketing Authorisation Holder**
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This medicinal product is authorised in the Member States of the EEA under the following names:
<To be completed nationally>

**Product Licence Nos.:**
<To be completed nationally>

### TECHNICAL PRESCRIBING INFORMATION

#### NAME OF THE MEDICINAL PRODUCT
Ceftazidime 2 g Powder for Solution for Injection or Infusion

#### PHARMACEUTICAL FORM
Powder for solution for injection or infusion

### 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 ‘Special precautions for use and handling’

#### 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 a microbiological point of view, the product should 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 2°C - 8°C when prepared in 0.9% (9mg/ml) Sodium Chloride Injection and 5% (50mg/ml) Dextrose Injection
- 12 hours at 2°C - 8°C when prepared in Sterile Water for Injection
- 12 hours at 2°C - 8°C when prepared in 5% (50mg/ml) Dextrose Injection, Compound Sodium Lactate Injection, Dextran 40 Injection 10% in 0.9% (9mg/ml) Sodium Chloride Injection and Dextran 40 Injection in 10% in 5% (50mg/ml) Dextrose Injection
- 12 hours at 2°C - 8°C when Ceftazidime for Injection 2g (4mg/mL) is prepared with Cefuroxime Sodium (3mg/mL), Heparin (10µ/mL), Potassium Chloride (10mEq/L) and Cloxacillin Sodium (4mg/mL) in 0.9% (9mg/ml) Sodium Chloride Injection.
- 24 hours at 2°C - 8°C when prepared in 0.9% (9mg/ml) Sodium Chloride Injection

Special precautions for use and 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 discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

**Instructions for reconstitution:**

**Preparation of solutions of Ceftazidime**

<table>
<thead>
<tr>
<th>Amount of diluent to be added (ml)</th>
<th>Approximate ceftazidime concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous-Injection</strong></td>
<td></td>
</tr>
<tr>
<td>2 g</td>
<td>10.0*</td>
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<tr>
<td></td>
<td>170</td>
</tr>
<tr>
<td><strong>Intravenous-Infusion</strong></td>
<td></td>
</tr>
<tr>
<td>2 g</td>
<td>50.0**</td>
</tr>
<tr>
<td></td>
<td>40‡</td>
</tr>
</tbody>
</table>

* Sterile Water for Injection

** Note: Addition should be in two stages

‡ Note: Use 0.9% (9mg/ml) Sodium Chloride Injection, 5% (50mg/ml) Dextrose Injection, 5% (50mg/ml) Dextrose and 0.9% (9mg/ml) Sodium Chloride Injection, Dextran 40 Injection BP 10% in 0.9% (9mg/ml) Sodium Chloride Injection, Dextran 40 Injection BP 10% in 5% (50mg/ml) Dextrose Injection and Compound Sodium Lactate Injection as Sterile Water for Injection produces hypotonic solutions at this concentration

Compatibility of Ceftazidime for Injection 2g (4mg/mL) has been demonstrated with Cefuroxime Sodium (3mg/mL), Heparin (10µ/mL), Potassium Chloride (10mEq/L) and Cloxacillin Sodium (4mg/mL) in 0.9% (9mg/ml) Sodium Chloride Injection.

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 2 g**

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 or introduced into the tubing of the giving set if the patient is receiving parenteral fluid (see above for compatible fluids).

**Preparation for administration of 2 g vials by infusion**

This vial may be constituted for short intravenous infusion (e.g. up to 30 minutes).

Prepare using a total of 50 ml of compatible diluent, added in TWO stages as below:

1. Insert the syringe needle through the vial closure and add 10 ml of diluent.
2. 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. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.
5. Transfer the reconstituted solution to the final delivery vehicle, making up to a total volume of at least 50 ml, and administer by intravenous infusion over 15-30 minutes.

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 discolouration. Only clear and colourless solution free from particles should be used.

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United Kingdom

**Product Licence Nos.:**
<To be completed nationally>
Module 4
Labelling

Outer Labelling

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT</strong>&lt;br&gt;&lt;To be completed nationally&gt;&lt;br&gt;Ceftazidime</td>
</tr>
<tr>
<td>2.</td>
<td><strong>STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
</tr>
<tr>
<td>3.</td>
<td><strong>LIST OF EXCIPIENTS</strong>&lt;br&gt;250 mg: Each vial contains 291 mg of ceftazidime pentahydrate, equivalent to 250 mg of ceftazidime&lt;br&gt;Excipient: each 250 mg vial of powder contains 30 mg of sodium carbonate</td>
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<tr>
<td>4.</td>
<td><strong>PHARMACEUTICAL FORM AND CONTENTS</strong>&lt;br&gt;Powder for Solution for Injection&lt;br&gt;1 x 250 mg&lt;br&gt;5 x 250 mg&lt;br&gt;10 x 250 mg</td>
</tr>
<tr>
<td>5.</td>
<td><strong>METHOD AND ROUTE(S) OF ADMINISTRATION</strong>&lt;br&gt;Read the package leaflet before use&lt;br&gt;For intramuscular or intravenous use</td>
</tr>
<tr>
<td>6.</td>
<td><strong>SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong>&lt;br&gt;Keep out of the reach and sight of children</td>
</tr>
<tr>
<td>7.</td>
<td><strong>OTHER SPECIAL WARNING(S), IF NECESSARY</strong>&lt;br&gt;&lt;To be completed nationally&gt;</td>
</tr>
<tr>
<td>8.</td>
<td><strong>EXPIRY DATE</strong>&lt;br&gt;EXP:</td>
</tr>
<tr>
<td>9.</td>
<td><strong>SPECIAL STORAGE CONDITIONS</strong>&lt;br&gt;Unopened: Store below 25°C. Keep the vial in the outer carton&lt;br&gt;For in use shelf life of the medicinal product see guidance in the leaflet</td>
</tr>
<tr>
<td>10.</td>
<td><strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong>&lt;br&gt;For single use only – discard any unused contents appropriately&lt;br&gt;Use immediately following vial opening</td>
</tr>
<tr>
<td>11.</td>
<td><strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong>&lt;br&gt;Cardinal Health, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, UK</td>
</tr>
<tr>
<td>12.</td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong>&lt;br&gt;&lt;To be completed nationally&gt;</td>
</tr>
<tr>
<td>13.</td>
<td><strong>BATCH NUMBER</strong>&lt;br&gt;Lot:</td>
</tr>
<tr>
<td>14.</td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong>&lt;br&gt;Medicinal product subject to medical prescription</td>
</tr>
</tbody>
</table>
### 15. INSTRUCTIONS ON USE

- **PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

  1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**
  2. **METHOD OF ADMINISTRATION**
     - <To be completed nationally>
     - Ceftazidime
     - For intramuscular or intravenous use
  3. **EXPIRY DATE**
     - EXP:
  4. **BATCH NUMBER**
     - Lot:
  5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**
     - 250 mg
  6. **OTHER**
     - <To be completed nationally>

Must be reconstituted before use.
Outer Labelling

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>&lt;To be completed nationally&gt; Ceftazidime</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>500 mg: Each vial contains 582 mg of ceftazidime pentahydrate, equivalent to 500mg of ceftazidime.</td>
</tr>
<tr>
<td>Excipient: each 500 mg vial of powder contains 60 mg of sodium carbonate</td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>Powder for Solution for Injection</td>
</tr>
<tr>
<td>1 x 500mg</td>
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<tr>
<td>5 x 500mg</td>
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<tr>
<td>10 x 500mg</td>
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<tr>
<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
<tr>
<td>For intramuscular or intravenous use</td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE</td>
</tr>
<tr>
<td>REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the reach and sight of children</td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING(S), IF NECESSARY</td>
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<td>&lt;To be completed nationally&gt;</td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP:</td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td>Unopened: Store below 25°C. Keep the vial in the outer carton</td>
</tr>
<tr>
<td>For in use shelf life of the medicinal product see guidance in the leaflet</td>
</tr>
<tr>
<td>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE</td>
</tr>
<tr>
<td>MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
</tr>
<tr>
<td>For single use only – discard any unused contents appropriately</td>
</tr>
<tr>
<td>Use immediately following vial opening</td>
</tr>
<tr>
<td>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Cardinal Health, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, UK</td>
</tr>
<tr>
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<td>&lt;To be completed nationally&gt;</td>
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<tr>
<td>13. BATCH NUMBER</td>
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<tr>
<td>Lot:</td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
</tr>
<tr>
<td>Medicinal product subject to medical prescription</td>
</tr>
</tbody>
</table>
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inner Labelling

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
   Ceftazidime
   For intramuscular or intravenous use

2. METHOD OF ADMINISTRATION
   <To be completed nationally>

3. EXPIRY DATE
   EXP:

4. BATCH NUMBER
   Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
   500 mg

6. OTHER
   <To be completed nationally>
   Must be reconstituted before use
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT
   <To be completed nationally>
   Ceftazidime

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCipients
   1 g: Each vial contains 1165 mg of ceftazidime pentahydrate, equivalent to 1 g of ceftazidime
   Excipient: each 1 g vial of powder contains 121 mg of sodium carbonate

4. PHARMACEUTICAL FORM AND CONTENTS
   Powder for Solution for Injection
   1 x 1 g vial
   5 x 1 g vial
   10 x 1 g vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION
   Read the package leaflet before use
   For intramuscular or intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
   Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY
   <To be completed nationally>

8. EXPIRY DATE
   EXP:

9. SPECIAL STORAGE CONDITIONS
   Unopened: Store below 25°C. Keep the vial in the outer carton
   For in use shelf life of the medicinal product see guidance in the leaflet

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
   For single use only – discard any unused contents appropriately
   Use immediately following vial opening

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
   Cardinal Health, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, UK

12. MARKETING AUTHORISATION NUMBER(S)
   <To be complete nationally>

13. BATCH NUMBER
   Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
   Medicinal product subject to medical prescription
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inner Labelling

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
2. METHOD OF ADMINISTRATION
   <To be completed nationally>
   Ceftazidime
   For intramuscular or intravenous use

3. EXPIRY DATE
   EXP:

4. BATCH NUMBER
   Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
   1 g

6. OTHER
   <To be completed nationally>
   Must be reconstituted before use
Outer Labelling

<table>
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<tr>
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<td>1. NAME OF THE MEDICINAL PRODUCT</td>
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<tr>
<td>&lt;To be completed nationally&gt;</td>
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<tr>
<td>Ceftazidime</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>2 g: Each vial contains 2330 mg of ceftazidime pentahydrate, equivalent to 2 g of ceftazidime</td>
</tr>
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<td>Excipient: each 2 g vial of powder contains 242 mg of sodium carbonate</td>
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<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
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<tr>
<td>Powder for Solution for Injection or Infusion</td>
</tr>
<tr>
<td>1 x 2 g</td>
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<tr>
<td>5 x 2 g</td>
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<tr>
<td>10 x 2 g</td>
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<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
<tr>
<td>For intravenous use</td>
</tr>
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<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the reach and sight of children</td>
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<td>8. EXPIRY DATE</td>
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<tr>
<td>EXP:</td>
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<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
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<td>Unopened: Store below 25°C. Keep the vial in the outer carton</td>
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<td>Lot:</td>
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<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
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Medicinal product subject to medical prescription

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Inner Labelling

#### PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

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<td>Ceftazidime</td>
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<td></td>
<td>For intravenous use</td>
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<tr>
<td>2.</td>
<td>METHOD OF ADMINISTRATION</td>
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<tr>
<td></td>
<td></td>
<td>&lt;To be completed nationally&gt;</td>
</tr>
<tr>
<td>3.</td>
<td>EXPIRY DATE</td>
<td>EXP:</td>
</tr>
<tr>
<td>4.</td>
<td>BATCH NUMBER</td>
<td>Lot:</td>
</tr>
<tr>
<td>5.</td>
<td>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</td>
<td>2 g</td>
</tr>
<tr>
<td>6.</td>
<td>OTHER</td>
<td>&lt;To be completed nationally&gt;</td>
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<td>Must be reconstituted before use</td>
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Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for the Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion are approvable for the 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

These applications were submitted via the Decentralised Procedure (UK/H/1402/001-4/DC), with the UK as RMS and Denmark, Germany, Finland, Ireland, Norway and Sweden as CMSs. The legal basis for these applications was Article 10.1 of Directive 2001/83 EC, as amended, for Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion, containing the known active substance ceftazidime pentahydrate. The reference medicinal products for these applications are Fortum for Injection 250mg/vial, 500mg, 1g and 2g (Powder for Reconstitution), which were first licensed in the UK to Glaxo Operations UK Limited, in October 1983 (500mg, 1g and 2g) and May 1985 (250mg/vial).

Ceftazidime is a semi-synthetic bactericidal 3rd generation cephalosporin antibiotic, active against a wide range of Gram-positive and Gram-negative bacteria. Ceftazidime exerts antibacterial activity by inhibiting penicillin-binding proteins, which results in the interruption of cell wall biosynthesis at the final stage of peptidoglycan production, resulting in bacterial cell lysis and death.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

The drug products correspond to the current EU definition for generic medicinal products because they comply with the criteria of having the same qualitative and quantitative composition in terms of active substance, and the same dosage form as the reference medicinal products stated above.

The proposed products are developed using an approved drug substance that is to be administered as an aqueous intravenous solution, containing the same drug substance in the same concentration as the reference medicinal products stated above. Therefore, a bioequivalence study is not required in support of these applications.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.
The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Concerned Member States agreed to grant respective licences for the above products at the end of procedure (Day 210 – 13th September 2010). After a subsequent national phase, the UK granted licences for these products on 18th October 2010 (PL 25975/0046-9).
## II. ABOUT THE PRODUCT

| Name of the products in the Reference Member State | Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection
| Name(s) of the active substance(s) (USAN) | Ceftazidime pentahydrate
| Pharmacotherapeutic classification (ATC code) | Other beta-lactam antibacterial – Third generation-cephalosporins (J01D D02)
| Pharmaceutical form and strength(s) | 250mg, 500mg & 1g - Powder for Solution for Injection
| 2g - Powder for Solution for Injection/Infusion
| Reference numbers for the Decentralised Procedure | UK/H/1402/001-4/DC
| Reference Member State | United Kingdom
| Concerned Member States | Denmark, Germany, Finland, Ireland, Norway and Sweden
| Marketing Authorisation Number(s) | PL 25975/0046-9
| Name and address of the authorisation holder | Cardinal Health UK 434 Ltd.
| Bampton Road, Harold Hill
| Romford, Essex
| RM3 8UK
| United Kingdom
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Ceftazidime pentahydrate

Chemical Names: (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-8-oxo-3-[(1-pyridinio)methyl]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate pentahydrate

Structure:

![Structure of Ceftazidime](image)

Molecular formula: C_{22}H_{22}N_{6}O_{7}S_{2}5H_{2}O
Molecular weight: 636.6
Physical form: White to almost white crystalline powder. Slightly soluble in water and in methanol, practically insoluble in acetone and in alcohol, dissolves in acid and alkali solutions.

Ceftazidime pentahydrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Appropriate stability data have been generated, supporting a suitable retest period for active ceftazidime pentahydrate when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Sodium carbonate, anhydrous is the only excipient used. This complies with the European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for this excipient.

The above excipient does not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain stable products containing ceftazidime pentahydrate that could be considered generic medicinal products of Fortum for Injection 250mg/vial, 500mg, 1g and 2g (Powder for Reconstitution), which were first licensed in the UK to Glaxo Operations UK Limited, in October 1983 (500mg, 1g and 2g) and May 1985 (250mg/vial).

Suitable pharmaceutical development data have been provided for these applications.
Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of each product. The results are satisfactory.

Finished Product Specifications
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished products are supplied in 15ml (250mg, 500mg and 1g), 50ml (2g) Type I glass vials, closed with bromobutyl rubber stoppers and polypropylene flip-off aluminium seal. Pack sizes are 1, 5 and 10 vials.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

The Marketing Authorisation Holder has stated that not all packs are intended to be marketed. However, they have committed to submitting mock-ups of any relevant pack size to the appropriate regulatory authorities before marketing.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 1 year has been set when the product is unopened, with the storage conditions “Store below 25°C” and “Keep the vial in the outer carton in order to protect from light”.

It has been stipulated that the contents of the reconstituted concentrate should be used immediately after preparation.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the successful user-testing of the PIL for Ceftriaxone 500mg Injection/Infusion (parent PIL). The content and lay out of Ceftazidime 250mg, 500mg, 1g and 2g Injection/Infusion (daughter PIL) is comparable to that of the parent PIL. The products are from the same therapeutic class and have similar indications. The bridging report is accepted.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.
Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of ceftazidime pentahydrate are well-known.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of a detailed environmental risk assessment.

There are no objections to the approval of these products from a pre-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

These applications are for generic medicinal products of Fortum for Injection 250mg/vial, 500mg, 1g and 2g (Powder for Reconstitution), which were first licensed in the UK to Glaxo Operations UK Limited, in October 1983 (500mg, 1g and 2g) and May 1985 (250mg/vial). The use of the reference products is well-established in the UK.

All products contain the same quantitative and qualitative composition of the active substance as their respective reference products.

According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), there is no requirement for a bioequivalence study for products where the active ingredient is present in solution.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
Ceftazidime pentahydrate has an acceptable adverse events profile. No new safety data are supplied or required for these generic applications. Ceftazidime pentahydrate has a well-established side-effect profile and is generally well-tolerated.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Clinical Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Ceftazidime 250mg, 500mg & 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection/Infusion beyond those already described.

EFFICACY
These applications are for generic medicinal products of Fortum for Injection 250mg/vial, 500mg, 1g and 2g (Powder for Reconstitution), which were first licensed in the UK to Glaxo Operations UK Limited, in October 1983 (500mg, 1g and 2g) and May 1985 (250mg/vial). Use of the reference products is well-established in the UK, and all products contain the same quantitative and qualitative composition of the active substance as their respective reference product.

According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr*), there is no requirement for a bioequivalence study for products where the active ingredient is present in solution.

No new safety data are supplied or required for these generic applications. Ceftazidime pentahydrate has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with ceftazidime pentahydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
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