Public Assessment Report

Decentralised Procedure

Ceftazidime 3g Powder for solution for injection/infusion

PL 22805/0027

UK/H/1486/001/DC

Orchid Europe Ltd
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Orchid Europe Ltd a Marketing Authorisation (licence) for the medicinal product Ceftazidime 3g Powder for solution for injection/infusion (product licence number: 22805/0027). This medicine is available on prescription only.

Ceftazidime 3g Powder for solution for injection/infusion belongs to a group of medicines called cephalosporins, which kill bacteria. Ceftazidime is used to treat infections of the:
- Ear, nose, throat and chest, including pneumonia
- Urinary passage
- Skin and layers of flesh immediately under the skin
- Gut, gall bladder and abdomen
- Bones and joints
- Membranes and fluid surrounding the brain and spinal chord (this infection is called meningitis)

Ceftazidime can also be used to treat infections that may occur after dialysis or to prevent infections that may occur after some surgical operations.

The data submitted in support of this application for Ceftazidime 3g Powder for solution for injection/infusion raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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Module 1

Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ceftazidime 3g Powder for solution for injection/infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of application (Eudratrack details)</td>
<td>Level 1 Abridged</td>
</tr>
<tr>
<td></td>
<td>Level 2 Initial</td>
</tr>
<tr>
<td></td>
<td>Level 3 10.1</td>
</tr>
<tr>
<td></td>
<td>Level 4 Chemical substance</td>
</tr>
<tr>
<td></td>
<td>Level 5 Prescription only</td>
</tr>
<tr>
<td>Name of the active substance (INN)</td>
<td>Ceftazidime pentahydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Cephalosporin (J01DD02)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Powder for Solution for Injection/Infusion, 3 mg</td>
</tr>
<tr>
<td>Reference numbers for the decentralised Procedure</td>
<td>UK/H/1486/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Finland</td>
</tr>
<tr>
<td>Date of start of the procedure</td>
<td>6 June 2008</td>
</tr>
<tr>
<td>End date of decentralised procedure</td>
<td>7 December 2009</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 22805/0027</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Orchid Europe Ltd</td>
</tr>
<tr>
<td></td>
<td>Building 3, Chiswick Park,</td>
</tr>
<tr>
<td></td>
<td>566 Chiswick High Road,</td>
</tr>
<tr>
<td></td>
<td>Chiswick, London, W4 5YA</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ceftazidime 3g Powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains Ceftazidime 3 g (as Ceftazidime Pentahydrate).

This medicinal product contains 152mg (6.60mmol) of sodium/vial of powder for solution for injection/infusion.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection/infusion
White to cream coloured, crystalline powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Single infections
Mixed infections caused by two or more susceptible organisms
Severe infections in general
Respiratory tract infections
Ear, nose and throat infections
Urinary tract infections
Skin and soft tissue infections
Gastrointestinal, biliary and abdominal infections
Bone and joint infections
Dialysis: infections associated with haemo - and peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)

In meningitis it is recommended that the results of a sensitivity test are known before treatment with ceftazidime as a single agent. It may be used for infections caused by organisms resistant to other antibiotics including aminoglycosides and many cephalosporins. When appropriate, however, it may be used in combination with an aminoglycoside or other beta-lactam antibiotic for example, in the presence of severe neutropenia, or with an antibiotic active against anaerobes when the presence of bacteroides fragilis is suspected. In addition, ceftazidime is indicated in the perioperative prophylaxis of transurethral prostatectomy.
4.2 Posology and method of administration

Ceftazidime is to be used by the parenteral route, the dosage depending upon the severity, sensitivity and type of infection and the age, weight and renal function of the patient.

Adults: The adult dosage range for ceftazidime is 1 to 6g per day 8 or 12 hourly (im or iv). In the majority of infections, 1g 8-hourly or 2g 12-hourly should be given. In urinary tract infections and in many less serious infections, 500mg or 1g 12-hourly is usually adequate. In very severe infections, especially immunocompromised patients, including those with neutropenia, 2g 8 or 12-hourly or 3g 12-hourly should be administered.

When used as a prophylactic agent in prostatic surgery 1g (from the 1g vial) should be given at the induction of anaesthesia. A second dose should be considered at the time of catheter removal.

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.

Cystic fibrosis: In fibrocystic adults with normal renal function who have pseudomonal lung infections, high doses of 100 to 150mg/kg/day as three divided doses should be used. In adults with normal renal function 9g/day has been used.

Infants and children: The usual dosage range for children aged over two months is 30 to 100mg/kg/day, given as two or three divided doses.

Doses up to 150mg/kg/day (maximum 6g daily) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

Neonates and children up to 2 months of age: Whilst clinical experience is limited, a dose of 25 to 60mg/kg/day given as two divided doses has proved to be effective. In the neonate the serum half-life of ceftazidime can be three to four times that in adults.

Dosage in impaired renal function: Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50ml/min. In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.
Renal impairment: For patients in renal failure on continuous arteriovenous haemodialysis or high-flux haemofiltration in intensive therapy units, it is recommended that the dosage should be 1g daily in divided doses.

For low-flux haemofiltration it is recommended that the dosage should be that suggested under impaired renal function.

Recommended maintenance doses are shown below:

**RECOMMENDED MAINTENANCE DOSES OF CEFTAZIDIME IN RENAL INSUFFICIENCY**

<table>
<thead>
<tr>
<th>Creatinine clearance ml/min</th>
<th>Approx. serum creatinine* µmol/l(mg/dl)</th>
<th>Recommended unit dose of ceftazidime (g)</th>
<th>Frequency of dosing (hourly)</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 guidelines and may not accurately predict renal function in all patients especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

In patients with severe infections, especially in neutropenics, who would normally receive 6g of ceftazidime daily were it not for renal insufficiency, the unit dose given in the table above may be increased by 50% or the dosing frequency increased appropriately. In such patients it is recommended that ceftazidime serum levels should be monitored and trough levels should not exceed 40mg/litre.

When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

**Males:**

\[
\text{Creatinine clearance} = \frac{\text{Weight (kg) x (140 - age in years)}}{72 x \text{serum creatinine (mg/dl)}}
\]

**Females:**

0.85 x above value.
To convert serum creatinine in µmol/litre into mg/dl divide by 88.4.

In children the creatinine clearance should be adjusted for body surface area or lean body mass and the dosing frequency reduced in cases of renal insufficiency as for adults.

The serum half-life of ceftazidime during haemodialysis ranges from 3 to 5 hours. The appropriate maintenance dose of ceftazidime should be repeated following each haemodialysis period.

Dosage in peritoneal dialysis: Ceftazidime may also be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD). As well as using ceftazidime intravenously, it can be incorporated into the dialysis fluid (usually 125 to 250mg for 2L of dialysis fluid).

Administration: Ceftazidime may be given intravenously 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.

4.3 Contraindications
Ceftazidime is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics.

4.4 Special warnings and precautions for use
Hypersensitivity reactions:
As with other beta-lactam antibiotics, before therapy with ceftazidime is instituted, careful inquiry should be made for a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other drugs. Special care is indicated in patients who have experienced an allergic reaction to penicillins or beta-lactams. Ceftazidime should be given only with special caution to patients with type I or immediate hypersensitivity reactions to penicillin. If an allergic reaction to ceftazidime occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.

Renal function:
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs, e.g. aminoglycoside antibiotics, or potent diuretics such as frusemide, as these combinations are suspected of affecting renal function adversely. Clinical experience with ceftazidime has shown that this is not likely to be a problem at the recommended dose levels. There is no evidence that ceftazidime adversely affects renal function at normal therapeutic doses: however, as for all antibiotics eliminated via the kidneys, it is necessary to reduce the dosage according to the degree of reduction in renal function to avoid the clinical consequences of elevated antibiotic levels,
e.g. neurological sequelae, which have occasionally been reported when the dose has not been reduced appropriately (see 4.2 Dosage in Impaired Renal Function and 4.8 Undesirable Effects).

Overgrowth of non-susceptible organisms:
As with other broad spectrum antibiotics, prolonged use of ceftazidime may result in the overgrowth of non-susceptible organisms (e.g. Candida, Enterococci and Serratia spp) which may require interruption of treatment or adoption of appropriate measures. Repeated evaluation of the patient's condition is essential.

4.5 Interaction with other medicinal products and other forms of interaction
Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed. Ceftazidime does not interfere in the alkaline picrate assay for creatinine. The development of a positive Coombs' test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood.

Chloramphenicol is antagonistic in vitro with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime with chloramphenicol is proposed, the possibility of antagonism should be considered.

In common with other antibiotics, ceftazidime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, alternative non-hormonal methods of contraception are recommended.

4.6 Pregnancy and lactation
Pregnancy

There is no evidence of embryo toxicity or teratogenicity in animal studies (see Section 5.3), but there is no experience of safety in use during human pregnancy. Ceftazidime should therefore only be used during pregnancy if considered essential by the physician.

Lactation
Ceftazidime is excreted in human milk in low concentrations and should be used with caution in nursing mothers. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that breast-feeding might have to be discontinued. The infant may also become allergic to Ceftazidime.

4.7 Effects on ability to drive and use machines
Ceftazidime has no known influence on the ability to drive and use machine. However, side effects may occur (See also section 4.8), which may influence the ability to drive and use machines.
4.8 Undesirable effects
The following convention has been used for the classification of frequency:

very common \( \geq 1/10 \),
common \( \geq 1/100 \) and \(<1/10\),
uncommon \( \geq 1/1000 \) and \(<1/100\),
rare \( \geq 1/10,000 \) and \(<1/1000\),
very rare \(<1/10,000\).
not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse drug reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Candidiasis (including vaginal infection and oral candidiasis)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia, thrombocytosis, Coomb’s test positive</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Leucopenia, neutropenia, thrombocytopenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis, haemolytic anaemia, agranulocytosis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>Very rare</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse drug reactions</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Tremor, myoclonus, convulsions, encephalopathy, coma (These reports of neurological sequelae were reported in patients with renal impairment in whom the dose of ceftazidime was not appropriately reduced)</td>
<td>Not known</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Phlebitis, thrombophlebitis</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting, abdominal pain, colitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous colitis</td>
<td>Not known</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Alanine aminotransferase increased transient, aspartate aminotransferase increased transient, blood lactate dehydrogenase increased transient, gamma-glutamyl transferase increased transient, blood alkaline phosphatase increased transient</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
<td>Very rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Maculopapular rash, urticaria</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Blood urea increased transient, blood creatinine increased transient</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
4.9 Overdose

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

General symptomatic and supportive measure should be instituted, together with specific measures to control any seizures. In case of severe overdose, especially in a patient with renal failure, combined haemodialysis and haemoperfusion may be considered if response to more conservative therapy fails.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Third generation Cephalosporin, J01DD02

Mode of Action

Ceftazidime is a semi-synthetic bactericidal antibacterial agent of the cephalosporin class. Like other beta-lactam drugs, ceftazidime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes (transpeptidases). Inhibition of one or more of these essential penicillin-binding proteins results in the interruption of cell wall biosynthesis at the final stage of peptidoglycan production, resulting in bacterial cell lysis and death.

Mechanisms of resistance

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

- hydrolysis by beta-lactamases. Ceftazidime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamas (ESBLs) and by the chromosomally-encoded (AmpC) enzymes that may be induced or stably derepressed in certain aerobic gram-negative bacterial species

- reduced affinity of penicillin-binding proteins for Ceftazidime

- outer membrane impermeability, which restricts access of ceftazidime to penicillin binding proteins in gram-negative organisms

- drug efflux pumps
More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and/or antibacterial drugs of other classes.

**Breakpoints**

According to the National Committee for Clinical Laboratory Standards Guidelines (NCCLS), the MIC breakpoints for sensitive, intermediately sensitive or resistant organisms are as follows:

**MIC (µg/mL) Interpretation**
- **<8 Sensitive**
- **16 Intermediately Sensitive**
- **>32 mg/L Resistant**
  - *Haemophilus spp.* Susceptible <2 µg/mL
  - *Neisseria gonorrhoeae* Susceptible <0.5 µg/mL

**Susceptibility**

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, i.e. resistance &lt;10% in all EU Member States +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive micro-organisms:</strong></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (Group B)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>, penicillin susceptible #</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><strong>Gram-negative micro-organisms:</strong></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Salmonella spp</em></td>
</tr>
</tbody>
</table>
Species for which acquired resistance may be a problem, i.e.
resistance ≥ 10% in at least one of the EU Member States +

Gram-negative micro-organisms:

* Acinetobacter spp.
* Burkholderia cepacia
* Citrobacter freundii
* Citrobacter spp.
* Enterobacter spp.
* Klebsiella pneumoniae
* Klebsiella spp.
* Morganella morganii
* Pseudomonas aeruginosa
* Pseudomonas spp.

Inherently resistant organisms

Gram-positive micro-organisms:

* Enterococcus spp.

* Micrococcus spp.

* Staphylococcus aureus, methicillin resistant (MRSA) *

* Staphylococcus – coagulase negative, methicillin resistant*

+ Based on published data from several different sources
* Shows some in-vitro activity against methicillin-susceptible strains but should not be relied upon to treat staphylococcal infections.
# Shows some in-vitro activity against penicillin-susceptible strains but should not be relied upon to treat pneumococcal infections

5.2 Pharmacokinetic properties

Ceftazidime administered by the parenteral route reaches high and prolonged serum levels in man. After intramuscular administration of 500mg and 1g serum mean peak levels of 18 and 37mg/litre respectively are rapidly achieved. Five minutes after an intravenous bolus injection of 500mg, 1g or 2g, serum mean levels are respectively 46, 87 and 170mg/litre.

Therapeutically effective concentrations are still found in the serum 8 to 12 hours after both intravenous and intramuscular administration. The serum half-life is
about 1.8 hours in normal volunteers and about 2.2 hours in patients with apparently normal renal function. The serum protein binding of ceftazidime is low at about 10%.

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration. Approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile, significantly limiting the amount entering the bowel.

Concentrations of ceftazidime in excess of the minimum inhibitory levels for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids. Transplacental transfer of the antibiotic readily occurs. Ceftazidime penetrates the intact blood brain barrier poorly and low levels are achieved in the csf in the absence of inflammation. Therapeutic levels of 4 to 20mg/litre or more are achieved in the csf when the meninges are inflamed.

5.3 Preclinical safety data
Long term studies in animals have not been performed to evaluate carcinogenic potential. However, a mouse micronucleus test and an Ames test were both negative for mutagenic effects.

The teratogenicity of Ceftazidime has been studied in rabbits (i.m) and in mice (s.c.). Embryotoxicity and toxicity to rabbits were detected, but no teratogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium carbonate, anhydrous (E500)

6.2 Incompatibilities
Ceftazidime should not be mixed with solutions with a pH above 7.5 for example sodium bicarbonate solution for injection. Ceftazidime and aminoglycosides should not be mixed in the solution for injection because of the risk for precipitation.

Cannulae and catheters for intravenous use should be flushed with physiological salt-solution between administrations of ceftazidime and vancomycin to avoid precipitation.

6.3 Shelf life
Unopened - 24 months

After reconstitution:— Reconstituted product has demonstrated chemical and physical stability for 24 hrs when stored in a refrigerator 2-8°C.
From a microbiological point of view, once opened, 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 and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Keep vial in the outer carton to protect from light.
For storage condition of the reconstituted product see section 6.3.

6.5 Nature and contents of container
Type I glass vials (100 ml) with grey bromobutyl rubber stopper and red coloured flip-off seal.
Pack size of 1 vial in a carton.

6.6 Special precautions for disposal
For single use only. Discard any unused solution.
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: See table for addition volumes and solution concentrations, which may be useful when fractional doses are required.

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Route of Administration</th>
<th>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3g</td>
<td>Intravenous bolus</td>
<td>15.0</td>
<td>170</td>
</tr>
<tr>
<td>3g</td>
<td>Intravenous Infusion</td>
<td>75.0</td>
<td>40‡</td>
</tr>
</tbody>
</table>

*Note: Addition should be in two stages.
‡Note: Use Sodium Chloride Injection 0.9%, Dextrose Injection 5% or other approved diluent, as Water for Injections produces hypotonic solutions at this concentration.

Ceftazidime (at the given concentration) has been shown to be compatible with the following diluent solutions:-

At Ceftazidime concentrations between 1mg/ml and 40mg/ml in:-
0.9% Sodium Chloride Injection BP
M/6 Sodium Lactate Injection BP
Compound Sodium Lactate Injection BP (Hartmann's Solution)
5% Dextrose Injection BP
0.225% Sodium Chloride and 5% Dextrose Injection BP
0.45% Sodium Chloride and 5% Dextrose Injection BP
0.9% Sodium Chloride and 5% Dextrose Injection BP
0.18% Sodium Chloride and 4% Dextrose Injection BP
10% Dextrose Injection BP
Dextran 40 Injection BP 10% in 0.9% Sodium Chloride Injection BP
Dextran 40 Injection BP 10% in 5% Dextrose Injection BP
Dextran 70 Injection BP 6% in 0.9% Sodium Chloride Injection BP
Dextran 70 Injection BP 6% in 5% Dextrose Injection BP

At concentrations of between 0.05mg/ml and 0.25mg/ml in Intraperitoneal Dialysis Fluid (Lactate) BPC 1973.

When admixed at 4mg/ml with (both components retain satisfactory potency):

Potassium Chloride 10mEq/L or 40 mEq/L in 0.9% Sodium Chloride Injection BP

Vials as supplied are under reduced pressure. As the product dissolves, carbon dioxide is released and a positive pressure develops. For ease of use, it is recommended that the following techniques of reconstitution are adopted.

3g i.v. bolus vial:

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. The vacuum may assist entry of the diluent. Remove the syringe needle.

2. Shake to dissolve: carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.

3. Invert the 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. The withdrawn solution may contain small bubbles of carbon dioxide; they may be disregarded.

3g i.v. infusion vial:

Prepare using a total 75ml (for 3g vials) of compatible diluent, added in TWO stages as below:-

1. Insert the syringe needle through the vial closure and inject 15ml for 3g vial. The vacuum may assist entry of the diluent. Remove the syringe needle.

2. Shake to dissolve: carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
3. 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.

4. Transfer the reconstituted solution to final delivery vehicle (e.g. mini-bag or burette-type set) making up a total volume of at least 75ml and administer by intravenous infusion over 15-30 minutes.

NOTE: To preserve product sterility, it is important that a vent needle is not inserted through the vial closure before the product has dissolved.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Orchid Europe Ltd
Building 3, Chiswick Park,
566 Chiswick High Road,
Chiswick, London, W4 5YA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 22805/0027

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/12/2009

10 DATE OF REVISION OF THE TEXT
08/12/2009
Module 3

Product Information Leaflet
Ceftazidime 3g Powder for Solution for Injection/Infusion

Ceftazidime

The name of your medicine is Ceftazidime 3g Powder for Solution for injection/infusion, which will be referred to as Ceftazidime throughout the rest of this document.

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need it later.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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

In this leaflet:
1. What Ceftazidime is and what it is used for
2. Before you take Ceftazidime
3. How to take Ceftazidime
4. Possible side effects
5. How to store Ceftazidime
6. Further information

1. WHAT CETAZIDIME IS AND WHAT IT IS USED FOR

Ceftazidime belongs to a group of antibiotic called cephalosporins, which act by killing bacteria. Ceftazidime is used to treat infections caused by one or more bacteria, a mixture of bacteria, and severe infections in general.

Ceftazidime is used to treat infections of the:
- ears, nose, throat, and chest, including pneumonia
- skin and skin structures
- joints and tendons
- urinary tract
- blood
- skin and the tissues under the skin
- meningitis and fluid surrounding the brain and spinal cord (this infection is called meningitis).

Ceftazidime can also be used to treat infections that occur after surgery or to prevent infections that may occur after some surgical operations. Your doctor may sometimes need to use Ceftazidime at the same time as another antibiotic to help treat or prevent infection.

2. BEFORE YOU TAKE CETAZIDIME

Do not take Ceftazidime if:
- you are allergic (hypersensitive) to ceftazidime, cephalosporins, any penicillin-like antibiotics, or any of the other ingredients listed in Section 6 of this leaflet.
- you have ever been told that your kidneys do not work very well or if you are having any sort of treatment to help your kidneys work properly, such as dialysis.
- you may be given Ceftazidime but you need a lower dose
- you are taking antidiabetic (diabetes) tablets or injections, such as insulin, which causes low blood sugar levels.
- it is often necessary to check your kidney function if you are taking Ceftazidime. This can be done with blood and urine tests.
- you are taking other antibiotics
- you are on a low salt diet

Ceftazidime is not suitable for everyone. Before treatment with Ceftazidime, talk to your doctor or pharmacist about the possible benefits and risks of Ceftazidime and what other medicines you are taking.

If you have been on Ceftazidime before for a prolonged period, it may result in the overgrowth of bacteria. Antibiotics do not work against bacteria. This may need you to be treated by other medicines.

If you are taking any blood or urine tests, inform your doctor that you are taking Ceftazidime, as Ceftazidime can affect the results of some of these tests. The use of Ceftazidime may interfere with blood cross-matching in some patients. Patients can also be aware of the results of some tests for sugar such as samples of urine or stools.

Taking other medicines

Tell your doctor or pharmacist about any other medicines you are taking. If you are not sure whether any medicine is a medicine, ask your doctor or pharmacist.

Chloramphenicol, which is also an antibiotic, weakens the effects of Ceftazidime and other cephalosporins. They should not be used together.

Technical Information Leaflet

The following information is intended for medical or healthcare professionals only:

Ceftazidime 3g Powder for Solution for Injection/Infusion

This is an extract from the Summary of Product Characteristics to assist in the administration of Ceftazidime 3g Powder for solution for injection/infusion. When determining appropriate references of use in a particular patient, the prescriber should be familiar with the BNF/PC.

Method and route of administration:

Ceftazidime may be given intravenously 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.

Incompatible medicines:

Ceftazidime should not be mixed with solutions with a pH above 7.5 or for example sodium bicarbonate solution for injection. Ceftazidime and iron(III) complexes should not be mixed in the solution for injection because of the risk for precipitation.

Change and storage for intravenous use should be flushed with physiological saline solution between administrations of ceftazidime and vancomycin to avoid precipitation.

Rearrangement of solutions:

For single use only. Discard any unused solution.

The solution is to be made up 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 particulate.

Oral contraceptives (the "pill") that contain estrogens (female sex hormones). Taking Ceftazidime may make and contraceptives less effective. You should take advice from your doctor on extra precautions needed to avoid pregnancy.

Taking Ceftazidime with food and drink

Food/Drinks have no influence on the effectiveness of Ceftazidime as it is given by injection or infusion.

Pregnancy and breast-feeding

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding

Before starting treatment, you must tell your doctor if you are pregnant or if you intend to become pregnant. Ceftazidime is not known to harm the unborn child, but has not been studied. If it will only be given to a pregnant woman if it is absolutely necessary.

Breast-feeding

Small amounts of Ceftazidime pass into the mother's milk and it may affect the child. Ask your doctor or pharmacist for advice before taking Ceftazidime if you are breast-feeding your child. If you cannot stop breast-feeding while you are taking Ceftazidime, you should wash your baby carefully for any signs of dermatitis or the other symptoms in this leaflet and tell your doctor if you notice anything wrong.

Driving and using machines

Ceftazidime can cause dizziness. If affected, you should not drive or operate machinery.

Important information about some of the ingredients of this product:

To be taken into consideration by patients under controlled sodium diet. This medicinal product contains 6 63 mmol (153g) of sodium per.

2. HOW TO TAKE CETAZIDIME

Doseage

A doctor or nurse will usually administer the correct dose of Ceftazidime depending on the nature and severity of your illness and your general condition, including your kidney function. Always take Ceftazidime exactly as your doctor has told you. You should check with your doctor or pharmacist if you have not taken.

The usual dosage is:

Adults

The adult dosage range for Ceftazidime is 3g to 6g per day given in two or three divided doses. In the majority of infections, 3g three times a day or 2g twice a day is given.

For infections of the urinary passage and in many less severe infections, 500mg or 1g twice a day is usually given.

For very severe infections, especially in patients with very low immunity, including those with low counts of the white blood cells, 3g two or three times a day or 2g twice a day is given.

Children

Children under 3 months of age are given 30mg to 100mg per kg body weight daily, given as two or three divided doses.

Children up to 100 per kg body weight daily (maximum 6g daily) in three divided doses may be given to infected children with low immunity, fibroblastic children, children with meningitis.

For infants and children less than 3 months of age

Although the clinical experience is limited, a dose of 30mg to 100mg per kg body weight daily given as two divided doses has proved to be effective.

Adverse reactions (including the most serious) related to kidney problems

In patients with impaired kidney function (the dosage of Ceftazidime is usually reduced to compensate for its slower excretion, except in mild impairment). In patients with suspected kidney dysfunction, an initial loading dose of 3g of Ceftazidime may be given. Your doctor will calculate the right dose for you according to the results of blood or urine tests that measure how well your kidneys are functioning.

Ventricular arrhythmia

In patients with renal failure on continuous arteriovenous haemofiltration or high-flux haemofiltration the dose of Ceftazidime is divided.

Instructs for reconstitution: See table for addition volumes and solution concentrations, which may be useful when fractional doses are required.

Vial size Route of Administration Amount of Diluent to be added (ml) Appropriate Concentration (mg/l)

3g Intravenous bolus 15.0 150
3g Intravenous Infusion 750* 402

*Note: Addition should be in two stages.

Note: Use Sodium Chloride Injection 0.9%, Dextrose Injection 5% or other approved equivalent, as a vehicle for injection prepared hypotonic solutions at this concentration.

Ceftazidime (as the given concentration) has been shown to be compatible with the following diluent solutions:

- Saline injection concentrations between 10mg/ml and 20mg/ml;
- 0.3% Sodium Chloride Injection BP;
- Methylene Blue Injection BP
- Lactic Acid Solution Injection BP
- Compound Sodium Lactate Injection BP (Human's Solution);
- 5% Dextrose Injection BP;
- 0.25% Sodium Chloride and 5% Dextrose Injection B P;
- 0.15% Sodium Chloride and 5% Dextrose Injection BP;
- 5% Sodium Chloride and 5% Dextrose Injection BP;
- 1.5% Sodium Chloride and 5% Dextrose Injection BP;
- 10% Dextrose Injection BP.
For patients who have had a caesarean section, the doses are appropriate near the end of pregnancy. The dosage of Ceftazidime can be increased or decreased in accordance with the patient's response to therapy. The dosage is based on the severity of the infection and the susceptibility of the causative organism.

**How to prepare and administer Ceftazidime**

Ceftazidime is supplied as a powder for injection and must be made into a solution before it can be given. Only aqueous solutions can be used to mix the powder to make it ready for use. Your doctor or nurse will use the appropriate solution to prepare a fresh solution of Ceftazidime for administration. If you have been instructed to give Ceftazidime to a child, you must make sure that you are familiar with the technique of giving the injection. Ceftazidime will usually be given by a doctor or nurse either intramuscularly (directly into a muscle) or by injection under the skin to a patient who is not able to tolerate a cephalosporin. Ceftazidime is given intravenously (into the vein) of the upper arm or leg.

**How frequently you should be given Ceftazidime**

Ceftazidime is usually given two to three times a day.

**Duration of treatment**

Your doctor will advise you how long your treatment should last. The duration of therapy depends on the course of the disease. Typically, this is between one to two weeks for infections.

If you take more Ceftazidime than you should

Since a doctor or nurse will give you Ceftazidime, it is very unlikely that you will be taking too much Ceftazidime. However, if you accidently take more than one dose, it is important to contact your doctor or pharmacist immediately.

If you forget to take Ceftazidime

Since a doctor or nurse will give you Ceftazidime, it is very unlikely that you will miss a dose. However, if you miss a dose, it is important to contact your doctor or pharmacist immediately.

If you stop taking Ceftazidime

Your doctor or pharmacist will advise you how long your treatment should last. The duration of therapy depends on the course of the disease. Typically, this is between one to two weeks for infections.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Ceftazidime can cause side effects, although not everyone gets them.

**Side Effects**

Serious allergic reactions to Ceftazidime are very rare (affect fewer than one in ten thousand people).

Other possible side effects include:

- Headache
- Nausea
- Abdominal pain
- Diarrhoea
- Vomiting
- Rash
- Swelling of the face, lips, tongue or throat
- Inflammation of the skin
- Pain at the injection site
- Tiredness
- Anxiety
- Dizziness
- Diarrhoea
- Vomiting
- Abdominal pain
- Nausea
- Rash
- Swelling of the face, lips, tongue or throat
- Inflammation of the skin
- Pain at the injection site
- Tiredness
- Anxiety
- Dizziness
- Diarrhoea
- Vomiting
- Abdominal pain
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- Anxiety
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- Vomiting
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- Nausea
- Rash
- Swelling of the face, lips, tongue or throat
- Inflammation of the skin
- Pain at the injection site
- Tiredness
- Anxi
Module 4
Labelling

Label:

Each vial contains Ceftazidime 3 g (as Ceftazidime Penta hydrate).
Also contains Sodium carbonate, anhydrous (5000) equivalent
to 6.60 mmol (152 mg) of sodium.
Single use only.
Effervescence occurs on addition of Water for Injections.
This product is for reconstitution before administration.
Read the leaflet carefully before reconstitution.
Keep out of the reach and sight of children.
This medicinal product does not require any special storage
conditions. Keep vial in the outer carton to protect from light.
The reconstituted solution should be used immediately.
After reconstitution, the solution may be stored between
(2 - 8°C) for up to 24 hours if the reconstitution has taken
place in controlled aseptic conditions.

PL 22805/0027  M.L. No. 763  P0M
Module 5

Scientific discussion during initial procedure

I RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Ceftazidime 3g Powder for solution for injection/infusion, in the treatment of bacterial infections, is approvable.

II EXECUTIVE SUMMARY

Problem statement
This decentralised application concerns a generic version of ceftazidime, submitted under Article 10.1.

The originator product is Fortum 3g injection (PL 00004/0294), which was licensed to Glaxo Operations UK Ltd in the UK on 17 October 1983.

With the UK as the Reference Member State in this Decentralised Procedure, Orchid Europe Ltd is applying for a marketing authorisation for Ceftazidime 3g Powder for solution for injection/infusion in Finland.

About the product
Ceftazidime is a semi-synthetic bactericidal antibacterial agent of the cephalosporin class. Like other beta-lactam drugs, ceftazidime exerts antibacterial activity by binding to and inhibiting the action of certain bacterial cell wall synthetic enzymes (transpeptidases).

Ceftazidime is to be used by the parenteral route, the dosage depending upon the severity, sensitivity and type of infection and the age, weight and renal function of the patient. It can be used for the following indications:

- Single infections
- Mixed infections caused by two or more susceptible organisms
- Severe infections in general
- Respiratory tract infections
- Ear, nose and throat infections
- Urinary tract infections
- Skin and soft tissue infections
- Gastrointestinal, biliary and abdominal infections
- Bone and joint infections
- Infections associated with haemo - and peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)
- Meningitis
General comments on the submitted dossier
The dossier is considered adequate.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
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 this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

III SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Ceftazidime 3g Powder for solution for injection/infusion are of sufficient quality in view of the present European regulatory requirements. The active substance, ceftazidime pentahydrate, is the subject of a monograph in the European Pharmacopoeia. The drug substance specification for the drug substance is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the results support the proposed re-test period.

Drug Product
The development of the product has been described, the choice of the excipient is justified and its functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished product meets the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The stability data support the proposed shelf-life of 24 months with the storage precaution “Keep vial in the outer carton to protect from light.”

Non clinical aspects
The pharmacological, pharmacokinetic and toxicological properties of ceftazidime pentahydrate are well known. As ceftazidime pentahydrate is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.
The non-clinical overview has been written by two experts; one has a medical degree, the other is qualified in microbiology. The overview, that was written in 2008, refers to 74 references from the published literature dated up to 2006. The overview is considered to be acceptable in view of the fact that the toxicological properties of ceftazidime pentahydrate are well known.

There are no objections to the approval of Ceftazidime 3g Powder for solution for injection/infusion from a non-clinical point of view.

Clinical aspects
No clinical studies were conducted in support of this application and all the relevant clinical information provided in the Clinical Overview is literature based. The Clinical Overview was written in 2008 by an expert qualified in medicine and is adequate. There are about 118 references up to 2007.

No new safety data have been submitted and none are required for this application. As this is a parenteral preparation no bioequivalence studies are necessary and the applicant has provided none.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system fulfils the requirements. The Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this generic application.

Assessment of User Testing
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

IV BENEFIT RISK ASSESSMENT
The benefit-risk ratio is considered favourable. A Marketing Authorisation should be granted