Ceftazidime 1g Powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT
   Ceftazidime 1g Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each vial contains ceftazidime 1g (as pentahydrate).

   Each gram of ceftazidime contains approximately 52mg (2.26mmol) of sodium.

   For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
   Powder for solution for injection (Powder for injection).

   White to cream coloured, crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
   Ceftazidime is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5.1) and when parenteral therapy is required:

   - Respiratory tract infections, including lower respiratory tract infections in patients with cystic fibrosis

   - Urinary tract infections; ceftazidime may also be used for peri-operative prophylaxis during trans-urethral prostatectomy

   - Skin and soft tissue infections

   - Biliary tract infections

   - Intra-abdominal infections
- Bone and joint infections

- Infections associated peritoneal dialysis and with continuous ambulatory peritoneal dialysis (CAPD)

- Meningitis due to aerobic gram-negative organisms

Whenever possible, it is recommended that the results of bacterial cultures and susceptibility tests are known before commencing treatment. This is especially important if ceftazidime is to be used as monotherapy. Ceftazidime should be used in combination with an additional antibacterial agent(s) when treating infections that are likely to be due to a mixture of susceptible and resistant bacterial species.

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

4.2 Posology and method of administration

**Posology**

The range of usual dose regimens in patients with normal renal function for the age groups defined is as follows:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Infection</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Most uses</td>
<td>1 g 8-hourly OR 2 g 12-hourly</td>
</tr>
<tr>
<td></td>
<td>Severe infections and infections in neutropenic patients</td>
<td>2 g 8-hourly OR 3 g 12-hourly</td>
</tr>
<tr>
<td></td>
<td>UTI</td>
<td>500 mg 12-hourly OR 1 g 12-hourly</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis for prostatectomy</td>
<td>1 g at induction ± 1g at catheter removal</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
<td>100-150 mg/kg/day in three divided doses; not to exceed 9 g/day</td>
</tr>
<tr>
<td>Elderly</td>
<td>All infections, especially in those &gt; 80 years</td>
<td>Not to exceed 3 g daily total</td>
</tr>
<tr>
<td>Infants &gt; 2 months and children</td>
<td>Most uses</td>
<td>30-100 mg/kg/day in two or three divided doses</td>
</tr>
<tr>
<td></td>
<td>Severe infections</td>
<td>up to 150 mg/kg/day (max 6 g total per day) in three divided doses</td>
</tr>
<tr>
<td>Neonates and infants &lt; 2 months</td>
<td>Most uses</td>
<td>25 – 60 mg/kg/day in two divided doses</td>
</tr>
</tbody>
</table>

**Dosage in renal insufficiency:**

Ceftazidime is almost exclusively excreted by glomerular filtration and the dose should be reduced when the glomerular filtration rate (GFR) is less than 50ml/min.

In adults with renal insufficiency, an initial loading dose of 100 mg of ceftazidime may be given, followed by an appropriate maintenance dose as in the table:
Recommended maintenance doses of ceftazidime in adults with 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 renal insufficiency and 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 40 mg/ litre.

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

In patients on haemodialysis

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.

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.

In patients on peritoneal dialysis

Ceftazidime may also be used in patients who are undergoing peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD) at a dose adjusted according to renal function. In such patients, a loading dose of 1g of ceftazidime may be given, followed by 500mg every 24 hours. In addition, for intra-peritoneal infections, ceftazidime can be incorporated into the dialysis fluid (usually 125 to 250 mg for 2 L of dialysis fluid).

Dosage in hepatic insufficiency

No dose adjustment is required unless there is concomitant renal insufficiency.

Method of Administration

Ceftazidime may be given intravenously by slow bolus injection over a few minutes 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. See section 6.6 for information on preparation of solutions for intravenous or intramuscular administrations.

4.3 Contraindications

Hypersensitivity to ceftazidime, to any of the cephalosporins or to sodium carbonate.

Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other type of beta-lactam drug.

4.4 Special warnings and precautions for use

Before therapy with ceftazidime is instituted, careful inquiry should be made to determine whether the patient has had any previous hypersensitivity reactions to ceftazidime, cephalosporins, penicillins, or other beta-lactam drugs.

Ceftazidime is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin. It is also contraindicated in patients who have had a previous immediate and/or any severe hypersensitivity reaction to any penicillin or to any other beta-lactam drug. Ceftazidime should be given with caution to patients who have had any other type of hypersensitivity reaction to a penicillin or any other beta-lactam drug.

Antibiotic-associated diarrhoea and pseudomembranous colitis have all been reported with the use of ceftazidime. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Ceftazidime should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted.

Ceftazidime should be used with caution in individuals with a previous history of gastro-intestinal disease.

Ceftazidime has not been shown to be nephrotoxic. However, the total daily dosage should be reduced when ceftazidime is administered to patients with acute or chronic renal insufficiency in order to avoid potential clinical consequences, such as seizures (see section 4.2).

Cephalosporin antibiotics should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs such as aminoglycoside antibiotics or potent diuretics (such as furosemide) as these combinations may have an adverse effect on renal function.

As with other cephalosporins, prolonged use of ceftazidime may result in the overgrowth of non-susceptible organisms, such as enterococci and Candida spp.

This vial contains 2.26mmol of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycoside antibiotics and diuretics: Nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics or potent diuretics, such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity of aminoglycoside antibiotics.

Antibiotics: In vitro, chloramphenicol has been shown to be antagonistic with respect to 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.

Interference with Laboratory Tests:

Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinitest) may be observed.
A false positive Coombs test may be seen during treatment with cephalosporins. This phenomenon may occur during treatment with ceftazidine and can interfere with blood cross-matching.

4.6 Pregnancy and lactation

Pregnancy

It is known that ceftazidime crosses the placental barrier. Reproduction studies have not revealed any evidence of impaired fertility or harm to the foetus due to ceftazidime. However, as animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Ceftazidime is excreted in the milk in small amounts and is usually compatible with breast feeding, but careful monitoring of the infant is recommended. Consequently caution should be exercised when ceftazidime is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Dizziness can occur which can affect the ability to drive and to use machines.

4.8 Undesirable effects

The most common adverse reactions during ceftazidime treatment are local reactions following intravenous injection, allergic reactions, and effects on the gastro-intestinal tract.

Local effects: Phlebitis or thrombophlebitis, and pain and/or inflammation at the site of injection.

Hypersensitivity: Pruritus, rash, urticaria, erythema multiforme and fever. Toxic epidermal necrolysis and Stevens Johnson syndrome have been reported rarely. Angioedema and anaphylaxis (bronchospasm and/or hypotension) have been reported very rarely.

Gastro-intestinal: Diarrhoea (diarrhoea may sometimes be a symptom of pseudomembranous colitis, see 4.4.Special warnings and special precautions for use), nausea, vomiting and abdominal pain. Very rarely, oral thrush or colitis.

Central nervous system: Headache, dizziness, paraesthesiae and bad taste. There have been reports of neurological sequelae, including tremor, myoclonia, convulsions, encephalopathy and coma in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.

Genito-urinary: Candidiasis and vaginitis.

Blood and lymphatic system disorders (usually transient):

Eosinophilia, positive Coombs' test without haemolysis, haemolytic anaemia, thrombocytosis and very rarely leucopenia, neutropenia, agranulocytosis, and thrombocytopenia.

Hepatobiliary: Slight elevations in one or more hepatic enzymes: (AST (SGOT), ALT (SGPT), LDH, GGT and alkaline phosphatase), hepatitis. Very rarely, clinically apparent jaundice has been reported.

Renal and urinary disorders: Elevations of blood urea, blood urea nitrogen and/or serum creatinine have been observed occasionally. Rare cases of interstitial nephritis have been reported in patients treated with ceftazidime. Acute renal tubular necrosis may occur with ceftazidime.

Psychiatric disorders: Confusion and hallucinations.

4.9 Overdose

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

Overdose or the administration of inappropriately large doses in the presence of renal insufficiency can lead to neurological sequelae including dizziness, paraesthesiae, headache, encephalopathy, convulsion and coma.

Laboratory abnormalities that may occur after an overdose include elevations in creatinine, BUN, liver enzymes and bilirubin, a positive Coombs’ test, thrombocytosis, thrombocytopenia, eosinophilia, leucopenia and prolongation of the prothrombin time.

General symptomatic and supportive measures should be instituted, together with specific measures to control any seizures. In cases 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

General properties

ATC classification: J01DA11

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-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzymes that may be induced or stably derepressed in certain aerobic gram-negative bacteria

− 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:

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>
Intermediately Sensitive

≥32 mg/L

- *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>
</tbody>
</table>

| **Gram-negative micro-organisms:**                           |
| *Escherichia coli*                                           |
| *Haemophilus influenzae*                                     |
| *Moraxella catarrhalis*                                      |
| *Proteus mirabilis*                                          |
| *Proteus vulgaris*                                           |
| *Salmonella* spp.                                            |
| *Serratia* spp.                                              |

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem, i.e. resistance ≥10% in at least one of the EU Member States +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative micro-organisms:</strong></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>Citrobacter</em> spp.</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Inherently resistant organisms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive micro-organisms:</strong></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><em>Micrococcus</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>
+ 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

The approximate $C_{\text{max}}$ of ceftazidime after different doses and modes of administration to subjects with normal renal function were as follows:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Intramuscular injection (after 1 hour)</th>
<th>Intravenous bolus-injection (after 5 min)</th>
<th>Intermittent infusion (after 20 – 30 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>18mg/l</td>
<td>45mg/l</td>
<td>40mg/l</td>
</tr>
<tr>
<td>1g</td>
<td>39mg/l</td>
<td>90mg/l</td>
<td>70mg/l</td>
</tr>
<tr>
<td>2g</td>
<td>170mg/l</td>
<td>170mg/l</td>
<td></td>
</tr>
</tbody>
</table>

In general, plasma concentrations at 8 hours after intravenous or intramuscular administration of 500 mg or more ceftazidime are in excess of 2 mg/l. Following multiple intravenous doses of 1 g and 2g every 8 hours for 10 days, there was no evidence of accumulation of ceftazidime in the serum of individuals with normal renal function.

Distribution

Less than 10% of ceftazidime is protein bound and the degree of protein binding is independent of concentration. Concentrations of ceftazidime in excess of the minimum inhibitory levels of common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, 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 20 mg/l or more are achieved in the CSF when the meninges are inflamed.

Elimination

Approximately 80% to 90% of a dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period, resulting in high urinary concentrations.

In subjects with normal renal function, the half life of ceftazidime is approximately 2 hours after intravenous or intramuscular administration.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals who received 2g intravenously every 8 hours for 5 days. Therefore dosage adjustment is not required for patients with hepatic dysfunction, unless renal function is also impaired.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate (anhydrous sterile)

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Ceftazidime is less stable in Sodium Bicarbonate Injection than other intravenous fluids. It is not recommended as a diluent.

Ceftazidime and aminoglycosides should not be mixed in the same giving set or syringe.

Precipitation has been reported when vancomycin has been added to ceftazidime in solution. It is recommended that giving sets and intravenous lines are flushed between administration of these two agents.

Ceftazidime is incompatible with aminophylline. There is a possible incompatibility with pentamidine.

6.3 Shelf life

Unopened - 2 years.

For reconstituted solution, chemical and physical in-use stability has been demonstrated for eight hours at 25°C and 24 hours at 4°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

Unopened: Do not store above 25°C. Keep the vials in the outer carton.

After reconstitution: Store at 2-8°C (see 6.3 Shelf Life).

6.5 Nature and contents of container

Packs of one or five Type III colourless glass 25ml vials stoppered with coated rubber stopper, capped with flip-off cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use. Discard any unused contents.

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>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
<th>Approximate available volume(ml)</th>
<th>Approximate displacement volume(ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>Intramuscular 3.0</td>
<td>260</td>
<td>3.58</td>
<td>0.58</td>
</tr>
<tr>
<td>1g</td>
<td>Intravenous 10.0</td>
<td>95</td>
<td>10.56</td>
<td>0.56</td>
</tr>
</tbody>
</table>

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

Solvents for 40mg/ml ceftazidime concentration:

Sodium Chloride 0.9%

Ringer Solution
Ringer Lactate Solution
Glucose 5%
Glucose 10%
Glucose 5% and Sodium Chloride 0.9%
Glucose 5% and Sodium Chloride 0.45%
Glucose 5% and Sodium Chloride 0.2%
Dextran 40%/10% and Sodium Chloride 0.9%
Dextran 70%/6% and Sodium Chloride 0.9%
Lidocaine Hydrochloride 0.5%
Lidocaine Hydrochloride 1%

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used.

All sizes of 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 is adopted.

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.

7. MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham LL13 9UF
UK

8. MARKETING AUTHORISATION NUMBER(S)
PL 29831/0031
PA 1339/3/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 15 October 2007 (UK)
19 December 2007 (Ireland)
10. DATE OF REVISION OF THE TEXT
July 2011