CEFTAZIDIME 1G POWDER FOR SOLUTION FOR INJECTION
(PL 24598/0004)
CEFTAZIDIME 2G POWDER FOR SOLUTION FOR INJECTION
OR INFUSION (PL 24598/0005)

UKPAR

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Lay Summary

On 2nd September 2008, the MHRA granted Noridem Enterprises Ltd Marketing Authorisations (licences) for the medicinal products Ceftazidime 1g Powder for Solution for Injection (PL 24598/0004) and Ceftazidime 2g Powder for Solution for Injection or Infusion (PL 24598/0005). These are prescription-only medicines (POM).

Ceftazidime is a type of medicine called an antibiotic. Antibiotics work by killing the bacteria (germs) that cause an infection. If the infection is not treated by your medicine, the bacteria (germs) can continue to grow in your body, which will make you feel very unwell, and could even be life-threatening.

Ceftazidime is used to treat infections caused by bacteria (germs), including infections of:
- the lungs and breathing airways, including infections in patients with cystic fibrosis
- the urinary tract (such as your bladder or tubes leading to the kidneys)
- the skin and soft tissue (such as wound infections)
- the biliary tract (such as your gall bladder or its tubes)
- the abdomen (such as your stomach)
- the bones and joints (such as osteomyelitis and infected arthritis)
- infections that may occur after dialysis. This is a procedure to clean your blood when you have kidney problems
- the brain or spinal cord (also called meningitis)

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ceftazidime 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection or Infusion outweigh the risks, hence Marketing Authorisations have been granted.
CEFTAZIDIME 1G POWDER FOR SOLUTION FOR INJECTION
(PL 24598/0004)
CEFTAZIDIME 2G POWDER FOR SOLUTION FOR INJECTION OR INFUSION (PL 24598/0005)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Ceftazidime 1g Powder for Solution for Injection (PL 24598/0004) and Ceftazidime 2g Powder for Solution for Injection or Infusion (PL 24598/0005) on 2nd September 2008 to Noridem Enterprises Ltd.

The products are prescription-only medicines, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Fortum 1g and 2g Powder for Solution for Injection (PL 0004/0293-4), which were originally licensed to Glaxo Operations UK in 1983.

The products contain the active ingredient ceftazidime, as ceftazidime pentahydrate. Ceftazidime is a third-generation cephalosporin and is indicated for use in a wide-range of bacterial infections in both adults and children, where the causative microorganism is susceptible, such as the treatment of sepsicaemia, pneumonia, meningitis, and other severe infections. It may be used in infections caused by organisms resistant to other anti-infectives including aminoglycosides and many cephalosporins, and can be given in combination with other anti-infective agents in difficult-to-treat infections.

Ceftazidime has potent bactericidal activity against a wide range of gram-positive and, especially, gram-negative organisms. Its antibacterial action is a result of its ability to suspend the composition of the bacterial cell wall. The aminothiazolyl side chain provides high affinity for gram-negative bacteria, producing characteristic filamentous changes, cell swelling and bacterial cell lysis. Ceftazidime has considerable stability against degradation by most bacterial beta-lactamases, penicillinas and cephalosporinas. Ceftazidime is a third generation cephalosporin with greater activity than second-generation cephalosporins against certain gram-negative bacteria, such as Enterobacteriaceae (including multi-drug resistant strains), and it also shows enhanced activity against Pseudomonas aeruginosa. It is particularly useful in the treatment of seriously ill patients where gram-negative organisms are the suspected pathogens, or where resistant gram-negative organisms are suspected or demonstrated to have resistance to other anti-infective agents.

Ceftazidime is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms 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
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Ceftazidime pentahydrate

Chemical name: \((6R,7R)-7-[[\{Z\}-2-(2-aminothiazol-4-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]8-o xo-3-\{(1-pyridino)methyl\}-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate.\)

Structure:

![Structure of Ceftazidime](image)

Physical form: A white or almost white crystalline powder, slightly soluble in water and in methanol, practically insoluble in acetone and in alcohol. It dissolves in acid and alkali solutions.

Molecular formula: \(C_{22}H_{22}N_{6}O_{7}S_{2}.5H_{2}O\)

Molecular weight: 637.65 (Anhydrous 546.59)

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance ceftazidime pentahydrate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.
DRUG PRODUCT
Other ingredients
The other ingredients are the excipients sodium carbonate and nitrogen. Sodium carbonate complies with its European Pharmacopoeia monograph. Nitrogen complies with a suitable in-house specification.

None of the excipients are of animal or human origin. None of the excipients contain any genetically modified material.

Product development
The objective of the development programme was to produce solutions for injection (and infusion in the case of the 2g strength), containing ceftazidime pentahydrate, which are safe and could be considered as generic medicinal products to Fortum 1g and 2g Powder for Solution for Injection (PL 0004/0293-4).

A suitable product development section has been provided.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength of product. The results appear satisfactory.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificate of analysis have been provided for all working standards used.

Container-closure system
The 1g strength is packed in Type III glass vials with rubber (Type I) closures sealed with aluminium caps. The vials are placed in cartons in pack sizes of 1, 5 and 20 vials.

The 2g strength is packed in Type I glass vials with rubber (Type I) closures sealed with aluminium caps. The vials are placed in cartons in pack sizes of 1, 5 and 20 vials.

Specifications and Certificates of Analysis for the proposed packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding contact with solutions for injection.

The marketing authorisation holder has stated that not all pack sizes are intended for marketing at the present time. However, they have committed to providing mock-ups of the packaging for all pack sizes before marketing.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for both strengths,
with the storage instructions “Store below 25°C. Keep vial in outer carton”. The shelf-life and storage conditions after reconstitution is dependent on the solvent used, full instructions on this are given in the Summary of Product Characteristics.

**Bioequivalence**
No bioequivalence study was submitted for these applications, which is acceptable as this is a product to be administered by injection or infusion.

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
These are consistent with those for the reference products and are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory

**Patient Information Leaflet**
A package leaflet has been 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 it contains.

**MAA Forms**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products.
PRECLINICAL ASSESSMENT

These applications are for generic medicinal products of Fortum 1g and 2g Powder for Solution for Injection (PL 0004/0293-4), which have been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

1. INDICATIONS
The indications are consistent with those for the reference products and are satisfactory.

2. DOSE & DOSE SCHEDULE
The dose and dosage schedule are consistent with those for the reference products and are satisfactory.

3. CLINICAL PHARMACOLOGY
The clinical (and preclinical) expert reports provide an adequate review of the known pharmacodynamics and pharmacokinetics of ceftazidime pentahydrate. No reference is made to any new data that would affect the products under consideration.

4. EFFICACY
The clinical expert report provides an adequate review of the efficacy of ceftazidime pentahydrate for the listed indications.

5. SAFETY
The clinical expert report provides an adequate review of the clinical safety of ceftazidime pentahydrate. The toxicity from ceftazidime pentahydrate is described in detail per organ system. No reference is made to any new data that would affect the marketing authorisations for the products under consideration.

6. EXPERT REPORTS
The expert reports are written by appropriately qualified experts.

7. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with the reference products and are satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference products and is satisfactory.

9. LABELLING
Full colour mock-ups are provided and are satisfactory.

10. MEDICAL CONCLUSION
Marketing authorisations may be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ceftazidime 1g Powder for Solution for Injection and Ceftazidime 2g Powder for Solution for Injection or 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
As the products are solutions for injection, and are of identical composition to the brand leaders, no bioequivalence data were required and the proposed products are considered to be generic medicinal products of the brand leader products.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ceftazidime pentahydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 23rd January 2006</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the applications valid on 13th February 2006</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 2nd September 2008.</td>
</tr>
</tbody>
</table>
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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
Summary of Product Characteristics

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1.165g of ceftazidime pentahydrate (equivalent to 1g of ceftazidime) with 0.118 g sodium carbonate.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection

A white to almost white coloured powder for solution for injection.

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

The dosage and mode of administration of ceftazidime should be determined by the severity of the infection, susceptibility of the causative organism and the condition of the patient, such as age, weight and renal function.

<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 ± 1 g 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>

Renal impairment

Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. It is therefore recommended that the dosage of ceftazidime should be reduced when the creatinine clearance is less than 50 ml/min.

In patients with suspected renal insufficiency, an initial loading dose of 1 g of ceftazidime may be given. An estimate of creatinine clearance should be made to determine the appropriate maintenance dose.

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 1 g daily in divided doses. For low-flux haemofiltration it is recommended that the dosage should be that suggested above for those with suspected renal insufficiency.

Recommended maintenance doses in renal insufficiency are shown below:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Approx. serum creatinine* (micromol/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 those patients with neutropenia, who would normally receive 6 g 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 the serum concentration of ceftazidime should be monitored and that trough concentrations should not exceed 40 mg/l.
When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. To convert serum creatinine in mol/l into mg/dl divide by 88.4. The serum creatinine should represent a steady state of renal function:

Males:
Creatinine clearance = \( \frac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dl)}} \)

Females:
0.85 x above value.

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

**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.

**Hepatic impairment**
No dosage adjustment is required in patients with hepatic impairment.

**Dosage in 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).

**Method of Administration**

*Intravenous injection or infusion*
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered intravenously.

*Intramuscular injection*
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered 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
Hypersensitivity to ceftazidime or to any of the cephalosporins.

Hypersensitivity 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, colitis 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, particularly colitis.

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 and have been associated with ototoxicity (see section 4.5).

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
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.

Laboratory Tests
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.

Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's test, Fehling's test, Clinitest) may be observed.

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics or potent diuretics, such as furosemide (frusemide). 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 and ototoxicity of aminoglycoside antibiotics.

4.6 Pregnancy and lactation
Pregnancy
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 human milk in low concentrations, and consequently caution should be exercised when ceftazidime is administered to a nursing mother.

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 treatment with ceftazidime treatment are local reactions following intravenous injection, allergic reactions, and effects on the gastro-intestinal tract.

A table of the MedDRA System Organ Class and Frequency of Adverse Reactions is provided below.

<table>
<thead>
<tr>
<th>MedRA System Organ Class</th>
<th>Frequency of Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Transient elevation of blood urea, blood urea nitrogen and/or serum creatinine</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td>Leucopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Maculopapular or urticarial rash, fever, pruritus.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>Angioedema and anaphylaxis (including bronchospasm and/or hypotension).</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache, dizziness, paraesthesia and bad taste.</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Tremor, myoclonia, myoclonus, convulsions, and encephalopathy in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, nausea, vomiting, abdominal pain.</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Oral thrush or colitis. As with other cephalosporins, colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>Reproductive system disorders</td>
<td></td>
</tr>
<tr>
<td>Candidiasis, vaginitis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs’ test, haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase.</td>
<td>Very rare (≤1/10,000)</td>
</tr>
</tbody>
</table>

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
Pharmacotherapeutic group:
Third generation cephalosporins (ATC code: 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-lactamases (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
Clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens according to EUCAST are:
- Enterobacteriaceae: S ≤ 1.0 mg/l; R > 8 mg/l.
- Pseudomonas spp.: S ≤ 8 mg/l; R > 8 mg/l.
- Non-species related breakpoints: S ≤ 4 mg/l; R > 8 mg/l.

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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive micro-organisms:</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
</tr>
<tr>
<td>Gram-negative micro-organisms:</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
</tr>
<tr>
<td><em>Providencia species</em></td>
</tr>
</tbody>
</table>
Species for which acquired resistance may be a problem

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative micro-organisms:</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td>Klebsiella species</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td></td>
</tr>
</tbody>
</table>

Inherently resistant organisms

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive micro-organisms:</td>
<td></td>
</tr>
<tr>
<td>Enterococcus species</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus species, Coagulase negative*</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus milleri</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>#</td>
<td></td>
</tr>
<tr>
<td><em>Viridans Streptococci</em></td>
<td></td>
</tr>
</tbody>
</table>

Anaerobes

<table>
<thead>
<tr>
<th>Anaerobes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides species</td>
<td></td>
</tr>
<tr>
<td>Clostridium species</td>
<td></td>
</tr>
<tr>
<td>Fusobacterium species</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
<td></td>
</tr>
</tbody>
</table>

Others

<table>
<thead>
<tr>
<th>Others</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia species</td>
<td></td>
</tr>
<tr>
<td>Campylobacter species</td>
<td></td>
</tr>
<tr>
<td>Legionella species</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium species</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma species</td>
<td></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

Absorption

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

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%.

Metabolism

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration.

Distribution

Concentrations of ceftazidime in excess of the minimum inhibitory concentrations 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 concentrations are achieved in the cerebrospinal fluid in the absence of inflammation. Therapeutic concentrations of 4 - 20 mg/l or more are achieved in the cerebrospinal fluid when the meninges are inflamed.

**Excretion**
Excretion is almost exclusively by the kidney. Approximately 80 - 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.

### 5.3 Preclinical safety data
No additional data of relevance.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
Sodium carbonate

#### 6.2 Incompatibilities
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.

Solutions containing ceftazidime should not be mixed with or added to solutions containing other agents than listed below (see section 6.6).

### 6.3 Shelf life
*Unopened vial:*
Three years.

*Reconstituted solution:*
Chemical and physical stability has been demonstrated in the following conditions:
- for 24 hours at 25°C and
- for 7 days at 5±3°C
when dissolved in 10 or 3 ml of WFI.

- for 6 hours at 25°C and
- for 36 hours at 5±3°C
when dissolved in 0.5% or 1% Lidocaine HCl injection.

- for 6 hours at 25°C and
- for 24 hours at 5±3°C
when dissolved in all the solutions studied (see table in Section 6.6).

*From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately*

If not used immediately, the 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 opening, reconstitution, and dilution has taken place in controlled and validated aseptic conditions.
6.4 Special precautions for storage

*Unopened vial:*
Store below 25°C. Keep the vial in the outer carton.

*Reconstituted solution:*
Store below 2 - 8°C. See section 6.3 for further information on shelf life of reconstituted solutions.

6.5 Nature and contents of container

Type III glass vials with rubber (Type I) closures sealed with aluminium caps. The vials are placed in cartons.

Boxes of one, five or twenty vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The use of freshly prepared solutions is recommended (see section 6.3).

The reconstituted solution should be clear. Do not use if particles are present.

Ceftazidime solutions range from a light yellow to amber solution depending on the concentration, diluent and storage conditions used. Within the stated recommendations, variations in the intensity of the colour will not affect the potency of the drug.

Each 1 g vial contains 52 mg (2.26 mmol) of sodium.

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.

1g Intramuscular/Intravenous injection:
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.

*Intramuscular injection:*
Ceftazidime 1 g Powder for Solution for Injection should be dissolved in 3 ml of 0.5% or 1.06% Lidocaine Hydrochloride BP. The resulting solution contains approximately 260 mg/ml ceftazidime.

Solutions in Lidocaine should not be administered intravenously.
**Intravenous injection:**

Ceftazidime 1 g Powder for Solution for Injection should be dissolved in 10 ml of Water for Injections Ph. Eur. The resulting solution contains approximately 90 mg/ml ceftazidime.

<table>
<thead>
<tr>
<th>Reconstitution Diluent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Ceftazidime concentration 1 mg/ml - 40 mg/ml:</strong></td>
<td></td>
</tr>
<tr>
<td>0.9% Sodium Chloride Injection BP</td>
<td></td>
</tr>
<tr>
<td>0.225% Sodium Chloride and 5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>0.45% Sodium Chloride and 5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>0.9% Sodium Chloride and 5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>0.18% Sodium Chloride and 4% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>M/6 Sodium Lactate Injection BP</td>
<td></td>
</tr>
<tr>
<td>Compound Sodium Lactate Injection BP (Hartmann's Solution)</td>
<td></td>
</tr>
<tr>
<td>5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>10% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>Dextran 40 Injection BP 10% in 0.9% Sodium Chloride Injection BP</td>
<td></td>
</tr>
<tr>
<td>Dextran 40 Injection BP 10% in 5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td>Dextran 70 Injection BP 6% in 0.9% Sodium Chloride Injection BP</td>
<td></td>
</tr>
<tr>
<td>Dextran 70 Injection BP 6% in 5% Dextrose Injection BP</td>
<td></td>
</tr>
<tr>
<td><strong>At Ceftazidime concentration 0.05 mg/ml - 0.25 mg/ml:</strong></td>
<td></td>
</tr>
<tr>
<td>Intrapertoneal Dialysis Fluid (Lactate) BPC 1973</td>
<td></td>
</tr>
</tbody>
</table>

When admixed at 4 mg/ml, either components will retain satisfactory potency:

- Cefuroxime (cefuroxime sodium) 3mg/ml in 0.9% Sodium Chloride Injection BP
- Cloxacillin (cloxacillin sodium) 4mg/ml in 0.9% Sodium Chloride Injection BP
- Heparin 10 IU/ml in 0.9% Sodium Chloride Injection BP
- Heparin 50 IU/ml in 0.9% Sodium Chloride Injection BP
- Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 0.9% Sodium Chloride Injection BP
- Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 5% Dextrose Injection BP
- Potassium Chloride 10 mEq/L in 0.9% Sodium Chloride Injection BP
- Potassium Chloride 40 mEq/L in 0.9% Sodium Chloride Injection BP

---

7 **MARKETING AUTHORISATION HOLDER**
Noridem Enterprises Ltd., (trading as Demo)
Evagorou & Makariou,
Mitsi Building 3, Suit.115,
1065 Nicosia,
Cyprus.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24598/0004

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
02/09/2008

10 **DATE OF REVISION OF THE TEXT**
02/09/2008
1 NAME OF THE MEDICINAL PRODUCT
Ceftazidime 2 g Powder for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 2.330g of ceftazidime pentahydrate (equivalent to 2g of ceftazidime) with 0.236 g sodium carbonate.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion

A white to almost white coloured powder for solution for injection or infusion.

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**

The dosage and mode of administration of ceftazidime should be determined by the severity of the infection, susceptibility of the causative organism and the condition of the patient, such as age, weight and renal function.

<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 ± 1 g 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>

**Renal impairment**

Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. It is therefore recommended that the dosage of ceftazidime should be reduced when the creatinine clearance is less than 50ml/min.

In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of creatinine clearanceshould be made to determine the appropriate maintenance dose.

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 1 g daily in divided doses. For low-flux haemofiltration it is recommended that the dosage should be that suggested above for those with suspected renal insufficiency.

Recommended maintenance doses in renal insufficiency are shown below:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Approx. serum creatinine* (micromol/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 those patients with neutropenia, who would normally receive 6 g 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 the serum concentration of ceftazidime should be monitored and that trough concentrations should not exceed 40 mg/l.
When only serum creatinine is available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. To convert serum creatinine in mol/l into mg/dl divide by 88.4. The serum creatinine should represent a steady state of renal function:

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

Females:
0.85 x above value.

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

**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.

**Hepatic impairment**
No dosage adjustment is required in patients with hepatic impairment.

**Dosage in 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).

**Method of Administration**

*Intravenous injection or infusion*
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered intravenously.

*Intramuscular injection*
After reconstitution of the solution according to the directions provided (see Section 6.6), ceftazidime may be administered 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
Hypersensitivity to ceftazidime or to any of the cephalosporins.

Hypersensitivity 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, colitis 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, particularly colitis.

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 and have been associated with ototoxicity (see section 4.5).

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 4.52mmol 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

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.

Laboratory Tests
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.

Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's test, Fehling's test, Clinitest) may be observed.

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics or potent diuretics, such as furosemide (frusemide). 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 and ototoxicity of aminoglycoside antibiotics.

4.6 Pregnancy and lactation

Pregnancy
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 human milk in low concentrations, and consequently caution should be exercised when ceftazidime is administered to a nursing mother.

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 treatment with ceftazidime treatment are local reactions following intravenous injection, allergic reactions, and effects on the gastro-intestinal tract.

A table of the MedDRA System Organ Class and Frequency of Adverse Reactions is provided below.

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Frequency of Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Transient elevation of blood urea, blood urea nitrogen and/or serum creatinine</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td>Leucopenia, neutropenia, agranulocytosis, thrombocytopenia and lymphocytosis</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Maculopapular or urticarial rash, fever, pruritus.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td>Angioedema and anaphylaxis (including bronchospasm and/or hypotension).</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache, dizziness, paraesthesia and bad taste.</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Tremor, myoclonia, myoclonus, convulsions, and encephalopathy in patients with renal impairment in whom the dose of ceftazidime has not been appropriately reduced.</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, nausea, vomiting, abdominal pain.</td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Oral thrush or colitis. As with other cephalosporins, colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Very rare (≤1/10,000)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td><strong>Reproductive system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Candidiasis, vaginitis.</td>
<td>Rare (≥1/10,000 to ≤1/1,000)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Uncommon (≥1/1,000 to ≤1/100)</td>
</tr>
<tr>
<td>Phlebitis or thrombophlebitis with intravenous administration, pain and/or inflammation after intramuscular injection.</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td>Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs’ test, haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase.</td>
<td>Very rare (≤1/10,000)</td>
</tr>
</tbody>
</table>

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
Pharmacotherapeutic group:
Third generation cephalosporins (ATC code: 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-lactamases (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
Clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens according to EUCAST are:
- Enterobacteriaceae: S≤1.0 mg/l; R>8 mg/l.
- Pseudomonas spp.: S≤8 mg/l; R>8 mg/l.
- Non-species related breakpoints: S≤4 mg/l; R>8 mg/l.

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.

Commonly susceptible species

<table>
<thead>
<tr>
<th>Gram-positive micro-organisms:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative micro-organisms:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td><em>Morganella morganii</em></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td></td>
</tr>
<tr>
<td><em>Providencia species</em></td>
<td></td>
</tr>
</tbody>
</table>
Species for which acquired resistance may be a problem

<table>
<thead>
<tr>
<th>Gram-negative micro-organisms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>Klebsiella species</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
</tbody>
</table>

Inherently resistant organisms

<table>
<thead>
<tr>
<th>Gram-positive micro-organisms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus species</td>
</tr>
<tr>
<td>Staphylococcus species, Coagulase negative*</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Streptococcus milleri</em></td>
</tr>
<tr>
<td>Streptococcus pneumoniae#</td>
</tr>
<tr>
<td>Viridans Streptococci</td>
</tr>
</tbody>
</table>

Anaerobes

<table>
<thead>
<tr>
<th>Bacteroides species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium species</td>
</tr>
<tr>
<td>Fusobacterium species</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
</tr>
</tbody>
</table>

Others

<table>
<thead>
<tr>
<th>Chlamydia species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter species</td>
</tr>
<tr>
<td>Legionella species</td>
</tr>
<tr>
<td>Mycobacterium species</td>
</tr>
<tr>
<td>Mycoplasma species</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

Absorption

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

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%.

Metabolism

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration.

Distribution

Concentrations of ceftazidime in excess of the minimum inhibitory concentrations 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 concentrations are achieved in the cerebrospinal fluid in the absence of inflammation. Therapeutic concentrations of 4 - 20 mg/l or more are achieved in the cerebrospinal fluid when the meninges are inflamed.

**Excretion**
Excretion is almost exclusively by the kidney. Approximately 80 - 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.

### 5.3 Preclinical safety data
No additional data of relevance.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
Sodium carbonate

#### 6.2 Incompatibilities
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.

Solutions containing ceftazidime should not be mixed with or added to solutions containing other agents than listed below (see section 6.6).

#### 6.3 Shelf life
**Unopened vial:**
Three years.

**Reconstituted solution:**
Chemical and physical stability has been demonstrated in the following conditions:
- for 24 hours at 25°C and
- for 7 days at 5±3°C
when dissolved in 10 or 3 ml of WFI.

- for 6 hours at 25°C and
- for 36 hours at 5±3°C
when dissolved in 0.5% or 1% Lidocaine HCl injection.

- for 6 hours at 25°C and
- for 24 hours at 5±3°C
when dissolved in all the solutions studied (see table in Section 6.6).

*From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately*

If not used immediately, the 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 opening, reconstitution, and dilution has taken place in controlled and validated aseptic conditions.
6.4 Special precautions for storage

**Unopened vial:**
Store below 25°C. Keep the vial in the outer carton.

**Reconstituted solution:**
Store below 2 - 8°C. See section 6.3 for further information on shelf life of reconstituted solutions.

6.5 Nature and contents of container

Type I glass vials with rubber (Type I) closures sealed with aluminium caps. The vials are placed in cartons.

Boxes of one, five or twenty vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The use of freshly prepared solutions is recommended (see section 6.3).

The reconstituted solution should be clear. Do not use if particles are present.

Ceftazidime solutions range from a light yellow to amber solution depending on the concentration, diluent and storage conditions used. Within the stated recommendations, variations in the intensity of the colour will not affect the potency of the drug.

Each 2 g vial contains 104 mg (4.52 mmol) of sodium.

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.

**2g Intravenous bolus injection:**
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.

**2 g Intravenous infusion:**
1. Insert the syringe needle through the vial closure and inject 10ml 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 obtained in about 1 to 2 minutes.
3. Insert a gas relief needle through the vial closure to relieve the internal pressure and, with the gas relief in position, add a further 40ml of diluent. Remove the gas relief needle and syringe needle; shake the vial and set up for infusion use in the normal way.

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

**Intravenous bolus injection:**
Ceftazidime 2 g Powder for Solution for Injection or Infusion should be dissolved in 10 ml of Water for Injections Ph. Eur. The resulting solution contains approximately 170 mg/ml ceftazidime.
Intravenous infusion:
Ceftazidime 2 g Powder for Solution for Injection or Infusion should be dissolved in 50 ml of
diluent by the technique recommended above. Sodium Chloride Injection 0.9%, Dextrose
Injection 5% or other approved diluent (see below) must be used as Water for Injections Ph.
Eur produces hypotonic solutions at this concentration. The resulting solution contains
approximately 40 mg/ml ceftazidime.

<table>
<thead>
<tr>
<th>Reconstitution Diluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Ceftazidime concentration 1 mg/ml - 40 mg/ml:</td>
</tr>
<tr>
<td>0.9% Sodium Chloride Injection BP</td>
</tr>
<tr>
<td>0.225% Sodium Chloride and 5% Dextrose Injection BP</td>
</tr>
<tr>
<td>0.45% Sodium Chloride and 5% Dextrose Injection BP</td>
</tr>
<tr>
<td>0.9% Sodium Chloride and 5% Dextrose Injection BP</td>
</tr>
<tr>
<td>0.18% Sodium Chloride and 4% Dextrose Injection BP</td>
</tr>
<tr>
<td>M/6 Sodium Lactate Injection BP</td>
</tr>
<tr>
<td>Compound Sodium Lactate Injection BP (Hartmann's Solution)</td>
</tr>
<tr>
<td>5% Dextrose Injection BP</td>
</tr>
<tr>
<td>10% Dextrose Injection BP</td>
</tr>
<tr>
<td>Dextran 40 Injection BP 10% in 0.9% Sodium Chloride Injection BP</td>
</tr>
<tr>
<td>Dextran 40 Injection BP 10% in 5% Dextrose Injection BP</td>
</tr>
<tr>
<td>Dextran 70 Injection BP 6% in 0.9% Sodium Chloride Injection BP</td>
</tr>
<tr>
<td>Dextran 70 Injection BP 6% in 5% Dextrose Injection BP</td>
</tr>
</tbody>
</table>

At Ceftazidime concentration 0.05 mg/ml - 0.25 mg/ml:
Intraperitoneal Dialysis Fluid (Lactate) BPC 1973

When admixed at 4 mg/ml, either components will retain satisfactory potency:
Cefuroxime (cefuroxime sodium) 3mg/ml in 0.9% Sodium Chloride Injection BP
Cloxacillin (cloxacillin sodium) 4mg/ml in 0.9% Sodium Chloride Injection BP
Heparin 10 IU/ml in 0.9% Sodium Chloride Injection BP
Heparin 50 IU/ml in 0.9% Sodium Chloride Injection BP
Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 0.9% Sodium Chloride Injection BP
Hydrocortisone (hydrocortisone sodium succinate) 1mg/ml in 5% Dextrose Injection BP
Potassium Chloride 10 mEq/L in 0.9% Sodium Chloride Injection BP
Potassium Chloride 40 mEq/L in 0.9% Sodium Chloride Injection BP

MARKETING AUTHORIZATION HOLDER
Noridem Enterprises Ltd., (trading as Demo)
Evagorou & Makariou,
Mitsi Building 3, Suit.115,
1065 Nicosia,
Cyprus.

MARKETING AUTHORIZATION NUMBER(S)
PL 24598/0005

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
02/09/2008

DATE OF REVISION OF THE TEXT
02/09/2008
UKPAR Ceftazidime 1g Powder for Solution for Injection
UKPAR Ceftazidime 2g Powder for Solution for Injection or Infusion

In this leaflet:
- What Ceftazidime is and what it is used for
- How to use Ceftazidime
- Possible side-effects
- Further information

1. What Ceftazidime is and what it is used for

Ceftazidime is a type of medicine called an antibiotic. Antibiotics kill or stop the growth of bacteria — the cause of many types of infections. This medicine is not for use in people who are allergic to cephalosporin-type antibiotics (such as cefuroxime, cefuroxime axetil, or cefuroxime axetil for injection).

Ceftazidime is used to treat infections caused by bacteria (including infections of:
- the ears and breathing tubes, especially in children
- the skin and soft tissues (such as itchy redness, swelling, pain, and warmth)
- the urinary tract (such as pain on passing urine and kidney infections)
- the bones and joints (such as osteomyelitis)
- the brain and spinal fluid (such as meningitis)
- the mouth (such as toothache or gum infection)
- the liver or gall bladder (such as cholangitis)
- the small or large intestine (such as typhoid fever)

Ceftazidime is also used to treat infections that occur after surgery. This medicine is also prescribed for some people with meningitis due to certain types of bacteria.

2. Before you use Ceftazidime

The doctor or nurse giving you this medicine may ask you some questions about you. They need the following information before you have this medicine to help decide how best to treat you.

Do not take Ceftazidime if:
- You are allergic to this medicine or any other similar medicines (such as cefuroxime, cefuroxime axetil, or cefuroxime axetil for injection).
- You are allergic to any of the components of this medicine.
- You have an allergy to the inclusion of any other type of antibiotics (such as sulphonamides). Do not take Ceftazidime if any of the above statements are true.

Take care with Ceftazidime

Before treatment starts, tell your doctor or nurse:
- You have any allergy to food, such as dairy products and nuts
- You have any other allergies
- You have any history of drug allergies
- You have or have had any other infections
- You have blood disorders or kidney problems
- You are on any other medicines

Tell your doctor or nurse immediately if:
- You develop skin rash or pruritus (itchy skin)
- You have any sign of infection
- You have any unusual bleeding or bruising

Before treatment starts, tell your doctor or nurse:
- You have any history of allergy to the inclusion of any other type of antibiotics (such as sulphonamides). Do not take Ceftazidime if any of the above statements are true.

Tell your doctor or nurse immediately if:
- You develop skin rash or pruritus (itchy skin)
- You have any sign of infection
- You have any unusual bleeding or bruising

Tell your doctor or nurse immediately if:
- You develop skin rash or pruritus (itchy skin)
- You have any sign of infection
- You have any unusual bleeding or bruising

Important information about some of the ingredients of Ceftazidime

If you are on a low-sodium diet, it is important to know how much sodium is in your medicine. Each 1 g of ceftazidime contains 1.97 g of sodium. Each 2 g of ceftazidime contains 3.93 g of sodium.

3. How to use Ceftazidime

A doctor or nurse will give you this medicine.

Your doctor will give you the correct dose as an injection or a drip infusion. Ceftazidime may be given as an IV (Intravenous injection) or intramuscular injection.

4. Possible side-effects

Infants over two months old and children:
- The usual dose is 50–100 mg/kg bodyweight per day in 3 doses every 8 hours.
- The maximum dose is 1 g daily.

Young babies (neonates) and babies up to 3 months of age:
- The usual dose is 60–80 mg/kg bodyweight per day in 3 doses every 8 hours.

Young babies (neonates) and babies up to 3 months of age:
- The usual dose is 60–80 mg/kg bodyweight per day in 3 doses every 8 hours.

Perioperative and continuous ambulatory perioperative dialysis (CAPD)
- The maximum dose is 1 g given to patients on CAPD.

Patients with kidney problems:
- If you have a problem with your kidneys the usual dose will be reduced by your doctor to make sure you receive the dose that is correct for you.
- If you have a serious infection and problems with your kidneys, your doctor may also want to test your blood to decide the dose you need.
- If you take more Ceftazidime than you should:
- Your doctor or nurse will usually give you this medicine. If you think you have taken too much medicine, please tell the doctor or nurse at once.

Too much ceftazidime in your blood will cause problems. Please read carefully the important advice at the beginning of the next section, section 5.4, before stopping the use of ceftazidime in your blood.

If you forget to take Ceftazidime:
- If you forget to take Ceftazidime, you must take the next dose as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor, nurse, pharmacist, or another medical professional.

5. How to store Ceftazidime

Your doctor, nurse, or pharmacist will usually store this medicine for you.

Keep this medicine out of the reach and sight of children.

Do not use this medicine after the expiry date (EXP) on the container and label.

The expiry date is the last day of the month written on the packaging.

Store below 25°C.

Always keep your medicine in the outer container.

Open it and use it straight after.

Microscope point of view unless the method of opening reconstitutes the risk of bacterial contamination, the product should be used immediately.

Your medicine should not be mixed with other medicines and should not be given by injection.

Ask your doctor, nurse, or pharmacist if you want more information about this.

Any left-over medicines should be returned to your doctor, nurse, or pharmacist.

If you do this, it will help protect the environment. Do not dispose of the medicine in the drain or on the ground.

6. Further Information

Ceftazidime contains
- The active ingredient is ceftazidime, belonging to the cephalosporin family.
- The other ingredient is sodium lactate.

What Ceftazidime looks like and contains of the pack
- Ceftazidime is available in packs of 500 mg of ceftazidime.
- Each pack contains 1 or 2 g of ceftazidime.

This leaflet was prepared in July 2009.

If this leaflet is difficult to see or read please contact the following address for help:
- Fannin, Pinkett’s Kiln Industrial Park, Reading, RG31 7SB, United Kingdom, Telephone Number: +44 118 930 5333.
UKPAR Ceftazidime 1g Powder for Solution for Injection

UKPAR Ceftazidime 2g Powder for Solution for Injection or Infusion

Technical Information Leaflet

Ceftazidime 1g Powder for Solution for Injection

Ceftazidime 2g Powder for Solution for Injection or Infusion

Ceftazidime

This leaflet provides technical information for the healthcare professional. There is a separate Patient Information Leaflet.

1. NAME OF THE MEDICINAL PRODUCT

UKPAR Ceftazidime 1g Powder for Solution for Injection  PL 24598/0004

UKPAR Ceftazidime 2g Powder for Solution for Injection or Infusion  PL 24598/0005

2. QUANTITIES IN PACKAGE

3. PHARMACEUTICAL FORM

Ceftazidime 1g Powder for Solution for Injection

Ceftazidime 2g Powder for Solution for Injection or Infusion

4. clinCal PARTICULARS

4.1 Therapeutic indications

4.1.1 Ceftazidime 1g Powder for Solution for Injection

4.1.2 Ceftazidime 2g Powder for Solution for Injection or Infusion

4.2 Pharmacokinetic and Metabolism

4.2.1 Ceftazidime 1g Powder for Solution for Injection

4.2.2 Ceftazidime 2g Powder for Solution for Injection or Infusion

4.3 Pharmacodynamics

4.3.1 Ceftazidime 1g Powder for Solution for Injection

4.3.2 Ceftazidime 2g Powder for Solution for Injection or Infusion

5. PHARMACOLOGICAL PROPERTIES

5.1 General properties

5.2 Pharmacokinetic properties

5.3 Pharmacodynamic properties

5.4 Pharmacological effects

5.5 Pharmacological effects

6. WAY OF ADMINISTRATION

6.1 Injection

6.2 Infusion

7. POSITIVE SAFETY DATA

7.1 Adverse effects

7.2 Special precautions for disposal

7.3 Disposal of containers and packaging

8. OVERDOSAGE

8.1 Symptoms and acute toxicity

8.2 Management

9. MARKETING AUTHORISATION Holder

9.1 Introduction

9.2 Contact Details

9.3 References

10. LEGEND

10.1 Abbreviations

10.2 References

10.3 Acknowledgements

11. ANNEX

11.1 Documents

11.2 Acknowledgements

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UKPAR Ceftazidime 1g Powder for Solution for Injection  PL 24598/0004
UKPAR Ceftazidime 2g Powder for Solution for Injection or Infusion  PL 24598/0005

Ceftazidime 1g Powder for Solution for Injection
Each vial contains 1.16g of ceftazidime pentahydrate (equivalent to 1g ceftazidime) with 118mg of sodium carbonate. Please read the enclosed leaflet for further details on instructions for use and handling. Store below 25°C. Keep the vial in the outer carton. Single use only.

Ceftazidime 2g Powder for Solution for Injection or Infusion
Each vial contains 2.33g of ceftazidime pentahydrate (equivalent to 2g ceftazidime) with 236mg of sodium carbonate. Please read the enclosed leaflet for further details on instructions for use and handling. Store below 25°C. Keep the vial in the outer carton. Single use only.
| UKPAR Ceftazidime 1g Powder for Solution for Injection | PL 24598/0004 |
| UKPAR Ceftazidime 2g Powder for Solution for Injection or Infusion | PL 24598/0005 |

<table>
<thead>
<tr>
<th>CeftAZIDime 1g Powder for Solution for Injection</th>
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<th>CeftAZIDime 1g Powder for Solution for Injection</th>
<th>CeftAZIDime 1g Powder for Solution for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For Intramuscular or Intravenous Injection only</strong></td>
<td><strong>For Intramuscular or Intravenous Injection only</strong></td>
<td><strong>For Intramuscular or Intravenous Injection only</strong></td>
<td><strong>For Intramuscular or Intravenous Injection only</strong></td>
</tr>
<tr>
<td><strong>20 vials x 1g</strong></td>
<td><strong>20 vials x 1g</strong></td>
<td><strong>20 vials x 1g</strong></td>
<td><strong>20 vials x 1g</strong></td>
</tr>
</tbody>
</table>

**Instructions for Use:**
- Reconstitute 1 vial with 1 mL of solution provided in a vial. Stir gently.
- Further dilution is optional, for further details please refer to the product information leaflet.