Public Assessment Report

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

Ceftazidime Pentahydrate

PL 18559/0029
PL 18559/0030
PL 18559/0031
PL 18559/0032

ACS Dobfar Generics SA

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Lay Summary


The products contain the active ingredient ceftadizime pentahydrate. Ceftazidime, administered parenterally, is a third-generation cephalosporin which acts by inhibiting bacterial cell wall synthesis.

The products were found to be generic medicinal products of the reference product Fortum marketed by Glaxo Operations UK Ltd.
Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Ceftazidime 250mg Powder Solution for Injection (PL 18559/0029), Ceftazidime 500mg Powder Solution for Injection (PL 18559/0030) Ceftazidime 1g Powder Solution for Injection (PL 18559/0031) Ceftazidime 2g Powder Solution for Injection (PL 18559/0032) on 6th December 2007.

The applicant successfully claimed that these products were generic medicinal products of Fortum for Injection 250mg PL 00004/0304 (granted 1985), Fortum for Injection 500mg, PL 00004/0292 (granted 1983), Fortum for Injection 1g  PL 00004/0293 (granted 1983) and Fortum for Injection 2g  PL 00004/0294 (granted 1983), respectively, marketed by Glaxo Operations UK Ltd under Article 10.1 of Directive 2001/83/EC as amended.

The products contain the active ingredient ceftadizime pentahydrate. Ceftazidime, administered parenterally, is a third-generation cephalosporin which acts by inhibiting bacterial cell wall synthesis in both Gram-positive and Gram-negative bacteria by binding to penicillin-binding proteins and thereby inhibiting peptidoglycan cross-linking. It is administered by deep intramuscular injection or intravenous injection or infusion.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

General Information

Ceftazidime is a semi-synthetic broad spectrum, beta-lactam antibiotic with increased activity against Pseudomonas aeruginosa.

Nomenclature

Ceftazidime (INN)

CHEMICAL NAME

Structure

**Relative molecular mass** 636.6.

**General Properties**
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.

$[\alpha]^{20}_D = +24.5^\circ$

**pKa** = 1.9 ; 2.7 ; 4.1

**UV max** (water) = 258 nm

A satisfactory description of the manufacturing process was provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Ceftazidime pentahydrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months.
DRUG PRODUCT

Other Ingredients
The other ingredient in the drug product is sodium carbonate, which complies with its respective European Pharmacopoeial monograph. No excipients of human or animal origin are used.

Impurity profiles
Impurity profiles for all strengths of drug product were found to be similar to those for the reference products. These products do not require a bioequivalence study as they are solutions for injection.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The 250mg, 500mg and 1g products are filled into 10ml colourless Type III glass vials, whereas the 2g product is filled into a 50ml vial. The vials are stoppered with Type I bromobutyl closures. Specifications and Certificates of Analysis for all packaging types used have been provided.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months with the following storage instructions, “Protect from light” and “Keep container in the outer carton”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

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

CLINICAL PHARMACOLOGY

Pharmacodynamics
Ceftazidime is a bactericidal cephalosporin antibiotic, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital-acquired infections are susceptible to ceftazidime in vitro, including strains resistant to gentamicin and other aminoglycosides. It is highly stable to most clinically important beta-lactamases produced by both gram-positive and gram-negative organisms and consequently is active against many ampicillin- and cephalothin-resistant strains.

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

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

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration. Approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile, significantly limiting the amount entering the bowel. Concentrations of ceftazidime in excess of the minimum inhibitory levels for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids. Transplacental transfer of the antibiotic readily occurs. Ceftazidime penetrates the intact blood brain barrier poorly and low levels are achieved in the CSF in the absence of inflammation. Therapeutic levels of 4 to 20mg/litre or more are achieved in the CSF when the meninges are inflamed.

Bioequivalence
A bioequivalence study was not required for these products as their pharmaceutical form is a solution for injection. Quality aspects of bioequivalence have been demonstrated.

Efficacy and Safety
Efficacy and Safety is reviewed in the Clinical Expert Report which is written by an appropriately qualified expert.
Summary of Product Characteristics
This is satisfactory

Patient Information Leaflet
This is satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion
Marketing Authorisations were granted for these products.
Overall Conclusion and Risk/Benefit Analysis

**Quality**
The important quality characteristics of Ceftazidime Powder Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**Pre-Clinical**
No new preclinical data were submitted and none are required for applications of this type.

**Clinical**
No bioequivalence study was required for these applications. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product Fortum.

**Risk/Benefit Analysis**
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk: benefit is, therefore, considered to be positive.
### Steps Taken During Assessment

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the application on 16/08/2005.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 27/09/2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 04/08/2006, 22/05/2007 and 29/08/2007.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 19/03/2007, 28/07/2007 and 25/10/2007.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 06/12/2007.</td>
</tr>
</tbody>
</table>
Steps Taken after Assessment

None
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 250mg Ceftazidime (as pentahydrate)

Also contains sodium carbonate anhydrous (equivalent to 13mg sodium)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection

A white to cream-coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Single infections.
Mixed infections caused by two or more susceptible organisms.
Severe infections in general.
Respiratory tract infections.
Ear, nose and throat infections.
Urinary tract infections.
Skin and soft tissue infections.
Gastrointestinal, biliary and abdominal infections.
Bone and joint infections.
Dialysis: infections associated with haemo- and peritoneal dialysis and with continuous peritoneal dialysis (CAPD).
In meningitis it is recommended that the results of a sensitivity test are known before treatment with ceftazidime as a single agent. It may be used for infections caused by organisms resistant to other antibiotics including aminoglycosides and many cephalosporins. When appropriate, however, it may be used in combination with an aminoglycoside or other beta-lactam antibiotic for example, in the presence of severe neutropenia, or with an antibiotic active against anaerobes when the presence of bacteroides fragilis is suspected. In addition, ceftazidime is indicated in the perioperative prophylaxis of transurethral prostatectomy.
4.2 **Posology and method of administration**

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

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

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

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

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

**Infants and children:** The usual dosage range for children aged over two months is 30 to 100mg/kg/day, given as two or three divided doses. Doses up to 150mg/kg/day (maximum 6g daily) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

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

**Dosage in impaired renal function:** Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50ml/min. In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.

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 *Dosage in impaired renal function*.

Recommended maintenance doses of ceftazidime in renal insufficiency:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Approx. serum creatinine* (µmol/l (mg/dl))</th>
<th>Recommended unit dose of ceftazidime (g)</th>
<th>Frequency of dosing (hourly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-31</td>
<td>150-200 (1.7-2.3)</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>30-16</td>
<td>200-350 (2.3-4.0)</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>15-6</td>
<td>350-500 (4.0-5.6)</td>
<td>0.5</td>
<td>24</td>
</tr>
<tr>
<td>&lt;5</td>
<td>&gt;500 (&gt;5.6)</td>
<td>0.5</td>
<td>48</td>
</tr>
</tbody>
</table>

* These values are guidelines and may not accurately predict renal function in all patients, especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

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

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

**Males:**

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

**Females:**

0.85 x above value.

To convert serum creatinine in µmol/litre into mg/dl divide by 88.4.

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

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

*Dosage in peritoneal dialysis:* Ceftazidime may also be used in peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD). As well as using ceftazidime intravenously, it can be incorporated into the dialysis fluid (usually 125 to 250mg for 2L of dialysis fluid).
Method of administration: Ceftazidime may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. For instructions on dilution of the product before administration, see section 6.6.

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

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

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

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

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

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

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

4.6 **Pregnancy and lactation**

**Pregnancy:**
There is no experimental evidence of embryopathic or teratogenic effects attributable to ceftazidime but as with all drugs, it should be administered with caution during the early months of pregnancy and in early infancy. Use in pregnancy requires that the anticipated benefit be weighed against the possible risks.

**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**

Ceftazidime has no influence on the ability to drive and use machines.

4.8 **Undesirable effects**

Clinical trial experience has shown that ceftazidime is generally well tolerated.

*Hypersensitivity:* maculopapular or urticarial rash, fever, pruritus, and very rarely angioedema and anaphylaxis (including bronchospasm and/or hypotension).

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

Gastrointestinal disorders:
Diarrhoea, nausea, vomiting, abdominal pain, and very rarely oral thrush or colitis. As with other cephalosporins, colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis.

Hepatobiliary disorders:
Very rarely jaundice.

Skin and subcutaneous tissue disorders:
As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Reproductive system disorders:
Candidiasis, vaginitis

General disorders and administration site conditions:
Phlebitis or thrombophlebitis with intravenous administration; pain and/or inflammation after intramuscular injection.

Investigations:
Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs' test, very rarely haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase. As with some other cephalosporins, transient elevation of blood urea, blood urea nitrogen and/or serum creatinine have been observed occasionally. Very rarely, leucopenia, neutropenia, agranulcytosis, thrombocytopenia and lymphocytosis have been seen.

4.9 Overdose
Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Serum levels of ceftazidime can be reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances.
ATC code: J01DA11
Ceftazidime is a bactericidal cephalosporin antibiotic, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital-acquired infections are susceptible to ceftazidime in vitro, including strains resistant to gentamicin and other aminoglycosides. It is highly stable to most clinically important beta-lactamases produced by both gram-positive and gram-negative organisms and consequently is active against many ampicillin- and cephalothin-resistant strains. Ceftazidime has high intrinsic activity in vitro and acts within a narrow MIC range for most genera with minimal changes in MIC at varied inoculum levels. Ceftazidime has been shown to have in vitro activity against the following organisms:

**Gram-negative:** pseudomonas aeruginosa, pseudomonas spp (other), klebsiella pneumoniae, klebsiella spp (other), proteus mirabilis, proteus vulgaris, morganella morganii (formerly proteus morganii), proteus rettgeri, providencia spp, escherichia coli, enterobacter spp, citrobacter spp, serrata spp, salmonella spp, shigella spp,yersinia enterocolitica, pasteurella multocida, acinetobacter spp, neisseria gonorrhoeae, neisseria meningitidis, haemophilus influenzae (including ampicillin-resistant strains), haemophilus parainfluenzae (including ampicillin-resistant strains).

**Gram-positive:** staphylococcus aureus (methicillin-sensitive strains), staphylococcus epidermidis (methicillin-sensitive strains), micrococcus spp, streptococcus pyogenes, streptococcus group b, streptococcus pneumoniae, streptococcus mitis, streptococcus spp (excluding enterococcus (streptococcus) faecalis).

**Anaerobic strains:** peptococcus spp, peptostreptococcus spp, streptococcus spp, propionibacterium spp, clostridium perfringens, fusobacterium spp, bacteroides spp (many strains of bact fragilis are resistant).

Ceftazidime is not active in vitro against methicillin-resistant staphylococci, enterococcus (streptococcus) faecalis and many other enterococci, listeria monocytogenes, campylobacter spp or clostridium difficile.

**In vitro** the activities of ceftazidime and aminoglycoside antibiotics in combination have been shown to be at least additive; there is evidence of synergy in some strains tested. This property may be important in the treatment of febrile neutropenic patients.

### 5.2 Pharmacokinetic properties

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

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

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration. Approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile, significantly limiting the amount entering the bowel. Concentrations of ceftazidime in excess of the minimum inhibitory levels for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids. Transplacental transfer of the antibiotic readily occurs. Ceftazidime penetrates the intact blood brain barrier poorly and low levels are achieved in the CSF in the absence of inflammation. Therapeutic levels of 4 to 20mg/litre or more are achieved in the CSF when the meninges are inflamed.

5.3 Preclinical safety data
No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium carbonate, anhydrous (E500)

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.

6.3 Shelf life
Vial before opening: Two years.
After reconstitution: Chemical and physical stability has been demonstrated for 24 hours at 5°C and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage
times and conditions are the responsibility of the user and would normally be no 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
Keep vials in the outer carton to protect from light. For storage of the reconstituted product, see section 6.3.

6.5 Nature and contents of container
Type III glass vial with a bromobutyl rubber stopper.

Pack sizes of 1, 5, 10, 20, 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
This medicinal product is for single use only. Discard any unused contents. Reconstitute immediately before use.

Instructions for constitution: See table for addition volumes and solution concentrations.

Preparation of solution:

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250mg</td>
<td>Intramuscular 1.0</td>
<td>210</td>
</tr>
<tr>
<td>250mg</td>
<td>Intravenous 2.5</td>
<td>90</td>
</tr>
</tbody>
</table>

It is recommended that the following technique of reconstitution is adopted.

1. Insert the syringe needle through the vial closure and inject the recommended volume of 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. 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.

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.
These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids. Ceftazidime is compatible with the most commonly used intravenous fluids.

In keeping with good pharmaceutical practice, it is preferable to use freshly constituted solutions. If this is not practicable, satisfactory potency is retained for 24 hours in the refrigerator (2 - 8°C) when diluted in any of the injections listed below.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for injection EP</td>
<td>70mg/ml &amp; 280mg/ml</td>
</tr>
<tr>
<td>0.5% Lidocaine injection BP</td>
<td>260mg/ml</td>
</tr>
<tr>
<td>1.0% Lidocaine injection BP</td>
<td>280mg/ml</td>
</tr>
<tr>
<td>Bacteriostatic water for injection USP</td>
<td>250mg/ml</td>
</tr>
<tr>
<td>0.9% Sodium chloride injection BP</td>
<td>Up to 250mg/ml</td>
</tr>
<tr>
<td>5% Glucose intravenous infusion BP</td>
<td>Up to 40mg/ml</td>
</tr>
</tbody>
</table>

Solutions range from light yellow to amber depending on concentration, diluent and storage conditions used.
7 MARKETING AUTHORISATION HOLDER
ACS Dobfar Generics SA
5, Rue Eugene Ruppert,
L-2453 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/12/2007

10 DATE OF REVISION OF THE TEXT
06/12/2007
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 500mg Ceftazidime (as pentahydrate)
Also contains sodium carbonate anhydrous (equivalent to 26mg sodium)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection
A white to cream-coloured powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Single infections.
Mixed infections caused by two or more susceptible organisms.
Severe infections in general.
Respiratory tract infections.
Ear, nose and throat infections.
Urinary tract infections.
Skin and soft tissue infections.
Gastrointestinal, biliary and abdominal infections.
Bone and joint infections.
Dialysis: infections associated with haemo- and peritoneal dialysis and with continuous peritoneal dialysis (CAPD).
In meningitis it is recommended that the results of a sensitivity test are known before treatment with ceftazidime as a single agent. It may be used for infections caused by organisms resistant to other antibiotics including aminoglycosides and many cephalosporins. When appropriate, however, it may be used in combination with an aminoglycoside or other beta-lactam antibiotic for example, in the presence of severe neutropenia, or with an antibiotic active against anaerobes when the presence of bacteroides fragilis is suspected. In addition, ceftazidime is indicated in the perioperative prophylaxis of transurethral prostatectomy.
4.2 Posology and method of administration

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

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

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

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

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

**Infants and children:** The usual dosage range for children aged over two months is 30 to 100mg/kg/day, given as two or three divided doses. Doses up to 150mg/kg/day (maximum 6g daily) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

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

**Dosage in impaired renal function:** Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50ml/min. In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.
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 Dosage in impaired renal function.

Recommended maintenance doses of ceftazidime in renal insufficiency:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Approx. serum creatinine* (µmol/l (mg/dl))</th>
<th>Recommended unit dose of ceftazidime (g)</th>
<th>Frequency of dosing (hourly)</th>
</tr>
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<tr>
<td>50-31</td>
<td>150-200 (1.7-2.3)</td>
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<td>12</td>
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<td>&gt;500 (&gt;5.6)</td>
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<td>48</td>
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* These values are guidelines and may not accurately predict renal function in all patients, especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

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

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

Males:

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

Females:

0.85 x above value.

To convert serum creatinine in µmol/litre into mg/dl divide by 88.4.

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

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

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

**Method of administration:** Ceftazidime may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. For instructions on dilution of the product before administration, see section 6.6.

4.3 **Contraindications**
Ceftazidime is contraindicated in patients with known hypersensitivity to ceftazidime or other cephalosporin antibiotics.

4.4 **Special warnings and precautions for use**

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

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

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

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

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

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

4.6 Pregnancy and lactation

Pregnancy:
There is no experimental evidence of embryopathic or teratogenic effects attributable to ceftazidime but as with all drugs, it should be administered with caution during the early months of pregnancy and in early infancy. Use in pregnancy requires that the anticipated benefit be weighed against the possible risks.

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

Ceftazidime has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Clinical trial experience has shown that ceftazidime is generally well tolerated.

Hypersensitivity: maculopapular or urticarial rash, fever, pruritus, and very rarely angioedema and anaphylaxis (including bronchospasm and/or hypotension).
Adverse reactions:

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

*Gastrointestinal disorders:*
Diarrhoea, nausea, vomiting, abdominal pain, and very rarely oral thrush or colitis. As with other cephalosporins, colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.

*Hepatobiliary disorders:*
Very rarely jaundice.

*Skin and subcutaneous tissue disorders:*
As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

*Reproductive system disorders:*
Candidiasis, vaginitis

*General disorders and administration site conditions:*
Phlebitis or thrombophlebitis with intravenous administration; pain and/or inflammation after intramuscular injection.

*Investigations:*
Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs' test, very rarely haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase. As with some other cephalosporins, transient elevation of blood urea, blood urea nitrogen and/or serum creatinine have been observed occasionally. Very rarely, leucopenia, neutropenia, agranulcytosis, thrombocytopenia and lymphocytosis have been seen.

4.9 Overdose
Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Serum levels of ceftazidime can be reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances.
ATC code: J01DA11
Ceftazidime is a bactericidal cephalosporin antibiotic, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital-acquired infections are susceptible to ceftazidime in vitro, including strains resistant to gentamicin and other aminoglycosides. It is highly stable to most clinically important beta-lactamases produced by both gram-positive and gram-negative organisms and consequently is active against many ampicillin- and cephalothin-resistant strains. Ceftazidime has high intrinsic activity in vitro and acts within a narrow MIC range for most genera with minimal changes in MIC at varied inoculum levels. Ceftazidime has been shown to have in vitro activity against the following organisms:

Gram-negative: pseudomonas aeruginosa, pseudomonas spp (other), klebsiella pneumonae, klebsiella spp (other), proteus mirabilis, proteus vulgaris, morganella morganii (formerly proteus morganii), proteus rettgeri, providencia spp, escherichia coli, enterobacter spp, citrobacter spp, serratia spp, salmonella spp, shigella spp, yersinia enterocolitica, pasteurella multocida, acinetobacter spp, neisseria gonorrhoeae, neisseria meningitidis, haemophilus influenzae (including ampicillin-resistant strains), haemophilus parainfluenzae (including ampicillin-resistant strains).

Gram-positive: staphylococcus aureus (methicillin-sensitive strains), staphylococcus epidermidis (methicillin-sensitive strains), micrococcus spp, streptococcus pyogenes, streptococcus group b, streptococcus pneumoniae, streptococcus mitis, streptococcus spp (excluding enterococcus (streptococcus) faecalis).
Anaerobic strains: peptococcus spp, peptostreptococcus spp, streptococcus spp, propionibacterium spp, clostridium perfringens, fusobacterium spp, bacteroides spp (many strains of bact fragilis are resistant).

Ceftazidime is not active in vitro against methicillin-resistant staphylococci, enterococcus (streptococcus) faecalis and many other enterococci, listeria monocytogenes, campylobacter spp or clostridium difficile.

In vitro the activities of ceftazidime and aminoglycoside antibiotics in combination have been shown to be at least additive; there is evidence of synergy in some strains tested. This property may be important in the treatment of febrile neutropenic patients.

5.2 Pharmacokinetic properties
Ceftazidime administered by the parenteral route reaches high and prolonged serum levels in man. After intramuscular administration of 500mg and 1g serum mean peak levels of 18 and 37mg/litre respectively are rapidly achieved. Five minutes after an intravenous bolus injection of 500mg, 1g or 2g, serum mean levels are respectively 46, 87 and 170mg/litre.
Therapeutically effective concentrations are still found in the serum 8 to 12 hours after both intravenous and intramuscular administration. The serum half-life is about 1.8 hours in normal volunteers and about 2.2 hours in patients with apparently normal renal function. The serum protein binding of ceftazidime is low at about 10%.

Ceftazidime is not metabolised in the body and is excreted unchanged in the active form into the urine by glomerular filtration. Approximately 80 to 90% of the dose is recovered in the urine within 24 hours. Less than 1% is excreted via the bile, significantly limiting the amount entering the bowel. Concentrations of ceftazidime in excess of the minimum inhibitory levels for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial and pleural and peritoneal fluids. Transplacental transfer of the antibiotic readily occurs. Ceftazidime penetrates the intact blood brain barrier poorly and low levels are achieved in the CSF in the absence of inflammation. Therapeutic levels of 4 to 20mg/litre or more are achieved in the CSF when the meninges are inflamed.

5.3 Preclinical safety data
No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium carbonate, anhydrous (E500)

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.

6.3 Shelf life
Vial before opening: Two years.
After reconstitution: Chemical and physical stability has been demonstrated for 24 hours at 5°C and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no 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
Keep vials in the outer carton to protect from light.
For storage of the reconstituted product, see section 6.3.

6.5 Nature and contents of container
Type III glass vial with a bromobutyl rubber stopper.
Pack sizes of 1, 5, 10, 20, 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
This medicinal product is for single use only. Discard any unused contents. Reconstitute immediately before use.

Instructions for constitution: See table for addition volumes and solution concentrations.

Preparation of solution:

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>Intramuscular</td>
<td>1.5</td>
</tr>
<tr>
<td>500mg</td>
<td>Intravenous</td>
<td>5.0</td>
</tr>
</tbody>
</table>

It is recommended that the following technique of reconstitution is adopted.

4. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. Remove the syringe needle.

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

6. 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. 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.
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.

These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids. Ceftazidime is compatible with the most commonly used intravenous fluids.

In keeping with good pharmaceutical practice, it is preferable to use freshly constituted solutions. If this is not practicable, satisfactory potency is retained for 24 hours in the refrigerator (2 - 8°C) when diluted in any of the injections listed below.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for injection EP</td>
<td>70mg/ml &amp; 280mg/ml</td>
</tr>
<tr>
<td>0.5% Lidocaine injection BP</td>
<td>260mg/ml</td>
</tr>
<tr>
<td>1.0% Lidocaine injection BP</td>
<td>280mg/ml</td>
</tr>
<tr>
<td>Bacteriostatic water for injection USP</td>
<td>250mg/ml</td>
</tr>
<tr>
<td>0.9% Sodium chloride injection BP</td>
<td>Up to 250mg/ml</td>
</tr>
<tr>
<td>5% Glucose intravenous infusion BP</td>
<td>Up to 40mg/ml</td>
</tr>
</tbody>
</table>

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

7 MARKETING AUTHORISATION HOLDER
ACS Dobfar Generics SA
5, Rue Eugene Ruppert,
L-2453 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 18559/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/12/2007

10 DATE OF REVISION OF THE TEXT
06/12/2007
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 1g Ceftazidime (as pentahydrate)
Also contains sodium carbonate anhydrous (equivalent to 52mg sodium)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection
A white to cream-coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Single infections.
Mixed infections caused by two or more susceptible organisms.
Severe infections in general.
Respiratory tract infections.
Ear, nose and throat infections.
Urinary tract infections.
Skin and soft tissue infections.
Gastrointestinal, biliary and abdominal infections.
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In meningitis it is recommended that the results of a sensitivity test are known before treatment with ceftazidime as a single agent. It may be used for infections caused by organisms resistant to other antibiotics including aminoglycosides and many cephalosporins. When appropriate, however, it may be used in combination with an aminoglycoside or other beta-lactam antibiotic for example, in the presence of severe neutropenia, or with an antibiotic active against anaerobes when the presence of bacteroides fragilis is
suspected. In addition, ceftazidime is indicated in the perioperative prophylaxis of transurethral prostatectomy.

4.2 **Posology and method of administration**

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

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

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

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

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

**Infants and children:** The usual dosage range for children aged over two months is 30 to 100mg/kg/day, given as two or three divided doses. Doses up to 150mg/kg/day (maximum 6g daily) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

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

**Dosage in impaired renal function:** Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50ml/min. In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.
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 Dosage in impaired renal function.

Recommended maintenance doses of ceftazidime in renal insufficiency:

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\(^*\) These values are guidelines and may not accurately predict renal function in all patients, especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

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

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

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

**Females:**
\[
0.85 \times \text{above value.}
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To convert serum creatinine in µmol/litre into mg/dl divide by 88.4.

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

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

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

**Method of administration:** Ceftazidime may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh. For instructions on dilution of the product before administration, see section 6.6.

### 4.3 Contraindications

Ceftazidime is contraindicated in patients with known hypersensitivity to ceftazidime or other cephalosporin antibiotics.

### 4.4 Special warnings and precautions for use

**Hypersensitivity reactions:**

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

**Renal function:**

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

Overgrowth of non-susceptible organisms:

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

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

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

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

4.6 **Pregnancy and lactation**

**Pregnancy:**
There is no experimental evidence of embryopathic or teratogenic effects attributable to ceftazidime but as with all drugs, it should be administered with caution during the early months of pregnancy and in early infancy. Use in pregnancy requires that the anticipated benefit be weighed against the possible risks.

**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**

Ceftazidime has no influence on the ability to drive and use machines.

4.8 **Undesirable effects**

Clinical trial experience has shown that ceftazidime is generally well tolerated.

*Hypersensitivity:* maculopapular or urticarial rash, fever, pruritus, and very rarely angioedema and anaphylaxis (including bronchospasm and/or hypotension).
Adverse reactions:

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

Gastrointestinal disorders:
Diarrhoea, nausea, vomiting, abdominal pain, and very rarely oral thrush or colitis. As with other cephalosporins, colitis may be associated with Clostridium difficile and may present as pseudomembranous colitis.

Hepatobiliary disorders:
Very rarely jaundice.

Skin and subcutaneous tissue disorders:
As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Reproductive system disorders: Candidiasis, vaginitis

General disorders and administration site conditions:
Phlebitis or thrombophlebitis with intravenous administration; pain and/or inflammation after intramuscular injection.

Investigations:
Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs' test, very rarely haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase. As with some other cephalosporins, transient elevation of blood urea, blood urea nitrogen and/or serum creatinine have been observed occasionally. Very rarely, leucopenia, neutropenia, agranulcytosis, thrombocytopenia and lymphocytosis have been seen.

4.9 Overdose
Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Serum levels of ceftazidime can be reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cephalosporins and related substances.
ATC code: J01DA11
Ceftazidime is a bactericidal cephalosporin antibiotic, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital-acquired infections are susceptible to ceftazidime \textit{in vitro}, including strains resistant to gentamicin and other aminoglycosides. It is highly stable to most clinically important beta-lactamases produced by both gram-positive and gram-negative organisms and consequently is active against many ampicillin- and cephalothin-resistant strains. Ceftazidime has high intrinsic activity \textit{in vitro} and acts within a narrow MIC range for most genera with minimal changes in MIC at varied inoculum levels. Ceftazidime has been shown to have \textit{in vitro} activity against the following organisms:

**Gram-negative:** pseudomonas aeruginosa, pseudomonas spp (other), klebsiella pneumonieae, klebsiella spp (other), proteus mirabilis, proteus vulgaris, morganella morganii (formerly proteus morganii), proteus rettgeri, providencia spp, escherichia coli, enterobacter spp, citrobacter spp, serrata spp, salmonella spp, shigella spp, yersinia enterocolitica, pasteurella multocida, acinetobacter spp, neisseria gonorrhoeae, neisseria meningitidis, haemophilus influenzae (including ampicillin-resistant strains), haemophilus parainfluenzae (including ampicillin-resistant strains).

**Gram-positive:** staphylococcus aureus (methicillin-sensitive strains), staphylococcus epidermidis (methicillin-sensitive strains), micrococcus spp, streptococcus pyogenes, streptococcus group b, streptococcus pneumoniae, streptococcus mitis, streptococcus spp (excluding enterococcus (streptococcus) faecalis).

**Anaerobic strains:** peptococcus spp, peptostreptococcus spp, streptococcus spp, propionibacterium spp, clostridium perfringens, fusobacterium spp, bacteroides spp (many strains of bact fragilis are resistant).

Ceftazidime is not active \textit{in vitro} against methicillin-resistant staphylococci, enterococcus (streptococcus) faecalis and many other enterococci, listeria monocytogenes, campylobacter spp or clostridium difficile.

\textit{In vitro} the activities of ceftazidime and aminoglycoside antibiotics in combination have been shown to be at least additive; there is evidence of synergy in some strains tested. This property may be important in the treatment of febrile neutropenic patients.

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

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

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

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

5.3 Preclinical safety data
No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium carbonate, anhydrous (E500)

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.

6.3 Shelf life
Vial before opening: Two years.
After reconstitution: Chemical and physical stability has been demonstrated for 24 hours at 5°C and 25°C. From a microbiological point of view, the
product should be used immediately. If not used immediately, in-use storage
times and conditions are the responsibility of the user and would normally be
no 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
Keep vials in the outer carton to protect from light.
For storage of the reconstituted product, see section 6.3.

6.5 Nature and contents of container
Type III glass vial with a bromobutyl rubber stopper.

Pack sizes of 1, 5, 10 20, 50 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
This medicinal product is for single use only. Discard any unused contents.
Reconstitute immediately before use.

Instructions for constitution: See table for addition volumes and solution
concentrations.

Preparation of solution:

<table>
<thead>
<tr>
<th>Vial size</th>
<th>Amount of Diluent to be added (ml)</th>
<th>Approximate Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>Intramuscular 3.0</td>
<td>260</td>
</tr>
<tr>
<td>1g</td>
<td>Intravenous 10.0</td>
<td>90</td>
</tr>
</tbody>
</table>

It is recommended that the following technique of reconstitution is adopted.

7. Insert the syringe needle through the vial closure and inject the recommended
volume of diluent. Remove the syringe needle.

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

9. 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. 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.
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.

These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids. Ceftazidime is compatible with the most commonly used intravenous fluids.

In keeping with good pharmaceutical practice, it is preferable to use freshly constituted solutions. If this is not practicable, satisfactory potency is retained for 24 hours in the refrigerator (2 - 8°C) when diluted in any of the injections listed below.

<table>
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<tr>
<th>Solvent</th>
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<td>280mg/ml</td>
</tr>
<tr>
<td>Bacteriostatic water for injection USP</td>
<td>250mg/ml</td>
</tr>
<tr>
<td>0.9% Sodium chloride injection BP</td>
<td>Up to 250mg/ml</td>
</tr>
<tr>
<td>5% Glucose intravenous infusion BP</td>
<td>Up to 40mg/ml</td>
</tr>
</tbody>
</table>

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

7 MARKETING AUTHORISATION HOLDER
ACS Dobfar Generics SA
5, Rue Eugene Ruppert,
L-2453 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 18559/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/12/2007

10 DATE OF REVISION OF THE TEXT
06/12/2007
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 2g Ceftazidime (as pentahydrate)
Also contains sodium carbonate anhydrous (equivalent to 104mg sodium)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
A white to cream-coloured powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Single infections.
Mixed infections caused by two or more susceptible organisms.
Severe infections in general.
Respiratory tract infections.
Ear, nose and throat infections.
Urinary tract infections.
Skin and soft tissue infections.
Gastrointestinal, biliary and abdominal infections.
Bone and joint infections.
Dialysis: infections associated with haemo- and peritoneal dialysis and with
continuous peritoneal dialysis (CAPD).
In meningitis it is recommended that the results of a sensitivity test are known
before treatment with ceftazidime as a single agent. It may be used for
infections caused by organisms resistant to other antibiotics including
aminoglycosides and many cephalosporins. When appropriate, however, it
may be used in combination with an aminoglycoside or other beta-lactam
antibiotic for example, in the presence of severe neutropenia, or with an
antibiotic active against anaerobes when the presence of bacteroides fragilis is
suspected. In addition, ceftazidime is indicated in the perioperative
prophylaxis of transurethral prostatectomy.

4.2 Posology and method of administration
Ceftazidime is to be used by the parenteral route, the dosage depending upon
the severity, sensitivity and type of infection and the age, weight and renal
function of the patient.
Adults: The adult dosage range for ceftazidime is 1 to 6g per day 8 or 12
hourly via the intramuscular or intravenous route. In the majority of
infections, 1g 8-hourly or 2g 12-hourly should be given. In urinary tract infections and in many less serious infections, 500mg or 1g 12-hourly is usually adequate. In very severe infections, especially immunocompromised patients, including those with neutropenia, 2g 8 or 12-hourly or 3g 12-hourly should be administered.

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

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

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

**Infants and children:** The usual dosage range for children aged over two months is 30 to 100mg/kg/day, given as two or three divided doses. Doses up to 150mg/kg/day (maximum 6g daily) in three divided doses may be given to infected immunocompromised or fibrocystic children or children with meningitis.

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

**Dosage in impaired renal function:** Ceftazidime is excreted by the kidneys almost exclusively by glomerular filtration. Therefore, in patients with impaired renal function it is recommended that the dosage of ceftazidime should be reduced to compensate for its slower excretion, except in mild impairment, i.e. glomerular filtration rate (GFR) greater than 50ml/min. In patients with suspected renal insufficiency, an initial loading dose of 1g of ceftazidime may be given. An estimate of GFR should be made to determine the appropriate maintenance dose.

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 **Dosage in impaired renal function**.

**Recommended maintenance doses of ceftazidime in renal insufficiency:**

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Approx. serum creatinine* (µmol/l (mg/dl))</th>
<th>Recommended unit dose of ceftazidime (g)</th>
<th>Frequency of dosing (hourly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-31</td>
<td>150-200 (1.7-2.3)</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>30-16</td>
<td>200-350 (2.3-4.0)</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>15-6</td>
<td>350-500 (4.0-5.6)</td>
<td>0.5</td>
<td>24</td>
</tr>
<tr>
<td>&lt;5</td>
<td>&gt;500 (&gt;5.6)</td>
<td>0.5</td>
<td>48</td>
</tr>
</tbody>
</table>
These values are guidelines and may not accurately predict renal function in all patients, especially in the elderly in whom the serum creatinine concentration may overestimate renal function.

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

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

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

Females:
0.85 x above value.

To convert serum creatinine in μmol/litre into mg/dl divide by 88.4.

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

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

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

Method of administration: Ceftazidime may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

For instructions on dilution of the product before administration, see section 6.6.

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

4.4 Special warnings and precautions for use
Hypersensitivity reactions:
As with other beta-lactam antibiotics, before therapy with ceftazidime is instituted, careful inquiry should be made for a history of hypersensitivity reactions to ceftazidime, cephalosporins, penicillins or other drugs. Special care is indicated in patients who have experienced an allergic reaction to penicillins or beta-lactams. Ceftazidime should be given only with special caution to patients with type I or immediate hypersensitivity reactions to penicillin. If an allergic reaction to ceftazidime occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine (adrenaline), hydrocortisone, antihistamine or other emergency measures.
Renal function:
Cephalosporin antibiotics at high dosage should be given with caution to patients receiving concurrent treatment with nephrotoxic drugs, e.g. aminoglycoside antibiotics or potent diuretics such as furosemide, as these combinations are suspected of affecting renal function adversely. Clinical experience with ceftazidime has shown that this is not likely to be a problem at the recommended dose levels. There is no evidence that ceftazidime adversely affects renal function at normal therapeutic doses. However, as for all antibiotics eliminated via the kidneys, it is necessary to reduce the dosage according to the degree of reduction in renal function to avoid the clinical consequences of elevated antibiotic levels, e.g. neurological sequelae, which have occasionally been reported when the dose has not been reduced appropriately (see 4.2 Dosage in Impaired Renal Function and 4.8 Undesirable Effects).

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

4.5 Interaction with other medicinal products and other forms of interaction
Ceftazidime does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods (Benedict's, Fehling's, Clinistest) may be observed. Ceftazidime does not interfere in the alkaline picrate assay for creatinine. The development of a positive Coombs' test associated with the use of ceftazidime in about 5% of patients may interfere with the cross-matching of blood. Chloramphenicol is antagonistic in vitro with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown but if concurrent administration of ceftazidime with chloramphenicol is proposed, the possibility of antagonism should be considered. In common with other antibiotics, ceftazidime may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, alternative non-hormonal methods of contraception are recommended.

4.6 Pregnancy and lactation
Pregnancy:
There is no experimental evidence of embryopathic or teratogenic effects attributable to ceftazidime but as with all drugs, it should be administered with caution during the early months of pregnancy and in early infancy. Use in pregnancy requires that the anticipated benefit be weighed against the possible risks.

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
Ceftazidime has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Clinical trial experience has shown that ceftazidime is generally well tolerated. *Hypersensitivity:* maculopapular or urticarial rash, fever, pruritus, and very rarely angioedema and anaphylaxis (including bronchospasm and/or hypotension).

Adverse reactions:

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

*Gastrointestinal disorders:*
Diarrhoea, nausea, vomiting, abdominal pain, and very rarely oral thrush or colitis. As with other cephalosporins, colitis may be associated with *Clostridium difficile* and may present as pseudomembranous colitis.

*Hepatobiliary disorders:*
Very rarely jaundice.

*Skin and subcutaneous tissue disorders:*
As with other cephalosporins, there have been rare reports of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

*Reproductive system disorders:*
Candidiasis, vaginitis

*General disorders and administration site conditions:*
Phlebitis or thrombophlebitis with intravenous administration; pain and/or inflammation after intramuscular injection.

*Investigations:*
Laboratory test changes noted transiently during ceftazidime therapy include: eosinophilia, positive Coombs' test, very rarely haemolytic anaemia, thrombocytosis and elevations in one or more of the hepatic enzymes, ALT (SGPT), AST (SGOT), LDH, GGT and alkaline phosphatase. As with some other cephalosporins, transient elevation of blood urea, blood urea nitrogen and/or serum creatinine have been observed occasionally. Very rarely, leucopenia, neutropenia, agranulcytosis, thrombocytopenia and lymphocytosis have been seen.

4.9 Overdose
Overdosage can lead to neurological sequelae including encephalopathy, convulsions and coma. Serum levels of ceftazidime can be reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

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Pharmacotherapeutic group: Cephalosporins and related substances.

ATC code: J01DA11

Ceftazidime is a bactericidal cephalosporin antibiotic, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide
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Gram-negative: *pseudomonas aeruginosa*, *pseudomonas spp* (other), *klebsiella pneumoniae*, *klebsiella spp* (other), *proteus mirabilis*, *proteus vulgaris*, *morganella morganii* (formerly *proteus morganii*), *proteus rettgeri*, *providencia spp*, *escherichia coli*, *enterobacter spp*, *citrobacter spp*, *serratia spp*, *salmonella spp*, *shigella spp*, *yersinia enterocolitica*, *pasteurella multocida*, *acinetobacter spp*, *neisseria gonorrhoeae*, *neisseria meningitidis*, *haemophilus influenzae* (including ampicillin-resistant strains), *haemophilus parainfluenzae* (including ampicillin-resistant strains).


Anaerobic strains: *peptococcus spp*, *peptostreptococcus spp*, *streptococcus spp*, *propionibacterium spp*, *clostridium perfringens*, *fusobacterium spp*, *bacteroides spp* (many strains of *bact fragilis* are resistant).

Ceftazidime is not active *in vitro* against *methicillin*-resistant *staphylococci*, *enterococcus* (*streptococcus*) faecalis and many other *enterococci*, *listeria monocytogenes*, *campylobacter spp* or *clostridium difficile*.

*In vitro* the activities of ceftazidime and aminoglycoside antibiotics in combination have been shown to be at least additive; there is evidence of synergy in some strains tested. This property may be important in the treatment of febrile neutropenic patients.

### 5.2 Pharmacokinetic properties

Ceftazidime administered by the parenteral route reaches high and prolonged serum levels in man. After intramuscular administration of 500mg and 1g serum mean peak levels of 18 and 37mg/litre respectively are rapidly achieved. Five minutes after an intravenous bolus injection of 500mg, 1g or 2g, serum mean levels are respectively 46, 87 and 170mg/litre. Therapeutically effective concentrations are still found in the serum 8 to 12 hours after both intravenous and intramuscular administration. The serum half-life is about 1.8 hours in normal volunteers and about 2.2 hours in patients with apparently normal renal function. The serum protein binding of ceftazidime is low at about 10%.

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

Concentrations of ceftazidime in excess of the minimum inhibitory levels for common pathogens can be achieved in tissues such as bone, heart, bile,
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5.3 Preclinical safety data
No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium carbonate, anhydrous (E500)

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.

6.3 Shelf life
Vial before opening: Two years. After reconstitution: Chemical and physical stability has been demonstrated for 24 hours at 5°C and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no 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
Keep vials in the outer carton to protect from light. For storage of the reconstituted product, see section 6.3.

6.5 Nature and contents of container
Type III glass vial with a bromobutyl rubber stopper. Pack sizes of 1, 5, 10, 20, 50 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
This medicinal product is for single use only. Discard any unused contents. Reconstitute immediately before use. Instructions for constitution: See table for addition volumes and solution concentrations.

Preparation of solution:
Vialsizer | Amount of Diluent to be added (ml) | Approximate Concentration (mg/ml)
--- | --- | ---
2g | Intravenousbolus | 10.0 | 170
2g | IntravenousInfusion | 50.0* | 40‡

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

It is recommended that the following techniques of reconstitution are adopted.

For 2g i.v. bolus dose:
10. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. Remove the syringe needle.
11. Shake to dissolve: carbon dioxide is released and a clear solution will be obtained in about 1 to 2 minutes.
12. 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. 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.

For 2g i.v. infusion:
This vial may be constituted for short intravenous infusion (e.g. up to 30 minutes) as follows:
1. Insert the syringe needle through the vial closure and inject 10ml of 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. These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids. Ceftazidime is compatible with the most commonly used intravenous fluids.

In keeping with good pharmaceutical practice, it is preferable to use freshly constituted solutions. If this is not practicable, satisfactory potency is retained for 24 hours in the refrigerator (2 - 8°C) when diluted in any of the injections listed below.

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

7 MARKETING AUTHORISATION HOLDER
ACS Dobfar Generics SA
5, Rue Eugene Ruppert,
L-2453 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)
PL 18559/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/12/2007

10 DATE OF REVISION OF THE TEXT
06/12/2007
Read this entire leaflet carefully before you start taking this medicine.

- Keep the leaflet: you may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- The medicine has been prescribed for you personally and you should not pass it on to others.

3. HOW CEFTAZIDIME INJECTION IS GIVEN

Ceftazidime injection is given as an injection directly into a vein (intravenous, IV) or muscle (intramuscularly). Ceftazidime injection is only given by a healthcare professional.

5. ADULTS AND THE ELDERLY

The usual adult dose is 1 to 3 g every 6 to 8 hours. Doses up to 10 g every 6 to 8 hours may be given to some patients. Doses in excess of 10 g every 6 to 8 hours may be given to some patients.

6. How to Store Ceftazidime injection

Ceftazidime injection should not be used if it looks cloudy or contains particles. Before each use, check that the injection is clear and contains no particles. If in doubt, do not use it.

7. IF YOU ARE ALLERGIC TO CEFTAZIDIME

If you have ever had an allergic reaction to ceftazidime, you should not take this medicine unless your doctor tells you to do so.

UKPAR ACS Dobfar Generics SA, Ceftazidime Powder Solution for Injection

PL 18559/0029-32
Storage of Cefazoline Injection:

- Keep out of reach of children.
- Do not mix with other drugs.
- Discard if the solution is yellow or cloudy.

Injection should be prepared on the day it is needed.

In stored with other medications, it is preferable to use a single-use ampoule.

Handling: If refrigerated, it should be allowed to warm to room temperature before use.

Stabilization in solution and pH should not be affected by temperature.

Incompatibilities:

Catheterization and antifungal drugs should not be mixed in the same administration line.

Preparation of Cefazoline Injection:

Cefazoline is dissolved in sodium bicarbonate solution in an intravenous solution, but it is not recommended for use as a diluent.

Dispersion of cefazoline in solution should not exceed 1 hour, especially in patients who are postoperative.

Recommended maintenance doses of cefazoline are as follows:

- For adults: 125 mg/kg (10 mg/mL) in 100 mL of normal saline or 5% dextrose in water (D5W).
- For children: 125 mg/kg (10 mg/mL) in 100 mL of normal saline or 5% dextrose in water (D5W).
Each vial contains 500 mg Ceftazidime (as Ceftazidime pentahydrate).
Also contains sodium carbonate, anhydrous (E503) equivalent to 35 mg sodium.
For intravenous or intramuscular use, for single-use only. Do not administer immediately following vial opening. To be given as directed by your physician.
For full directions for use see enclosed leaflet. Once reconstituted, store at 2-8°C for up to 24 hours. If reconstitution occurs add an addition of water for injections. Keep out of the reach and sight of children. Keep vial in outer carton to protect from light.

MA Holder: ACS Dobfar Generics S.A.
6, Rue Eugene Rytaup L-2452 Luxembourg

Distributed by: B overturn Limited
Chertsham G450 1WW, UK

ABCGSM081

Batch: Exp:

FACES002
Ceftazidime 2g
Powder for injection or infusion

Each vial contains 2g Ceftazidime (as pentahydrate). Also contains sodium carbonate anhydrous.
For intravenous use.
For single use only.

To be given as directed by the physician. See package leaflet. Keep vial in outer carton to protect from light.
Keep out of the reach and sight of children. POM

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