Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion

(Ceftazidime pentahydrate)

PL 22805/0011-12

UKPAR

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Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion

PL 22805/0011-12

LAY SUMMARY

On 26th July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Orchid Europe Limited Marketing Authorisations (licences) for the medicinal products Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion (PL 22805/0011-12). These medicines are only available on prescription from the doctor.

Ceftazidime is an antibiotic used in adults and children (including newborn babies). It works by killing bacteria that cause infections. It belongs to a group of medicines called cephalosporins.

Ceftazidime is used to treat severe bacterial infections of:

- the lungs or chest
- the lungs and bronchi in patients suffering from cystic fibrosis
- the brain (meningitis)
- the ear
- the urinary tract
- the skin and soft tissues
- the abdomen and abdominal wall (peritonitis)
- the bones and joints

Ceftazidime can also be used:

- to prevent infections during prostate surgery in men
- to treat patients with low white blood cell counts (neutropenia) who have a fever due to a bacterial infection.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of treatment with Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion outweigh the risks. Hence, Marketing Authorisations have been granted.
Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion (PL 22805/0011-12) on 26th July 2013. These are prescription only medicines (POM) used in treatment of the following infections in adults and children including neonates (from birth).

- Nosocomial pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Bacterial meningitis
- Chronic suppurative otitis media
- Malignant otitis externa
- Complicated urinary tract infections
- Complicated skin and soft tissue infections
- Complicated intra-abdominal infections
- Bone and joint infections
- Peritonitis associated with dialysis in patients on CAPD.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftazidime may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Ceftazidime may be used in the peri-operative prophylaxis of urinary tract infections for patients undergoing trans-urethral resection of the prostate (TURP).

The selection of ceftazidime should take into account its antibacterial spectrum, which is mainly restricted to aerobic Gram negative bacteria.

Ceftazidime should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum of activity.

These are national abridged applications for Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion submitted under article 10(1) of Directive 2001/83/EC, as amended and cross-referring to Fortum 1 g and 2 g Powder for Solution for Injection (PL 00004/0293-94), authorised to Glaxo Operations, UK on 17th October 1983.

Ceftazidime is a third-generation cephalosporin antibacterial with enhanced activity against Pseudomonas aeruginosa. Ceftazidime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the
notification of any adverse reaction suspected of occurring either in the Community or in a third country. A satisfactory Risk Management Plan (RMP) has been provided.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature
rINN: Ceftazidime pentahydrate

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

Structure:

Molecular Formula: \(C_{22}H_{22}N_6O_7S_2\cdot 5H_2O\)

Molecular Weight: 637.65 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: The substance is slightly soluble in water and in methanol, practically insoluble in acetone and in alcohol. It dissolves in acid and alkali solutions.

Ceftazidime pentahydrate is the subject of a European Pharmacopoeia monograph.

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

DRUG PRODUCT

Other ingredients
The only excipient present in these drug products is sodium carbonate, anhydrous (sterile).

Sodium carbonate, anhydrous complies with the European Pharmacopoeia. Satisfactory Certificates of Analysis has been provided for this excipient.

The applicant has confirmed that the above excipient is not from animal or human origin.

Pharmaceutical development
Suitable pharmaceutical development data have been provided for these applications.
The qualitative and quantitative composition of Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion is identical to the reference products.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The product is supplied in clear type I glass vials sealed with grey bromobutyl rubber stopper and coloured flip-off seal with packs of 1 or 5 vials per carton.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

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

Based on the results, a shelf-life of 24 months for unopened vials with storage conditions “Store below 25°C” and “Store in the original package in order to protect from light” have been set. These are satisfactory.

After reconstitution: Reconstituted product has demonstrated chemical and physical stability for 24 hours when stored in a refrigerator at 2-8°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.
Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report/Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

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

The pharmacodynamic, pharmacokinetic and toxicological properties of ceftazidime pentahydrate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment. This is satisfactory.

There are no objections to the approval of these products from a non-clinical point of view.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), a bioequivalence study is not required if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with these applications and none is required.

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

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

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

Clinical safety
Ceftazidime pentahydrate has an acceptable adverse event profile. No new safety data were supplied or required for these generic applications. Ceftazidime pentahydrate has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPCs, PIL and labelling are medically satisfactory.

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

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

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

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
No new efficacy data were submitted and none are required for applications of this type. As the safety profile of Ceftazidime pentahydrate is well-known, no additional data were required. No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory.

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

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<td><strong>1</strong></td>
<td>The MHRA received the Marketing Authorisation applications on 9th October 2006</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 21st January 2007</td>
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<td><strong>4</strong></td>
<td>The applicant responded to MHRA’s requests providing further information to the quality dossier on 16th November 2009 and to the clinical dossier on 17th December 2007, 3rd January 2008, 1st May 2008, 18th June 2008, 15th September 2008 and 6th January 2009</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>The applications were determined on 26th July 2013.</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

1. NAME OF THE MEDICINAL PRODUCT

CeFTAZIDIME 1g Powder for Solution for Injection/Infusion
Ceftazidime

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains Ceftazidime 1g (as Ceftazidime pentahydrate).

3. LIST OF EXCIPIENTS

Also contains Sodium carbonate, anhydrous equivalent to 51mg (2.22 mmol) of Sodium

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Solution for Injection/Infusion

1 x 1g vial
5 x 1g vial

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Single use only.

For intravenous or intramuscular use.

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

This product must be reconstituted before use.

Effervescence occurs on addition of Water for Injections.
8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Unopened: Store below 25°C. Store in the original package in order to protect from light. Once reconstituted, store at 2-8°C for up to 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

--

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Orchid Europe Limited
Building 3, Chiswick Park
566 Chiswick High Road,
Chiswick, London,
W4 5YA, United Kingdom

12. MARKETING AUTHORIZATION NUMBER (S)

PL 22805/0011

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription (POM)

15. INSTRUCTIONS ON USE

--

16. INFORMATION IN BRAILLE

<None – product is not for self-administration>
UKPAR Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion  PL 22805/0011-12

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CeFTAZIDime 1g Powder for Solution for Injection/Infusion
Ceftazidime

For IM or IV. Use

2. METHOD OF ADMINISTRATION

Single use only.

Read the package leaflet before use

This product must be reconstituted before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains Ceftazidime 1g (as Ceftazidime pentahydrate).

Also contains Sodium carbonate, anhydrous equivalent to 51mg (2.22 mmol) of Sodium

6. OTHER

Medicinal product subject to medical prescription (POM)

Special warnings:
Keep out of the sight and reach of children.

Storage conditions:
Unopened: Store below 25°C. Store in the original package in order to protect from light.
Once reconstituted, store at 2-8°C for up to 24 hours.

MA Number: PL 22805/0011

MA Holder:
Orchid Europe Limited
London, United Kingdom
Labelling for Ceftazidime 2g Powder for Solution for Injection/Infusion:

1. NAME OF THE MEDICINAL PRODUCT

CeftAZIDime 2g Powder for Solution for Injection/Infusion
Ceftazidime

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each vial contains Ceftazidime 2g (as Ceftazidime penta hydrate).

3. LIST OF EXCIPIENTS

Also contains Sodium carbonate, anhydrous equivalent to 101mg (4.39 mmol) of Sodium

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Solution for Injection/Infusion

1 x 2g vial
5 x 2g vial

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Single use only.
For intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

This product must be reconstituted before use.

Effervescence occurs on addition of Water for Injections
3. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Unopened: Store below 25°C. Store in the original package in order to protect from light. Once reconstituted, store at 2-8°C for up to 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Orchid Europe Limited
Building 3, Chiswick Park
566 Chiswick High Road,
Chiswick, London,
W4 5YA, United Kingdom

12. MARKETING AUTHORISATION NUMBER (S)

PL 22805/0012

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription (POM)

15. INSTRUCTIONS ON USE

--

16. INFORMATION IN BRAILLE

<None – product is not for self-administration>
UKPAR Ceftazidime 1 g and 2 g Powder for solution for Injection/Infusion

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CeftAZIDime 2g Powder for Solution for Injection/Infusion
Ceftazidime

For I.V. Use

2. METHOD OF ADMINISTRATION

Single use only.
Read the package leaflet before use
This product must be reconstituted before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains Ceftazidime 2g (as Ceftazidime pentahydrate).
Also contains Sodium carbonate, anhydrous equivalent to 101mg (4.39 mmol) of Sodium

6. OTHER

Medicinal product subject to medical prescription (POM)

Special warnings:
Keep out of the sight and reach of children.

Storage conditions:
Unopened: Store below 25°C. Store in the original package in order to protect from light.
Once reconstituted, store at 2-8°C for up to 24 hours.

MA Number: PL 22805/0012

MA Holder:
Orchid Europe Limited
London, United Kingdom