Public Assessment Report

Decentralised Procedure

Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion

(Imipenem monohydrate and cilastatin sodium)

UK/H/5423/001/DC

UK licence no: PL 41697/0003

ACIC Europe Limited
LAY SUMMARY
Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion
(Imipenem monohydrate and cilastatin sodium)

This is a summary of the public assessment report (PAR) for Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion (PL 41697/0003: UK/H/5423/001/DC). It explains how Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion.

For ease of reading this product will be referred to as Imipenem/Cilastatin infusion in this Lay Summary.

For practical information about using Imipenem/Cilastatin infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Imipenem/Cilastatin infusion and what is it used for?
Imipenem/Cilastatin infusion is a ‘generic medicine’. This means that Imipenem/Cilastatin infusion is similar to a ‘reference medicine’ already authorised in the UK called Primaxin IV 500 mg powder for solution for infusion (Merck Sharp & Dohme Ltd; PL 00025/0229).

Imipenem/Cilastatin infusion is used to treat the following infections:

• Complicated infections in the abdomen
• Infection affecting the lungs (pneumonia)
• Infections that you can catch during or after delivering a baby
• Complicated urinary tract infections
• Complicated skin and soft tissue infections

Imipenem/Cilastatin may be used in the management of patients with low white blood cell counts, who have fever that is suspected to be due to a bacterial infection.

Imipenem/Cilastatin may be used to treat bacterial infection of the blood which might be associated with a type of infection mentioned above.

How is Imipenem/Cilastatin infusion used?
Imipenem/Cilastatin infusion is given intravenously (into a vein) over 20-30 minutes for a dose of ≤500 mg/500 mg or 40-60 minutes for a dose of >500 mg/500 mg. This medicine is prepared and given by a doctor or a health care professional.

The usual dose for:
Adults and adolescents:
500 mg/500 mg every 6 hours or 1,000 mg/1,000 mg every 6 or 8 hours

Children
One year of age or older is 15/15 or 25/25 mg/kg of weight every 6 hours.

Imipenem/Cilastatin is not recommended in children under one year of age and children with kidney problems.

This medicine can only be obtained on prescription from a doctor.
For further information on how Imipenem/Cilastatin infusion is used, please see the Summary of Product Characteristics available on the MHRA website.

**How does Imipenem/Cilastatin infusion work?**
Imipenem/Cilastatin belongs to a group of medicines called carbapenem antibiotics. It kills a wide range of bacteria (germs) that cause infections in various parts of the body in adults and children one year of age and above.

**How has Imipenem/Cilastatin infusion been studied?**
As this product is a powder for solution for infusion; the applicant has not performed any clinical trials. No additional studies were needed as Imipenem/Cilastatin infusion is a generic medicine that is given intravenously and contains the same active substance and content as the reference medicine, Primaxin IV 500 mg powder for solution for infusion (Merck Sharp & Dohme Ltd; PL 00025/0229).

**What are the benefits and risks of Imipenem/Cilastatin infusion?**
As Imipenem/Cilastatin infusion is a generic medicine and is comparable to the reference medicine, its benefits and risks are taken as being the same as those for Primaxin IV 500 mg powder for solution for infusion (Merck Sharp & Dohme Ltd; PL 00025/0229).

**Why is Imipenem/Cilastatin infusion approved?**
It was concluded that, in accordance with EU requirements, Imipenem/Cilastatin infusion has been shown to have comparable quality and to be comparable to Primaxin IV 500 mg powder for solution for infusion. Therefore, the view was that, as for Primaxin IV 500 mg powder for solution for infusion, the benefit outweighs the identified risks.

**What measures are being taken to ensure the safe and effective use of Imipenem/Cilastatin infusion?**
A risk management plan has been developed to ensure that Imipenem/Cilastatin infusion is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Imipenem/Cilastatin infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Imipenem/Cilastatin infusion**
Poland and the UK agreed to grant a Marketing Authorisation for Imipenem/Cilastatin infusion on 10 April 2014. A Marketing Authorisation was granted in the UK on 13 May 2014.

The full PAR for Imipenem/Cilastatin infusion follows this summary.

This summary was last updated in January 2018.
SCIENTIFIC DISCUSSION

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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) considered that the application for Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion (PL 41697/0003; UK/H/5423/001/DC), is approvable.

Imipenem/Cilastatin is indicated for the treatment of the following infections in adults and children 1 year of age and above.

- complicated intra-abdominal infections
- severe pneumonia including hospital and ventilator-associated pneumonia
- intra- and post-partum infections
- complicated urinary tract infections
- complicated skin and soft-tissue infections

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

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

This application was submitted according to Article 10(1) of 2001/83/EC, as amended, as a generic application. The applicant has cross-referred to Primaxin IV 500 mg powder for solution for infusion (PL 00025/0229), originally authorised to Merck Sharp & Dohme Ltd, on 30 June 1988.

With UK as the RMS in this Decentralised Procedure (UK/H/5423/001/DC), ACIC Europe Limited applied for the Marketing Authorisation for Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion in Poland.

Imipenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs). Cilastatin is a competitive, reversible and specific inhibitor of dehydropeptidase-I, the renal enzyme which metabolizes and inactivates imipenem. It is devoid of intrinsic antibacterial activity and does not affect the antibacterial activity of imipenem.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application, of an originator product that has been in clinical use for over 10 years.

A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substances as the reference product.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All member states agreed to grant a licence for the above product at the end of the procedure on 10 April 2014. After a subsequent national phase, a licence was granted in the UK on 13 May 2014.
II QUALITY ASPECTS

II.1 Introduction
This product is a powder for solution for infusion. Each vial contains imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin and 32.15 mg (1.40 mmol) sodium as active ingredients.

The only ingredient consists of the pharmaceutical excipient sodium bicarbonate. A rationale for the inclusion of this excipient is provided.

The excipient sodium bicarbonate complies with the relevant European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided for this excipient.

The above excipients do not contain materials of animal or human origin. This product does not contain or consist of genetically modified organisms (GMO).'

The finished product is supplied in a clear type I borosilicate glass vial, closed with a chlorobutyl rubber stopper and a tamper-evident aluminium flip-off seal (aluminium cap and polypropylene button). The pack sizes are 1, 10 and 25 vials.

Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

II.2 Drug substance
INN: Imipenem
Chemical Names: [5R-[5α, 6α (R*)]]-6-(1-hydroxyethyl) -3-[[2-[(iminomethyl) amino] ethyl]thio]-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid monohydrate
Structure:

![Structure](image)

Molecular formula: C_{12}H_{17}N_{3}O_{4}S.H_{2}O
Molecular weight: 317.36g/mol
Physical form: white to almost white or pale yellow powder.
Solubility: sparingly soluble in water and slightly soluble in methanol.

The drug substance is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.
Satisfactory Certificates of Analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer.

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

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

INN: Cilastatin sodium
Chemical Names: [R-[R*, S*-(Z)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[2,2 dimethylcyclopropyl]carbonyl]amino]-2-heptenoic acid, monosodium salt
Structure:

Molecular formula: C_{16}H_{25}N_{2}NaO_{5}S
Molecular weight: 380.44 g/mol
Physical form: white or light yellow powder.
Solubility: very soluble in water and methanol, practically insoluble in acetone and methylene chloride.

The drug substance is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer.

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

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain a stable powder for solution for infusion containing imipenem monohydrate and cilastatin sodium that could be considered as a
generic medicinal product of Primaxin IV 500 mg powder for solution for infusion (Merck, Sharpe and Dohme Ltd).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, 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 specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability of the product**
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 2 years for unopened vial with no special storage conditions has been set.

**After reconstitution:**
Diluted solutions should be used immediately. If the diluted solution is not used immediately, the storage times and conditions are the responsibility of the user. Do not freeze the reconstituted solution.

The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two hours.

The shelf-life and the storage conditions are satisfactory.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of this product from a pharmaceutical point of view.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
The pharmacodynamic, pharmacokinetic and toxicological properties of imipenem monohydrate and cilastatin sodium are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

**III.2 Pharmacology**
No new pharmacology data are required for these applications and none have been submitted.

**III.3 Pharmacokinetics**
No new pharmacokinetic data are required for these applications and none have been submitted.
III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to tadalafil is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Clinical Pharmacology
In accordance with the 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 a solution containing the same active substance as the reference product. As this product is a solution at the time of administration, no bioequivalence studies have been submitted and none are required.

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

IV.2 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
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.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion.

A satisfactory Risk Management Plan (RMP) has been submitted for this product.

IV.7 Discussion of the clinical aspects
There are no objections to the approval of this product from a clinical point of view.
V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. 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 patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with imipenem monohydrate and cilastatin sodium is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text. No label mock-ups have been provided for this product. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING |
| OUTER CARTON |

1. **NAME OF THE MEDICINAL PRODUCT**

Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion

Imipenem/Cilastatin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains: imipenem monohydrate equivalent to 500 mg imipenem anhydrate and cilastatin sodium equivalent to 500 mg cilastatin

3. **LIST OF EXCIPIENTS**

Sodium bicarbonate (E500)

4. **PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion

1 vial of 20 ml
10 vials of 20 ml
25 vials of 20 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Intravenous use after reconstitution.
For single use only.

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**

8. **EXPIRY DATE**

EXP
9. SPECIAL STORAGE CONDITIONS

After reconstitution: Diluted solutions should be used immediately. If the diluted solution is not used immediately storage times and conditions are the responsibility of the user. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two 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

ACIC Europe Limited
Leonion, 163
CLERIMOS BUILDING, 2nd floor
3022 Limassol
Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 41697/0003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING VIAL

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

   Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion
   Imipenem/Cilastatin
   Intravenous use

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each vial contains: imipenem 500 mg and cilastatin 500 mg.

3. **LIST OF EXCIPIENTS**

   Sodium bicarbonate (E500)

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Powder for solution for infusion
   20 ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Read the package leaflet before use.
   IV. Single 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**

8. **EXPIRY DATE**

   EXP
9. SPECIAL STORAGE CONDITIONS

After reconstitution: Use within 2 hours. Do not freeze.

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

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Leontiou, 163
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Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that has been made to this Marketing Authorisation.

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<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<td>25/10/2017</td>
<td>14/12/2017</td>
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Annex 1

Reference: PL 41697/0003 - 0005

Product: Imipenem/Cilastatin 500 mg/500 mg powder for solution for infusion

Marketing Authorisation Holder: ACIC Europe Limited

Active Ingredient: imipenem monohydrate and cilastatin sodium

Reason:
To update Section 4.2 of the SmPC, in order to harmonize the product information with updates made to the reference product information 'Primaxin'.

Supporting evidence
The applicant has submitted an updated section of the SmPC.

Evaluation
The amended Section 4.2 of the SmPC is satisfactory.

Conclusion
The updated SmPC fragment has been incorporated into this Marketing Authorisation. The proposed change is acceptable.

Decision: Grant
Date: 14 December 2017