Public Assessment Report

Decentralised Procedure

Meropenem 500 mg and 1 g powder for solution for injection or infusion

UK/H/5288/001-02/DC

PL 41697/0001-02

Applicant: ACIC Europe Limited

Meropenem 500 mg and 1 g powder for solution for injection or infusion

PL 41697/0001-02

LAY SUMMARY

On 11th November 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to ACIC Europe Limited for the medicinal products Meropenem 500 mg and 1 g powder for solution for injection or infusion (PL 41697/0001-02; UK/H/5288/001-02/DC). These medicines are only available on prescription from the doctor.

Meropenem belongs to a group of medicines called carbapenem antibiotics. It works by killing bacteria, which can cause serious infections, including:

- Infection affecting the lungs (pneumonia)
- Lung and bronchial infections in patients suffering from cystic fibrosis
- Complicated urinary tract infections
- Complicated infections in the abdomen
- Infections that you can catch during or after the delivery
- Complicated skin and soft tissue infections
- Acute bacterial infection of the brain (meningitis)

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of treatment with Meropenem 500 mg and 1 g powder for solution for injection or infusion outweigh the risks, and Marketing Authorisations were granted.

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Module 1

Information about initial procedure

Product Name	Meropenem 500 mg and 1 g powder for solution for injection or infusion
Type of Application	Article 10.1
Active Substance	Meropenem trihydrate
Form	Powder for solution for injection or infusion
Strength	500 mg and 1 g
MA Holder	ACIC Europe Limited Leontiou, 163, CLERIMOS BUILIDING, 2nd floor 3022 Limassol Cyprus
RMS	UK
CMSs	Germany, Poland, Italy and Spain
Procedure Number	UK/H/5288/001-02/DC
Timetable	Day 210: 6th October 2013

Module 2
Summary of Product Characteristics

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

Module 3
Patient Information Leaflet

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

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Meropenem 500 mg powder for solution for injection or infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

3. LIST OF EXCIPIENTS

Anhydrous sodium carbonate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.
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:

The reconstituted solutions for intravenous injection or infusion should be used immediately.
The time interval between the beginning of reconstitution and the end of intravenous injection or infusion should not exceed 1 hour.
Do not freeze the reconstituted solution.

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
Leontiou, 163, CLERIMOS BUILIDING, 2nd floor
3022 Limassol
Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 41697/0001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MEROPENEM 500 MG

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Meropenem 1 g powder for solution for injection or infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

3. LIST OF EXCIPIENTS

Anhydrous sodium carbonate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion

1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.
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

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After reconstitution:
The reconstituted solutions for intravenous injection or infusion should be used immediately.
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ACIC Europe Limited
Leontiou, 163, CLERIMOS BUILIDING, 2nd floor
3022 Limassol
Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 41697/0002

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MEROPENEM 1 G

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for Meropenem 500 mg and 1 g powder for solution for injection or infusion for the following indications could be approved.

- Pneumonia, including community acquired pneumonia and nosocomial pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

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

These decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, for Meropenem 500 mg and 1 mg powder for solution for injection or infusion. The applicants cross refer to Meronem 500 mg and 1 g powder for solution for injection or infusion, originally granted to Zeneca Limited (PL 12619/0098-99) on 19th January 1995. The reference licences then under went Change of Ownership (CoA) procedures to the current Marketing Authorisation holder, AstraZeneca UK Limited (PL 17901/0029-30) on 11th May 2001.

With UK as the RMS in these Decentralised Procedures (UK/H/5288/001-02/DC), ACIC Europe Limited applied for Marketing Authorisations for Meropenem 500 mg and 1 g powder for solution for injection or infusion in Germany, Poland, Italy and Spain.

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. 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.

The RMS considers that 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 with these applications.

All member states agreed to grant a licence for each of the above products at the end of the procedure (Day 210 – 6th October 2013). After a subsequent national phase, the UK granted

licences for these products on 1st November 2013 (PL 41697/0001-02).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Meropenem 500 mg and 1 g powder for solution for injection or infusion
Name(s) of the active substance(s) (USAN)	Meropenem trihydrate
Pharmacotherapeutic classification (ATC code)	ATC code: J01DH02 antibacterials for systemic use, carbapenems
Pharmaceutical form and strength(s)	powder for solution for injection or infusion, 500 mg and 1 g
Reference numbers for the Decentralised Procedure	UK/H/5288/001-02/DC
Reference Member State	United Kingdom
Concerned Member States	Germany, Poland, Italy and Spain
Marketing Authorisation Number(s)	PL 41697/0001-2
Name and address of the authorisation holder	ACIC Europe Limited Leontiou, 163, CLERIMOS BUILIDING, 2nd floor 3022 Limassol Cyprus

III SCIENTIFIC OVERVIEW AND DISCUSSION

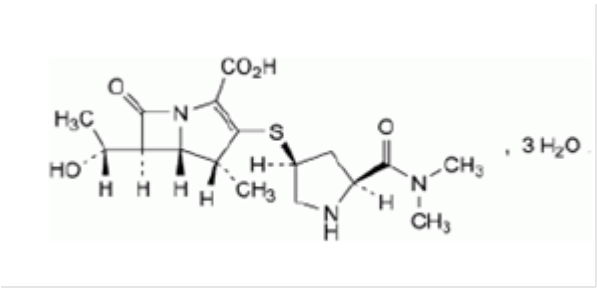
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Meropenem trihydrate

Chemical Names: (4R,5S,6S)-3 [[(3S,5S)-5-(Dimethylcarbamoyl) -3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxethyl]-4 methyl-7-oxo-1- azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid trihydrate, 1-Azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino) carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, and [4R-[3(3S*,5S*), 4α,5β,6β(R*)]]- (4R,5S,6S)-3- [[(3S,5S)-5- (Dimethyl carbamoyl) -3-pyrrolidinylthio]-6-[(1R)-1-hydroxyethyl]-4 methyl-7-oxo-1- azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Structure:



Molecular formula: $C_{17}H_{25}N_3O_5S$.$3H_2O$

Molecular weight: 437.5 g/mol

Physical form: white or light yellow crystalline powder.

Solubility: sparingly soluble in water, practically insoluble in ethanol (96%) and methylene chloride.

The drug substance is the subject of active substance master file (ASMF). A letter of access has been provided by the drug substance manufacturer.

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

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

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

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

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

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipient anhydrous sodium carbonate.

The excipient used complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for this excipient.

The above excipient does not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to develop a sterile solution for injection or infusion comparable in performance to the reference products, Meronem 500 mg and 1 g powder for solution for injection or infusion (AstraZeneca, Limited UK).

Suitable pharmaceutical development data have been provided for these applications.

Manufacture

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

Finished Product Specifications

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

Container Closure System

The finished product is supplied in Type I borosilicate glass vial with a grey halobutyl rubber stopper and sealed with an aluminium cap in a cardboard carton. The pack sizes are 1 vial or 10 vials.

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.

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 18 months for unopened vials with no special storage conditions is set.

After reconstitution: The reconstituted solutions for intravenous injection or infusion should be used immediately. The time interval between the beginning of reconstituition and the end of intravenous injection of infusion should not exceed one hour. Do not freeze the reconstituted solution.

The shelf-life and storage conditions are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PILs 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.

The Marketing Authorisation holder has stated that not all pack sizes may be marketed. They have committed to obtain approval of the mock-ups for unmarketed pack sizes before those packs are commercially marketed.

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

Expert Report
A pharmaceutical expert report has been 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.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of meropenem trihydrate 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 environmental risk assessment.

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

III.3 CLINICAL ASPECTS

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

Summary of Product Characteristics (SmPC)
The approved SmPCs are satisfactory for these products.

Patient Information Leaflet (PIL)
The final PILs are in line with approved SmPCs and are satisfactory.

Labelling
The labelling is 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 satisfactory from a clinical perspective.

CONCLUSION
There are no objections to the approval of these products from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Meropenem 500 mg and 1 g powder for solution for injection or infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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 meropenem trihydrate is well-known, no additional data were required. No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE

The SmPCs, PILs and labelling are satisfactory.

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 meropenem trihydrate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome