IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Meropenem 500 mg powder for solution for injection or infusion
Meropenem trihydrate
PA2168/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4034/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 31/10/2019] under procedure number IE/H/1091/001-002/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2168/002/001-002
Marketing Authorisation Holder: Acino AG

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

II. QUALITY ASPECTS

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

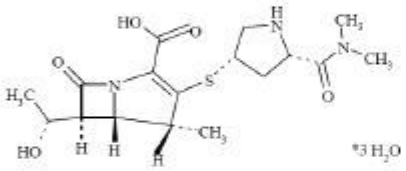
ACTIVE SUBSTANCES

Meropenem trihydrate

Nomenclature:

INN:	Meropenem trihydrate
Chemical names:	i) 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, [4*R*-[3(3*S**,5*S**),4α,5β,6β(*R**)]]
	ii) (4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylic acid, trihydrate
	iii) (1*R*,5*S*,6*S*)-2-[[(3*S*,5*S*)-5-(dimethylaminocarbonyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-carboxylic acid

Structure:



Molecular formula:	$C_{17}H_{25}N_3O_5S \cdot 3H_2O$ (trihydrate)
	$C_{17}H_{25}N_3O_5S$ (anhydrous)
Molecular weight:	437.52 g/mol (trihydrate)
	383.47 (anhydrous)
CAS No:	119478-56-7 (trihydrate)
	96036-03-2 (anhydrous)
Physical form:	A white to light yellow crystalline powder
Solubility:	Sparingly soluble in water, very slightly soluble in alcohol, practically insoluble in ethanol and ether

The active substance, meropenem trihydrate, is not the subject of a European Pharmacopeia (Ph. Eur) monograph.

Synthesis of the active substance from the designated starting materials 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. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been 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 specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturers during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been applied.

MEDICINAL PRODUCT

Description and Composition

Meropenem 500mg and 1g powder for solution for injection or infusion are presented as a sterile, white to light-yellow powder. The medicinal products are supplied in glass vials containing 500 mg or 1 g meropenem (as meropenem trihydrate). The infusion is prepared by dissolving the powder in an appropriate infusion solution, as detailed in Section 6.6 of the SmPC.

Other ingredients consist of a single pharmaceutical excipient, namely anhydrous sodium carbonate. Appropriate justification for the inclusion of this excipient has been provided, which complies with its European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to obtain stable, sterile, generic medicinal products, pharmaceutically equivalent to the reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

Comparative impurity profiles were provided for batches of the test and appropriate reference products.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished product specification

Finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. 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. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Meropenem 500mg powder for solution for injection or infusion is supplied in packs of 1 or 10 x 20 ml, type I glass vials complete with rubber stoppers and aluminium seals. Meropenem 1g powder for solution for injection or infusion is supplied in packs of 1 or 10 x 30 ml, type I glass vials complete with rubber stoppers and aluminium seals. The vials are packaged, with the product information leaflet, into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 3 years for the unopened vials. 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 one hour. The reconstituted solution must not be frozen. For full details and instructions for reconstitution, dilution and infusion, refer to section 6.6 of the SmPC.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

The quality grounds for these applications are considered adequate. There are no objections to the approval of Meropenem 500mg and 1g powder for solution for injection or infusion from a pharmaceutical point of view.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of meropenem, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

There are no objections to approval of Meropenem 500mg and 1g powder for solution for injection or infusion from a non-clinical point of view.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

INDICATIONS

Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age (see SmPC sections 4.4 and 5.1):

- 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. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The indications are consistent with those of the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of meropenem is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of meropenem is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

Clinical efficacy

No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview. The efficacy of meropenem is well-established from its extensive use in clinical practice.

Meropenem 500mg and 1g powder for solution for injection or infusion are to be administered as an aqueous intravenous solution and contain the same active substance, in the same concentrations, as the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited). Thus, in accordance with the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.

Clinical safety

No new safety data have been submitted and none are required for these types of application. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of meropenem is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

An article 30 referral for Meronem produced harmonised product information texts.

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the UK reference product and are acceptable.

Product Information Leaflet (PIL)

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Meropenem 500mg and 1g 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 data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview.

The applicant's Meropenem 500mg and 1g powder for solution for injection or infusion have been demonstrated to be generic versions of the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those for the UK reference products and are satisfactory.

The final PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Meropenem 500mg and 1g powder for solution for injection or infusion and the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited), are interchangeable. Extensive clinical experience with meropenem is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

VI. REVISION DATE

28/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/4034/001-002/DC to IE/H/1091/001-002/DC			