IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Meropenem 500mg Powder for Solution for Injection or Infusion
Meropenem
PA1122/015/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4931/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20th March 2019 under procedure number IE/H/0707/001-002/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/015/001-002
Marketing Authorisation Holder: Noridem Enterprises Ltd

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.

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Meropenem 500mg and 1g Powder for Solution for Injection or Infusion (PL 24598/0039-40; UK/H/4931/001-2/DC) could be approved. The products are prescription-only medicines (POM) for use in adults and children over 3 months of age for the treatment of:
• 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 500mg and 1g Powder for Solution for Injection or Infusion may also be used in the management of neutropenic patients with fever that is suspected to be due to bacteria infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Germany, Greece, Spain, Ireland and Poland as Concerned Member States (CMS). The applications were submitted under Article 10(1) of Directive 2001183/EC, as amended, claiming to be generic medicinal products of Meronem IV 500mg and 1g powder for solution for injection or infusion (AstraZeneca UK Limited, UK) which were first authorised in the UK on 19 Januruy 1995.

The active ingredient, meropenem trihydrate, belongs to a group of medicines called carbapenem antibiotics. Meropenem trihydrate exerts its bactericidal action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products.

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

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

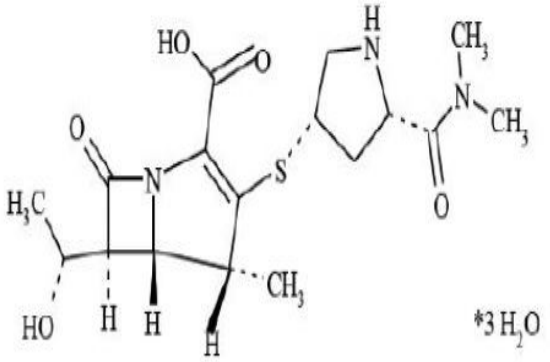
The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 15 June 2012. After a subsequent national phase, licences were granted in the UK on 23 July 2012.

Names of the products in the Reference Member State	UK/H/49311001/DC: Meropenem 500mg Powder for Solution for Injection or Infusion UK/H/49311002/DC: Meropenem lg Powder for Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Meropenem trihydrate
Pharmacotherapeutic classification (ATC code)	Antibacterials for systemic use, carbapenems, (ATC code: J01DH02)
Pharmaceutical form and strength(s)	Powder for solution for injection or infusion 500mg and 1g
Reference numbers for the Decentralised Procedure	UK/H/4931/001-2/DC
Reference Member State (RMS)	United Kingdom
Concerned Member States (CMS)	Austria, Germany, Greece, Spain, Ireland and Poland
Marketing Authorisation Number(s)	PL 24598/0039-40
Name and address of the authorisation holder	Noridem Enterprises Ltd Evagorou & Makaliou, Mitsi Building 3, Office ll5, 1065 Nicosia, Cyprus

II. QUALITY ASPECTS

ACTIVE SUBSTANCE

INN:	Meropenem trihydrate
Chemical name:	(4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-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; [4R- [3(3S*,5S*), 4α,5β,6β(R*)]]- (4R,5S,6S)-3- [[(3S,5S)-5- (Dimethyl carbamoyl) -3-pyrrolidinylthio]-6-[(1R)-1-hydroxyethyl]-4methyl-7-oxo-1- azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid trihydrate.
Structure:	



Molecular formula:	$C_{17}H_{25}N_3O_5S \cdot 3H_2O$ (trihydrate)
Molecular Mass:	437.52 (trihydrate)
Appearance:	A white to light yellow crystalline powder.
Solubility	Sparingly soluble in water, practically insoluble in ethanol and ether.

Meropenem trihydrate is the subject of a European Pharmacopoeia 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 specification tests 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 all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

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

MEDICINAL PRODUCT
Other Ingredient

Anhydrous sodium carbonate is the only pharmaceutical excipient. Appropriate justification for the inclusion of this excipient has been provided.

Anhydrous sodium carbonate complies with its European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided, showing compliance with the proposed specification.

Anhydrous sodium carbonate does not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this excipient.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered as generic medicinal products of the UK reference products Meronem IV 500mg and 1g powder for solution for injection or infusion (AstraZeneca UK Limited, UK).
Suitable pharmaceutical development data have been provided for these applications. Comparable impurity profiles have been provided for these products and the UK reference products Meronem IV 500mg and 1g powder for solution for injection or infusion (AstraZeneca UK Litnited, UK).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial-scale batches and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished products are supplied in 20ml (500 mg strength) and 30 ml (1 g strength) Type III glass vials with butyl rubber (Type I) stoppers and flip-off aluminium caps.

The products are available in pack sizes of 1 and 10 vials. Not all pack sizes may be marketed

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been proposed with no special storage instructions for the product when stored in the vial.

For the reconstituted solution, it is stated that this should be used immediately. Furthermore, it is stated that the time interval between the start of the reconstitution and the end of the intravenous injection or infusion should not exceed one hour. The reconstituted solution should not be refrigerated or frozen.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support these applications for parenteral products.

Summaries of Product Characteristics (SmPCs), Product Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council 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 the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are satisfactory from a pharmaceutical perspective.

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

Conclusion
The grant of Marketing Authorisations is recommended.

III. NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of meropenem trihydrate are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the pharmacology and toxicology of meropenem trihydrate.

Suitable justification has been provided for non-submission of an environmental risk assessment. As the applications are for generic versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.

IV. CLINICAL ASPECTS

Clinical Pharmacololgy
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications for parenteral products. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 (NfG on the Investigation of Bioavailability and Bioequivalence).

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

Safety
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications. Meropenem trihydrate as an active ingredient has a well-established and an acceptable level of safety in the proposed indications.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are clinically acceptable. The SmPCs are consistent with those for the innovator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossiers.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a risk management plan for these products.

Conclusion

The grant of Marketing Authorisations is recommended.

V. OVERALL CONCLUSIONS

QUALITY

The important quality characteristics of Meropenem 500mg and 1g Powder for Solution for Injection or Infusion (PL 24598/0039-40; UK/H/4931/001-2/DC) 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.

EFFICACY

No new clinical data were submitted for these applications. No bioequivalence studies were submitted or required for these applications.

SAFETY

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with meropenem trihydrate is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.

VI. REVISION DATE

June 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/4931/001-002/DC to IE/H/0707/001-002/DC	N/A	N/A	N/A	Approved 20/03/2019