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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Meropenem 500 mg and 1 g,

Powder for Solution for Injection or Infusion

(Meropenem Trihydrate)

IE/H/203-204/1-2/DC

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

This is a decentralised procedure (according to Article 28(3) of Directive 2001/83/EC) with Ireland as reference member state.

II QUALITY ASPECTS

II.1 Introduction

This applications for Meropenem 500 mg and 1 g Powder for Solution for Injection or Infusion are submitted via decentralised procedure under Article 10(1) of Directive 2001/83 (as amended) claiming essential similarity with the reference product Meronem 500 mg and 1g powder for solution for injection or infusion which has been registered in EEA by AstraZeneca A/S . Ireland is the Reference Member State (RMS).

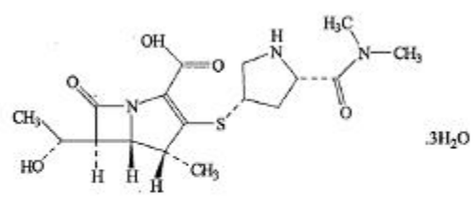
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The drug substance, meropenem, is well established active substance. It is not yet described in the European Pharmacopoeia (Ph.Eur.). Meropenem is the subject of a monograph in the USP. The Active Substance Master File (ASMF) procedure is followed for the drug substance. It is present in the drug product as meropenem trihydrate.

INN:	Meropenem
Chemical names:	(4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1 hydroxyethyl]-4-methyl-7-oxo-1-azabicylo[3.2.0]-hept-2-ene-carboxylic acid, trihydrate 1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[(3S,5S)-5-[(dimethylamino)-carbonyl]-3-pyrrolidinyl]thio]-6-[(1R)-hydroxyethyl]-4-methyl-7-oxo-, trihydrate,[4R,5S,6S)

Molecular Structure



Molecular Formula:	$C_{17}H_{25}N_3O_7S \cdot 3H_2O$
Relative Molecular Mass:	437.52 g/mol

Synthesis of the drug substance has been satisfactorily described and appropriate in-process controls and intermediate specifications are applied. The process used to sterilise meropenem is well described, controlled and validated.

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 for the active pharmaceutical ingredient.

The active substance specification is considered adequate to control the quality and meets the current requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

The container is suitable and provides adequate protection to the active substance.

Based on the stability data presented an appropriate re-test period has been set.

II.3 Medicinal Product

II.3.1 Composition

Meropenem 500 mg and 1 g Powder for Solution for Injection or Infusion is white to pale yellow crystalline powder in clear glass vial sealed with grey rubber stoppers and flip off seal (polypropylene button fitted on aluminium seal).. 500mg/vial filled in 30 ml and 1g/vial filled in 40 ml tubular clear glass type1 vials. The only excipient is sodium carbonate, anhydrous.

Prior to administration, the vial contents are dissolved in sterile water for injections. For infusion, this solution may be diluted further with appropriate infusion solutions only as specified in section 6.6 of the SmPC.

II.3.2 Pharmaceutical Development

The aim was to develop a stable, robust, generic injectable dosage form of Meropenem 500mg and 1g Powder for Solution for Injection or Infusion, which is pharmaceutically equivalent to the reference product Meronem IV/ Merrem IV of M/s Astra Zeneca Inc; marketed in various EU countries.

The pharmaceutical development is adequately described in accordance with the relevant European guidelines. Compatibility between the active substance and the excipient sodium carbonate is demonstrated. The packaging materials have shown to be suitable by acceptable stability studies.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). Manufacture is two step involving preparation of the sterile active substance and sodium carbonate blend and filling of sterile powder into the market containers. Batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process is considered adequately validated.

II.3.4 Control of Excipients

The excipient sodium carbonate anhydrous is a well known pharmaceutical excipient and it complies with its Ph. Eur. monograph and with additional requirements to monitor the quality of this excipient. None of the raw materials used in the manufacturing process of sodium carbonate, anhydrous (sterile) are of animal origin. Sodium carbonate anhydrous (sterile) is manufactured by aseptic filtration. Satisfactory description of the process is provided, together with the flow diagram.

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form and they are and in line with ICH Q6A and Ph Eur requirements for parenteral preparations.
Limits in the specification have been adequately justified and are considered appropriate for adequate quality control of the product. Satisfactory description and validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is packaged in Type 1 clear glass vial with a 20mm grey bromobutyl rubber plug and flip off seals (polypropylene button fitted on an aluminium seal) in a cardboard carton. The 500mg/vial is filled in 30 ml and 1g/vial is filled in 40 ml tubular clear glass type1 vials.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. Compliance statement is provided by supplier of the vials and rubber plugs (Ph Eur, USP). The rubber plugs comply with the extraction characteristics of Ph Eur General Chapters 3.2.9 and <381> USP. The packaging materials are widely used components in packaging of injectable dosage forms. The suitability of packaging materials has further been demonstrated by the absence of any interaction between the product and pack during stability testing. The packaging materials are therefore considered as suitable for Meropenem Powder for solution for injection or infusion.

II.3.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product as packaged for sale (unopened) for 2 years. The product as package for sale is to be stored below 25°C and it should not be frozen. 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 should not be frozen.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III NON-CLINICAL ASPECTS

Meropenem is a widely clinically used, well known active substance. No further non-clinical studies were submitted or deemed to be required. The company provided a comprehensive non-clinical bibliographic overview and an expert provided a sufficient detailed review of all relevant non-clinical data. There were considered to be no non-clinical concerns.

IV CLINICAL ASPECTS

IV.1 Introduction

The applicant has not conducted any clinical studies with meropenem and all the relevant clinical information provided is literature based.

IV.2 Pharmacokinetics

The applicant provided an appropriate review of the known pharmacokinetics of meropenem.

IV.3 Pharmacodynamics

The applicant provided an appropriate review of the known pharmacodynamics of meropenem.

IV.4 Clinical efficacy

The applicant has provided a review of the literature on efficacy.

IV.5 Clinical safety

The applicant has provided a review of the literature on safety.

IV.6 Discussion on the clinical aspects

The efficacy and safety of meropenem are well known and as this is a generic application, the indications in the Summary of Product Characteristics will be based on those of the reference product.

Pharmacovigilance System

Risk Management Plan

V OVERALL CONCLUSIONS

Meropenem is indicated for use by injection only and for such applications, according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) no bioequivalence studies are required.

The Applicant has reviewed the literature on safety and efficacy. The SmPC is based on that of the reference product. There were therefore no clinical objections regarding the clinical pharmacology, efficacy or safety of Meropenem powder for solution for injection.

VI REVISION DATE

July 2011