COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Meropenem Steriscience, powder for solution, for injection or infusion (meropenem trihydrate)

NL/H/5206/001-002/DC

18 May 2022

This module reflects the scientific discussion for the approval of Meropenem Steriscience. The procedure was finalised at 9 February 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Meropenem Steriscience, powder for solution, for injection or infusion, from Steriscience B.V.

Meropenem Steriscience is indicated for the treatment of the following infections in adults and children aged 3 months and older:

- Severe pneumonia, including hospital and ventilator-associated 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 Steriscience is also indicated for the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem Steriscience is also indicated for the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Meronem i.v., poeder voor oplossing voor injectie of infusie 500 mg en 1000 mg (NL RVG 17864) which has been registered in the Netherlands by Pfizer B.V. since 1995 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Romania, Spain, Slovakia, Slovenia and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Meropenem Steriscience is a white to pale yellow powder and is free from visual agglomerates.

Each vial contains as active substance 500 mg or 1000 mg of meropenem, as meropenem trihydrate.

The powder is packed in glass vials.

The only excipient present in the final product is sodium carbonate.

II.2 Drug Substance

The active substance is meropenem trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or light yellow, crystalline powder and is sparingly soluble in water, practically insoluble in ethanol (96%) and in dichloromethane. The drug substance exhibits polymorphism and contains six stereocenters. Polymorphism is not relevant for this product, as it will be dissolved before administration.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

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

Stability of drug substance

The active substance is stable for 24 months when stored in appropriate containers. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the drug product has been described and the choice of the excipient is justified. The main development studies performed were the characterisation of the reference product and the performance of compatibility studies. As the test and innovator drug product are to be administered as an aqueous intravenous infusion or bolus injection and contain the same drug substance (i.e. meropenem trihydrate) and excipient (sodium carbonate, anhydrous) in the same quantities as the reference product, no bioequivalence study is required in accordance with the Guideline on the investigation of bioequivalence.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. The holding time of six months has been justified by stability studies. The main steps of the manufacturing process are sterilisation of the components, mixing and vial filling. The whole manufacturing process is performed under aseptic conditions.

Control of excipients

Sodium carbonate (Sterile) is a pharmacopoeial excipient and is tested to the methods provided in Ph. Eur. monograph. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of meropenem and sodium, pH of reconstituted solution, loss on drying, average fill weight, fill weight variation, uniformity of dosage units, completeness and clarity of solution, assay, related substances, particulate matter bacterial endotoxins, sterility and reconstitution time. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production site has been provided, demonstrating compliance with the specification. A risk evaluation concerning the presence of nitrosamine impurities in the proposed product is provided and no risk is identified.

Stability of drug product

Stability data on the product have been provided for three batches stored at 40°C/75% RH (six months), 30°C/75% RH (up to 18 months) and 25°C/60% RH (up to 24 months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The drug product was stored in the proposed packaging. All tested parameters remained

within the specifications and no clear trends were observed. On basis of the data submitted, a shelf life was granted of 24 months with no special storage conditions.

For the reconstituted product the following has been substantiated with stability data and is considered acceptable:

Intravenous bolus injection
Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for three hours at up to 25 °C or six hours under refrigerated conditions (2-8 °C).

Intravenous infusion
Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution (9 mg/mL) has been demonstrated for three hours at up to 25 °C or 24 hours under refrigerated conditions (2-8 °C).

It should be noted that if not used immediately in-use storage times and conditions are the responsibility of the user.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Meropenem Steriscience have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Meropenem Steriscience is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Meronem i.v., poeder voor injectievloeistof 500/1 g which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Meropenem trihydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted no bioequivalence studies, which is acceptable.

IV.2 Pharmacokinetics

Meropenem Steriscience, powder for solution, for injection or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Meropenem Steriscience is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Meropenem Steriscience.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- None

Missing information	- None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Meronem i.v., poeder voor injectievloeistof 500/1 g. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Loperamide 2 mg oral lyophilizate (NL/H/4900/001/DC) for design/layout and Meronem i.v., poeder voor injectievloeistof 500/1 g (FR/H/0467) for content. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Meropenem Steriscience, powder for solution, for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Meronem i.v., poeder voor injectievloeistof 500/1 g. Meronem is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Meropenem Steriscience with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 February 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse