COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Meropenem Venus Pharma 500 mg, 1 g and 2 g, powder for solution for injection or infusion (meropenem trihydrate)

NL/H/5128/001-003/DC

Date: 16 February 2022

This module reflects the scientific discussion for the approval of Meropenem Venus Pharma 500 mg, 1 g and 2 g, powder for solution for injection or infusion. The procedure was finalised on 14 October 2021. 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 Venus Pharma 500 mg, 1 g and 2 g, powder for solution for injection or infusion, from Venus Pharma GmbH.

The products are indicated for the treatment of the following infections in adults and children aged 3 months and older (see sections 4.4 and 5.1 of the SmPC):

- 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 may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection. Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

This decentralised procedure concerns both a generic and a hybrid application claiming essential similarity with the innovator products Meronem, powder for solution for injection or infusion 500 mg and 1000 mg which have been registered in France by Pfizer since 16 April 1997. In the Netherlands, Meronem have been registered since June 1995 by mutual recognition procedure FR/H/0467/001-002/MR.

The concerned member states (CMS) involved in the current procedure for the 500 mg product were Belgium, Germany, Spain, Croatia and Romania. The CMS for the 1 g product were Belgium, Germany, Spain, France, Croatia and Romania. The CMS for the 2 g product were Belgium, Germany, Spain, France, Italy and the United Kingdom (Northern Ireland).

The marketing authorisation for the 500 mg and 1 g strength has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The marketing authorisation for the 2 g strength has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, since this strength differs from that of the reference products.

Orphan similarity assessment

The MAH has provided a similarity report due to potential similarity with the authorised orphan medicinal product under market exclusivity, TOBI Podhaler (tobramycin). For the similarity assessment the following criteria were considered: principal molecular structural features, mechanism of action and therapeutic indications. Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Meropenem Venus Pharma is considered not similar to TOBI Podhaler. Therefore, the existence of any market exclusivity for TOBI Podhaler in the treatment of broncho-pulmonary infections in cystic fibrosis, does not prevent the granting of the marketing authorisation of Meropenem Venus Pharma.

II. QUALITY ASPECTS

II.1 Introduction

Meropenem Venus Pharma is a powder for solution for injection or infusion. The powder is a white to slight yellow crystalline powder free from visual agglomerates. The pH of the reconstituted solution is 7.3 to 8.3.

Each vial contains meropenem trihydrate equivalent to 500 mg, 1 g or 2 g anhydrous meropenem.

The 500 mg powder product is packed as 674.5 mg powder in a 10 ml (Type II) moulded clear glass vials which are stoppered with 20 mm grey butyl rubber stoppers and sealed with 20 mm aluminium flip-off seal.
The 1 g powder product is packed as 1349 mg powder in a 20 ml (Type II) moulded clear glass vials which are stoppered with 20 mm grey butyl rubber stoppers and sealed with 20 mm aluminium flip-off seal.
The 2 g powder product is packed as 2698 mg powder in a 50 ml (Type II) moulded clear glass vials which are stoppered with 20 mm grey butyl rubber stoppers and sealed with 20 mm aluminium flip-off seal.

The excipient is anhydrous sodium carbonate (E500(I)).

II.2 Drug Substance

The drug substance is meropenem trihydrate, an established drug substance described in the European Pharmacopoeia (Ph. Eur.; monograph 2234). The drug substance is a white or light yellow, crystalline powder and is sparingly soluble in water and practically insoluble in ethanol (96%) and dichloromethane. The drug substance exhibits polymorphism and contains six stereocentres.

The active substance is produced by two manufacturers. The CEP procedure is used for the active substance for both manufacturers. 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

Two CEPs have been submitted; therefore no details on the manufacturing process have been included. In the last steps of the synthesis water for injections is used as a solvent. The method used for sterilisation is sterile filtration and the sterilisation process have been assessed and approved by the EDQM. The manufacturing process of the drug substance, as well as the manufacture of the sterile blend to be considered as an intermediate drug product, are carried out by both drug substance manufacturers.

Quality control of drug substance

Although the drug product manufacturer will only receive the intermediate blend from the drug substance manufacturers, a drug substance specification, applicable to the drug substance obtained from both suppliers, has been provided. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. and the CEPs. Since the analytical methods are in compliance with the Ph. Eur. and the CEPs, no validation or further justification is required.

Stability of drug substance

The active substance of manufacturer I is stable for three years when stored at a temperature not exceeding 30°C in a container that simulates the marketing container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Since the CEP for the drug substance manufactured by manufacturer II does not contain a re-test period, data were provided on a long-term and an accelerated stability study. The drug substance was stored for six months at 40°C/75% RH (six batches), for 36 months at 25°C/60% RH (three batches) and for six months at 30°C/75%RH (three batches). The batches were stored in a container that simulates the marketing container. No significant changes or trends were observed in the available stability data. Results of the photostability study demonstrate that the drug substance is not sensitive to light. The proposed retest period of 36 months for the drug substance is acceptable when stored in aluminium bottles with rubber stoppers and aluminium caps at a temperature of not more than 25°C.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. 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 products are to be administered as an aqueous intravenous infusion or bolus injection and contain the same drug substance (i.e. meropenem trihydrate) and excipient (anhydrous sodium carbonate) in the same quantities as the reference product, no bioequivalence study is required in accordance with the *Guideline on the investigation of bioequivalence*. For the 2000 mg strength of the proposed product a hybrid application is submitted, with respect to strength. It has the same ratio of drug substance and excipient and the same pharmaceutical form compared to the 500 mg and the 1000 mg strength of the proposed product and the reference product.

Manufacturing process

The drug products are prepared by using pre-sterilised components and an aseptic filling process. The selected sterilisation method has been adequately justified. The main steps of the manufacturing process are the mixing of the sterile meropenem trihydrate with sterile sodium carbonate followed by filling of the sterile blend into pre-sterilised vials. The process is performed under aseptic conditions, where the preparation of the sterile blend is performed by two different manufacturers and the final filling of the blend into vials is performed by the finished product manufacturer. The overall manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches for both sterile intermediate blends and the finished drug products.

Control of excipient

The drug product manufacturer did not provide an excipient specification for sodium carbonate, since the drug product manufacturer will receive the intermediate sterile blend only and not sodium carbonate itself. The proposed excipient specifications for sodium carbonate of both intermediate manufacturers were considered acceptable, as they are in line with the Ph. Eur. monograph for sodium carbonate. Additional limits for particulate contamination, residual solvents, bacterial endotoxins and sterility are included. The specification is acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance (before reconstitution and after reconstitution), clarity and colour of reconstituted solution, pH of reconstituted solution, uniformity of dosage units, loss on drying, identification, assay (meropenem and sodium), related substances, particulate matter, bacterial endotoxins, sterility and reconstitution time. The release and shelf life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

An adequate risk evaluation concerning the presence of nitrosamine impurities in the proposed product has been provided. The analytical methods have been adequately described and validated. Batch analytical results have been provided for three batches of each product strength, demonstrating compliance with the proposed specifications.

Stability of drug products

Stability data on the intermediate product has been provided on four batches (manufacturer I) stored at 40°C/75% RH, 30°C/65% RH and/or 25°C/60% RH, and on six batches (manufacturer II) stored at 40°C/75% RH and 30°C/75% RH. The stability data showed no clear trends or changes in any of the tested parameters at the storage conditions. For the sterile intermediate blend of manufacturer I, the holding time is 12 months when stored at a temperature not exceeding 30°C. For the sterile intermediate blend of manufacturer II, the hold time is 12 months when stored in a well closed container at a temperature not more than 25°C.

Stability data on the final drug products have been provided on three batches of each product strength stored at 40°C/75% RH (six months) and 30°C/65% RH (24 months). The conditions used in the stability studies are according to the ICH stability guideline. All tested parameters remained within the specifications.

The applicant proposes to calculate the product shelf life from the date of filling of the sterile mixture in the glass vials by the finished product manufacturer. Since it has been demonstrated that the sterile intermediate is stable up to 36 months and a hold time of 12 months is claimed, and based on the provided stability data, this is acceptable. Hence, the start of the shelf life calculated from the date of filling of the sterile mixture in the glass vials by the finished product manufacturer is acceptable. Based on the proposed calculation of shelf life, which is not in accordance with the *Note for Guidance on Start of shelf life of the dosage form*, the claimed shelf life of 24 months is acceptable. The labelled storage condition is: “This medicinal product does not require any special storage condition. Do not freeze the reconstituted solution.”

The proposed shelf lives after reconstitution have been substantiated with stability data and are considered acceptable. For storage conditions after reconstitution of the medicinal products, see section 6.3 of the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the products nor have any been used in the manufacturing of these products, 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 Venus Pharma have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Meropenem Venus Pharma are intended for substitution of the reference products, 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

The products are generic and hybrid formulations of Meronem which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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.

IV.2 Pharmacokinetics

Biowaiver

Meropenem Venus Pharma 500 mg, 1 g and 2 g, powder for solution for injection or infusion are a parenteral formulations and therefore fulfil 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative compositions of Meropenem Venus Pharma 500 mg and 1 mg are entirely the same as the originator. For the 2 g strength a hybrid application was submitted, with respect to strength. It has the same ratio of drug substance and excipient and the same pharmaceutical form compared to the 500 mg and the 1 g strength of the proposed products and reference products. Therefore, all three strengths may be considered as therapeutic equivalent, with the same efficacy/safety profiles as known for the active substance of the reference medicinal products. The current products can be used instead of the reference products.

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 Venus Pharma.

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

Important identified risks	• None
Important potential risks	• Medication error (accidental overdose)
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 products Meronem. No new clinical studies were deemed necessary since both the reference and current products are intended for parenteral use. A biowaiver has been granted. Risk management is adequately addressed. These medicinal products 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 Meropenem VENUS 500 mg and 1 g Powder for Solution for Injection or Infusion (IE/H/0999/001-002/DC, previously UK/H/4098/01-02/DC) for key safety messages and to Ceftriaxone 500 mg, 1 g and 2 g Powder for Solution for Injection Or Infusion (national procedure by UK) for design/layout and style of writing. 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 Venus Pharma 500 mg, 1 g and 2 g, powder for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Meronem, powder for solution for injection or infusion 500 mg and 1000 mg. Meronem are well-known medicinal products with established favourable efficacy and safety profiles. Since both the reference and current products are intended for parenteral use, no bioequivalence study is deemed necessary.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Meropenem Venus Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 October 2021.

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