

## **Public Assessment Report**

### **Scientific discussion**

**Meropenem BRADEX 500 mg and 1 g,  
powder for solution for injection/infusion**

**(meropenem trihydrate)**

**NL/H/3841/001-002/DC**

**Date: 9 April 2018**

This module reflects the scientific discussion for the approval of Meropenem BRADEX. The procedure was finalised on 21 February 2018. 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 BRADEX 500 mg and 1 g, powder for solution for injection/infusion from BRADEX S.A.

The product is 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 approved 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 a generic application claiming essential similarity with the innovator product Meronem 500 mg and 1 g powder for solution for injection/ infusion, which was first registered in Europe by Astra Zeneca in 1994. In the Netherlands, the innovator product Meronem i.v. powder for solution for injection 500 mg/1000 mg (NL License RVG 17864) has been registered since 13 June 1995.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Denmark, France, Hungary, Luxembourg, Norway 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 BRADEX is a white to light yellow powder.

The 500 mg powder is packed in 20 ml glass vial with stopper (bromobutyl rubber) and sealed with aluminium caps with a flip-top plastic cover. Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

The 1 g powder is packed in 30 ml glass vial with stopper (bromobutyl rubber) and sealed with aluminium caps with a flip-top plastic cover. Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

The only excipient is sodium carbonate anhydrous (E 500(I)).

## II.2 Drug Substance

The active substance is meropenem trihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or light yellow, crystalline powder and is sparingly soluble in water, practically insoluble in ethanol (96%) and in dichloromethane.

The active substance exhibits polymorphism. The active substance contains has 6 stereocentres, 4 of them in the  $\beta$ -lactam ring and 2 in the pyrrolidine ring.

Meropenem trihydrate is obtained from two different suppliers as sterile substance after the mixing of the sterile meropenem trihydrate with sterile sodium carbonate. For one supplier a CEP has been provided and for the other supplier the ASMF procedure is used.

Under the official Certification Procedures of the EDQM of the Council of Europe (CEP), 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 European Pharmacopoeia.

The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

### Manufacturing process

The manufacturing process of the first manufacturer is covered by the CEP. The method used for sterilisation is sterile filtration and the sterilisation process has been assessed and approved by the EDQM.

The manufacturing process by the ASMF-holder consists of a three step synthesis pathway. The crude active substance is sterilised by sterile filtration. No class 1 organic solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

### Quality control of drug substance

The active substance specification is in line with the Ph.Eur. and the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

The active substance specification by the ASMF-holder is in line with the Ph.Eur. monograph, with a number of appropriate additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six full scaled batches.

### Stability of drug substance

The active substance of the first manufacturer is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Stability data on the active substance from the second manufacturer have been provided for six full scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Based on the results, the proposed retest period of 36 months without any special storage requirements is justified.

## II.3 Medicinal Product

### Pharmaceutical development

The development of the product has been described, the choice of the excipients is justified and their functions explained. The main development studies performed were the characterisation of the reference product and the performance of compatibility studies. The choice of the sterilisation method, i.e. by aseptic compounding and filling using pre-sterilised individual components, has been justified.

The choices of the packaging are justified. As the test products are to be administered as an aqueous intravenous infusion and contain the same active substance (i.e. meropenem trihydrate) and excipient (sodium carbonate) in the same quantities as the reference products, no bioequivalence study is required in accordance with the Guideline on the investigation of bioequivalence. The pharmaceutical development of the drug product has been adequately performed.

#### Manufacturing process

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 (i.e. by the respective drug substance suppliers) and the final filling of the blend into vials is performed by a third 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 full scaled batches for the sterile blend (at each of the proposed sites) and final product.

#### Control of excipients

The sterile sodium carbonate (anhydrous) used in the preparation of the sterile blend is of Ph.Eur. quality with additional requirements for bacterial endotoxins and sterility according to the Ph.Eur. The specifications are acceptable.

#### Quality control of drug product

Stability data on the product has been provided on six batches (three pilot and three full scaled) per strength stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months).

The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in respectively 20 ml or 30 ml glass (Type III) vials, closed with 20 mm bromobutyl rubber (Type I) stoppers and sealed with 20 mm aluminium caps having a plastic flip-off cover. The stability data showed no clear trends or changes in any of the tested parameters at both storage conditions. Results of a photostability study, showed that the drug product is photostable in the immediate container and in the commercial package.

Based on the currently available data, the proposed shelf-life of 4 years without any special storage requirements is acceptable ('This medicinal product does not require any special storage conditions').

Stability data has been provided demonstrating that the product remains stable for 1 hour following reconstitution with water for injections, 0.9% NaCl or dextrose 5%, when stored in a refrigerator (2-8°C) or at 25°C. After 2 hours storage under these conditions out-of-specification results were observed. The storage precaution 'Do not freeze' has been adopted for the reconstituted product.

#### Specific measures for 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 BRADEX has 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 BRADEX 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, 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 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

Meropenem BRADEX 500 mg and 1 g, powder for solution for injection/infusion are 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Meropenem BRADEX 500 mg and 1 g 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 products 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 BRADEX.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> <li>• Serious and fatal hypersensitivity reactions including DRESS syndrome and serious skin reactions (i.e. toxic epidermal necrolysis, Stevens-Johnson syndrome)</li> <li>• Hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis)</li> <li>• Serious blood disorders – including neutropenia, agranulocytosis, haemolytic anaemia and thrombocytopenia</li> <li>• Antibiotic associated diarrhea (Pseudomonas colitis)</li> <li>• Convulsions</li> <li>• Concomitant use with valproic acid</li> <li>• Concomitant use with oral anti-coagulants</li> <li>• Concomitant use with Probenecid</li> <li>• Resistance to penems of <i>Enterobacteriaceae</i>, <i>Pseudomonas aeruginosa</i>, <i>Acinetobacter spp.</i>, across the European Union</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Nephrotoxicity</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Effect on pregnancy/lactation</li> <li>• Paediatric use in infants under 3 months</li> <li>• Paediatric use in children with renal or hepatic</li> </ul>

	impairment <ul style="list-style-type: none"> <li>• No studies on the ability to drive and use machines</li> </ul>
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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. No new clinical studies were conducted. The MAH demonstrated essential similarity based on quality attributes. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

### **V. USER CONSULTATION**

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. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

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.

### **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

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

Since both the reference and current product 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 BRADEX with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 February 2018.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

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