Public Assessment Report

UKPAR

Meropenem 500 mg powder for solution for injection/infusion
Meropenem 1 g powder for solution for injection/infusion

(meropenem trihydrate)

UK licence Number: PL 24780/0018-19

Villeton Invest S.A.
LAY SUMMARY

Meropenem 500 mg & 1 g powder for solution for injection/infusion (meropenem trihydrate)

This is a summary of the Public Assessment Report (PAR) for Meropenem 500 mg & 1 g powder for solution for injection/infusion (PL 36780/0004-5).

This summary explains how Meropenem 500 mg & 1 g powder for solution for injection/infusion were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about using Meropenem 500 mg & 1 g powder for solution for injection/infusion, patients should read the package leaflet available on the MHRA website or contact their doctor or pharmacist.

What are Meropenem 500 mg & 1 g powder for solution for injection/infusion and what are they used for?

Meropenem 500 mg & 1 g powder for solution for injection/infusion are ‘generic medicines’. This means that Meropenem 500 mg & 1 g powder for solution for injection/infusion are similar to ‘reference medicines’ already authorised in the European Union (EU) called Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion, which were granted Marketing Authorisations to AstraZeneca UK Limited.

Meropenem 500 mg & 1 g powder for solution for injection/infusion belongs to a group of medicines called carbapenem antibiotics.

Meropenem 500 mg & 1 g powder for solution for injection/infusion may be used to treat bacterial infection of the blood which might be associated with one of the infections mentioned below. These medicines may also be used in the management of neutropenic patients (patients with low levels of white blood cells) with fever that is suspected to be due to a bacterial infection.

How do Meropenem 500 mg & 1 g powder for solution for injection/infusion work?

The active substance in these medicines is called meropenem. It works by killing bacteria, which can cause the following serious infections:

- Infection affecting the lungs (pneumonia)
- Lung and bronchial infections in patients suffering from cystic fibrosis
- Complicated urinary tract infections
- Complicated infections in the abdomen (stomach)
- Infections that you can catch during or after giving birth
- Complicated skin and soft tissue infections
- Acute bacterial infection of the brain (meningitis)

How are Meropenem 500 mg & 1 g powder for solution for injection/infusion used?

The pharmaceutical form of this medicine is a powder for solution for injection or infusion and the route of administration is intravenous.
Meropenem 500 mg & 1 g powder for solution for injection/infusion will be given as an injection or infusion into a large vein.

The patient’s doctor or nurse will normally give Meropenem 500 mg & 1 g powder for solution for injection/infusion. However, some patients, parents and carers are trained to give Meropenem 500 mg & 1 g powder for solution for injection/infusion at home. Instructions for doing this are provided in this leaflet (in the section called ‘Instructions for giving Meropenem to yourself or someone else at home’).

Meropenem 500 mg & 1 g powder for solution for injection/infusion should always be used exactly as the patient’s doctor has told them. The patient should check with your doctor if you are not sure.

The patient’s injection should not be mixed with or added to solutions that contain other medicines. The injection may take about 5 minutes or between 15 and 30 minutes. The patient’s doctor will tell them how to give Meropenem 500 mg & 1 g powder for solution for injection/infusion. The patient should normally have their injections at the same times each day.

Use in adults
The dose depends on the type of infection, where the infection is in the body and how serious the infection is. The patient’s doctor will decide on the dose that is needed.

- The dose for adults is usually between 500 mg (milligrams) and 2 g (gram). The patient will usually receive a dose every 8 hours. However, he or she may receive a dose less often if their kidneys do not work very well.

Use in children and adolescents
- The dose for children over 3 months old and up to 12 years of age is decided using the age and weight of the child. The usual dose is between 10 mg and 40 mg of Meropenem for each kilogram (kg) that the child weighs. A dose is usually given every 8 hours. Children who weigh over 50 kg will be given an adult dose.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The medicine can only be obtained with a prescription.

**What benefits of Meropenem 500 mg & 1 g powder for solution for injection/infusion have been shown in studies?**

No additional studies were needed as Meropenem 500 mg & 1 g powder for solution for injection/infusion is a generic medicine that contains the same active substance in the same concentration as the reference medicine, Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion. For this reason, Meropenem 500 mg & 1 g powder for solution for injection/infusion is expected to be bioequivalent with the reference medicine. Two medicines are considered bioequivalent when they produce the same levels of active substance in the body.

**What are the possible side effects of Meropenem 500 mg & 1 g powder for solution for injection/infusion?**

Because Meropenem 500 mg & 1 g powder for solution for injection/infusion are generic medicines, their possible side effects are taken as being the same as those of the reference products, Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion (AstraZeneca UK Limited).
For the full list of all side effects reported with Meropenem 500 mg & 1 g powder for solution for injection/infusion, see Section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

**Why are Meropenem 500 mg & 1 g powder for solution for injection/infusion approved?**
It was concluded that, in accordance with EU requirements, Meropenem 500 mg & 1 g powder for solution for injection/infusion have been shown to have comparable quality and are expected to be bioequivalent to Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion. Therefore, the MHRA decided that, as for reference medicines called Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion, their benefits are greater than their risks and recommended that these medicines can be approved for use.

**What measures are being taken to ensure the safe and effective use of Meropenem 500 mg & 1 g powder for solution for injection/infusion?**
A Risk Management Plan (RMP) has been developed to ensure that Meropenem 500 mg & 1 g powder for solution for injection/infusion are used as safely as possible.
Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet of Meropenem 500 mg & 1 g powder for solution for injection/infusion, including the appropriate precautions to be followed by patients.

Known side-effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.

**Other information about Meropenem 500 mg & 1 g powder for solution for injection/infusion**
The UK granted Marketing Authorisations for Meropenem 500 mg & 1 g powder for solution for injection/infusion on 14 June 2017.

The Marketing Authorisation underwent a change of ownership procedure from the marketing authorisation holder (MAH) Infomed Fluids Srl to the MAH Villeton Invest S.À. (PL 24780/0018-19) on 01/08/2017.

The full PAR for Meropenem 500 mg & 1 g powder for solution for injection/infusion follows this summary.

For more information about treatment with Meropenem 500 mg & 1 g powder for solution for injection/infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2017.
Meropenem 500 mg & 1 g powder for solution for injection/infusion

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INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Meropenem 500 mg & 1 g powder for solution for injection/infusion (PL 36780/0004-5) could be approved. These products are ‘prescription-only medicines’ (legal status “POM”).

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Meronem IV 500 mg and Meronem IV 1 g. Powder for solution for injection or infusion, which were initially granted Marketing Authorisations to Zeneca Limited in the UK, on 19 January 1995.

Meropenem 500 mg & 1 g powder for solution for injection/infusion are indicated for the treatment of the following infections in adults and children over 3 months of age:

- 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 500 mg & 1 g powder for solution for injection/infusion may be used in the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. These medicines may also be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

These products contain the active substance meropenem which is a carbapenem antibiotic for parenteral use. Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis.

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

No new clinical data have been submitted and none are required for an application of this type. In line with the CPMP ‘guideline on the investigation of bioequivalence’ subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98, a bioequivalence study was not necessary to support this application, as both test and reference products are solutions at the time of administration.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture and assembly of these products.

A satisfactory summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) has been provided with these applications.

Marketing Authorisations were granted in the UK on 14 June 2017.
The Marketing Authorisation underwent a change of ownership procedure from the marketing authorisation holder (MAH) Infomed Fluids Srl to the MAH Villeton Invest S.A. (PL 24780/0018-19) on 01/08/2017.
II QUALITY ASPECTS

II.1 Introduction
Meropenem 500 mg powder for solution for injection/infusion contains 500 mg of the active substance anhydrous meropenem as meropenem trihydrate. Meropenem 1 g powder for solution for injection/infusion contains 1 g of the active substance anhydrous meropenem as meropenem trihydrate. The other ingredient is the pharmaceutical excipient anhydrous sodium carbonate.

The finished products are packaged in a type III glass vial with a grey, bromobutyl rubber stopper sealed with an aluminium flip-off cap coloured violet for the 500 mg product or grey for the 1 g product. The vials are placed in carton in a pack size of 10 vials.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

II.2. Drug Substance
INN: meropenem trihydrate
Chemical name: (4R,5S,6S)-3-[[[3S,5S)-5-(Dimethylamino)carbonyl]-pyrrolidin-3-yl]sulfanyl]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate.

Structural formula:

![Structural formula image]

Molecular formula: C_{17}H_{25}N_{3}O_{5}S *3 H_{2}O
Relative molecular mass: 437.52
Appearance: White or light yellow, crystalline powder.
Solubility: Sparingly soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

All aspects of the manufacture and control of the active substance, meropenem are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

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 for the active substance. 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 specification limits.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data that comply with the proposed specification are provided.

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.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic products of the reference products Meronem IV 500 mg and Meronem IV 1 g, Powder for solution for injection or infusion. A satisfactory account of the pharmaceutical development has been provided.

The only excipient used in the manufacture of this product is anhydrous sodium carbonate, which complies with its European Pharmacopoeia (Ph. Eur.) monograph.

These products contain no materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the pilot-scale batch size for each strength and shown satisfactory results. The manufacturing process has been validated at appropriate batch sizes for each strength. Where necessary commitment has been provided to validate the first three commercial production batches of each strength of product and a satisfactory process validation protocol to be followed has been submitted.

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

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with the storage conditions “do not store above 30°C” and “do not freeze the reconstituted solution”.


After reconstitution:

**Intravenous bolus injection administration**
A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml.

Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

**Intravenous infusion administration**
A solution for infusion is prepared by dissolving the drug product in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml.

Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

Reconstituted solution of the product in 5% dextrose solution should be used immediately. The reconstituted solutions should not be frozen.

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

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these products from a pharmaceutical perspective.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
The pharmacodynamic, pharmacokinetic and toxicological properties of Meropenem are well-known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

**III.2 Pharmacology**
No new pharmacology data are required for these applications and none have been submitted.
III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this product will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these products from a non-clinical perspective.

IV CLINICAL ASPECTS
IV.1 Introduction
No new clinical studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics
In healthy subjects, the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax values of approximately 23, 49 and 115 μg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 μg.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 μg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

The average plasma protein binding of meropenem is approximately 2 % and is independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynaecological tissues, skin, fascia, muscle, and peritoneal exudates.

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. In vitro meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor. Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 –75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.
In accordance, with the CPMP guideline “Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 Corr ** - subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98”, no bioequivalence data have been submitted with this application and none are required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for this type of application.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for this type of application.

IV.5 Clinical safety
No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), 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 these products.

A summary of safety concerns, as approved in the RMP is provided below:

| Important identified risks | • Hypersensitivity & anaphylactic reactions  
|                           | • Antibiotic-associated diarrhea & pseudomembranous colitis  
|                           | • Seizures  
|                           | • Hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis)  
|                           | • Serious blood disorders, including neutropenia, agranulocytosis, haemolytic anaemia and thrombocytopenia.  
|                           | • Concomitant use with valproic acid / sodium valproate / valpromide.  
|                           | • Probenecid co-administration  
|                           | • Anti-coagulant agent co-administration (warfarin)  |
| Important potential risks | • None  |
| Important missing information | • Limited data on pregnancy  
|                           | • No data on breast-feeding  
|                           | • Use in children under 3 month of age and premature neonates  
|                           | • No information about pediatric population with renal impairment.  |

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns, however, educational materials are an additional risk minimisation measure.
which is in place to ensure safe and effective use of the SmPC by healthcare professionals and care givers.

IV.7  **Discussion on the clinical aspects**
There are no objections to the approval of these products from a clinical perspective.

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 language used for the purpose of user testing the PIL was English. 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**
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Meropenem for systemic use is well-established and has an acceptable level of safety for indications approved for the reference product. The products are considered to be bioequivalent to the marketed reference products and their benefits and risks are considered similar. The benefit/risk balance is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Meropenem 500 mg & 1 g powder for solution for injection/infusion is presented below:
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
<th>Date of start of the procedure</th>
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<td>From: PL 36780/0004-5 To: PL 24780/0018-19</td>
<td>Label, package leaflet, SmpC</td>
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<td>01/08/2017</td>
<td>Approved</td>
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