Public Assessment Report

Decentralised Procedure

Meropenem 500mg powder for solution for injection or infusion

Meropenem 1g powder for solution for injection or infusion

(meropenem)

UK/H/4034/001-2/DC

UK licence numbers: PL 17277/0207-8

Pharmathen S.A.
LAY SUMMARY

On 08 December 2011, the MHRA granted Pharmathen S.A. Marketing Authorisations (licences) for the medicinal products, Meropenem 500mg and 1g powder for solution for injection or infusion (PL 17277/0207-8). These are prescription-only medicines (POM).

Meropenem belongs to a group of medicines called carbapenem antibiotics. It kills a wide range of bacteria (germs) that cause infections in various parts of the body in adults and children above 3 months of age. Meropenem infusion will usually be given by a doctor or nurse as an intravenous injection or infusion (‘drip’).

Meropenem 500mg and 1g powder for solution for injection or infusion are prescribed for one (or more) of the following types of infection:

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

Meropenem may be used in the management of patients with low white blood cell counts (neutropenic patients), who have fever that is suspected to be due to a bacterial infection.

Based on the data submitted by Pharmathen S.A., Meropenem 500mg and 1g powder for solution for injection or infusion were considered to be generic versions of the reference products, Meronem IV injection 500 mg/vial and 1 g/vial (PL 17901/0029-30, AstraZeneca UK Limited).

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Meropenem 500mg and 1g powder for solution for injection or infusion outweigh the risk; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>16</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>20</td>
</tr>
<tr>
<td>Module 5: Scientific discussion during initial procedure</td>
<td>22</td>
</tr>
<tr>
<td>I Introduction</td>
<td>22</td>
</tr>
<tr>
<td>II About the product</td>
<td>24</td>
</tr>
<tr>
<td>III Scientific Overview and discussion</td>
<td>25</td>
</tr>
<tr>
<td>III.1 Quality aspects</td>
<td>25</td>
</tr>
<tr>
<td>III.2 Non-clinical aspects</td>
<td>28</td>
</tr>
<tr>
<td>III.3 Clinical aspects</td>
<td>28</td>
</tr>
<tr>
<td>IV Overall conclusions and benefit-risk assessment</td>
<td>30</td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>31</td>
</tr>
</tbody>
</table>
## Module 1

### Information about Initial Procedure

| Product Name | Meropenem 500mg powder for solution for injection or infusion  
|              | Meropenem 1g powder for solution for injection or infusion |
| Type of Application | Generic, Article 10(1) |
| Active Substance(s) | Meropenem (as meropenem trihydrate) |
| Form | Powder for solution for injection or infusion |
| Strength | 500mg and 1g |
| MA Holder | Pharmathen S.A., 6 Dervenakion str., 153 51 Pallini, Greece |
| Reference Member State (RMS) | UK |
| Concerned Member State / s (CMS) | Iceland, Ireland, Poland |
| Procedure Number | UK/H/4034/001-2/DC |
| Timetable | Day 210 – 09 November 2011 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Meropenem 500mg and 1g powder for solution for injection or infusion (PL 17277/0207-8) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Meropenem 500mg powder for solution for injection or infusion
Meropenem 1g powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains meropenem trihydrate equivalent to 500mg/1g anhydrous meropenem.

Each 500 mg vial contains 104 mg sodium carbonate which equates to approximately 2.0 mEq of sodium (approximately 45 mg).

Each 1 g vial contains 208 mg sodium carbonate which equates to approximately 4.0 mEq of sodium (approximately 90 mg).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
A white to light yellow powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age (see sections 4.4 and 5.1):

- Pneumonia, including community acquired pneumonia and nosocomial 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.

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

4.2 Posology and method of administration
The tables below provide general recommendations for dosing.

The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter spp.*
Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

**Adults and adolescents**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dose to be administered every 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia including community-acquired pneumonia and nosocomial pneumonia.</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Broncho-pulmonary infections in cystic fibrosis</td>
<td>2 g</td>
</tr>
<tr>
<td>Complicated urinary tract infections</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Complicated intra-abdominal infections</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Intra- and post-partum infections</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Complicated skin and soft tissue infections</td>
<td>500 mg or 1 g</td>
</tr>
<tr>
<td>Acute bacterial meningitis</td>
<td>2 g</td>
</tr>
<tr>
<td>Management of febrile neutropenic patients</td>
<td>1 g</td>
</tr>
</tbody>
</table>

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see section 6.2, 6.3 and 6.6).

Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

**Renal impairment**

The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dose (based on “unit” dose range of 500 mg or 1 g or 2 g, see table above)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-50</td>
<td>one unit dose</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>10-25</td>
<td>half of one unit dose</td>
<td>every 12 hours</td>
</tr>
<tr>
<td>&lt;10</td>
<td>half of one unit dose</td>
<td>every 24 hours</td>
</tr>
</tbody>
</table>

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.

**Hepatic impairment**

No dose adjustment is necessary in patients with hepatic impairment (see section 4.4).

**Dose in elderly patients**

No dose adjustment is required for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

**Paediatric population**

**Children under 3 months of age**

The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen (see section 5.2).

**Children from 3 months to 11 years of age and up to 50 kg body weight**

The recommended dose regimens are shown in the table below:
Infection | Dose to be administered every 8 hours
---|---
Pneumonia including community-acquired pneumonia and nosocomial pneumonia | 10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis | 40 mg/kg
Complicated urinary tract infections | 10 or 20 mg/kg
Complicated intra-abdominal infections | 10 or 20 mg/kg
Complicated skin and soft tissue infections | 10 or 20 mg/kg
Acute bacterial meningitis | 40 mg/kg
Management of febrile neutropenic patients | 20 mg/kg

Children over 50 kg body weight,
The adult dose should be administered.

There is no experience in children with renal impairment.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3, and 6.6). Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

### 4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (eg anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins)

### 4.4 Special warnings and precautions for use
The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including meropenem, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem (see section 4.8). Discontinuation of therapy with meropenem and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Seizures have infrequently been reported during treatment with carbapenems, including meropenem (see section 4.8).

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).
A positive direct or indirect Coombs test may develop during treatment with meropenem.

The concomitant use of meropenem and valproic acid/sodium valproate is not recommended (see section 4.5).

Meropenem contains sodium.

This medicinal product contains approximately 2.0/4.0 mEq of sodium per 500 mg/1 g dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No specific medicinal product interaction studies other than probenecid were conducted.

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in a 60-100 % decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).

Oral anti-coagulants

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. There have been many reports of increases in the anti-coagulant effects of orally administered anti-coagulant agents, including warfarin in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of meropenem in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Lactation

It is unknown whether meropenem is excreted in human milk. Meropenem is detectable at very low concentrations in animal breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from meropenem therapy taking into account the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3%), rash (1.4%), nausea/vomiting (1.4 %) and injection site inflammation (1.1%). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased hepatic enzymes (1.5-4.3 %).
Adverse reactions listed in the table with a frequency of “not known” were not observed in the 2,367 patients who were included in pre-authorisation clinical studies with intravenous and intramuscular meropenem but have been reported during the post-marketing period.

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>oral and vaginal candidiasis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Common</td>
<td>thrombocythaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>eosinophilia, thrombocytopenia, leucopenia, neutropenia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>agranulocytosis, haemolytic anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>angioedema, anaphylaxis (see sections 4.3 and 4.4)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>paraesthesiae</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>convulsions (see section 4.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>diarrhoea, vomiting, nausea, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>antibiotic-associated colitis (see section 4.4)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Common</td>
<td>transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>blood bilirubin increased</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>rash, pruritus</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>urticaria</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>blood creatinine increased, blood urea increased</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>inflammation, pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>pain at the injection site</td>
</tr>
</tbody>
</table>

4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In individuals with normal renal function, rapid renal elimination will occur.

Haemodialysis will remove meropenem and its metabolite.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems, ATC code: J01DH02
**Mode of action**
Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

**Pharmacokinetic/Pharmacodynamic (PK/PD) relationship**
Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC (T>MIC) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40% of the dosing interval. This target has not been established clinically.

**Mechanism of resistance**
Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.

There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

**Breakpoints**
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Susceptible (S) (mg/l)</th>
<th>Resistant (R)(mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><strong>Pseudomonas</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><strong>Acinetobacter</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><strong>Streptococcus groups A, B, C, G</strong></td>
<td>≤2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>≤2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Enterococcus</strong></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Staphylococcus</strong></td>
<td>note 3</td>
<td>note 3</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong> and <strong>Moraxella catarrhalis</strong></td>
<td>≤2</td>
<td>&gt; 2</td>
</tr>
<tr>
<td><strong>Neisseria meningitidis</strong></td>
<td>≤0.25</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td><strong>Gram-positive anaerobes</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><strong>Gram-negative anaerobes</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
<tr>
<td><strong>Non-species related breakpoints</strong></td>
<td>≤2</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

1 Meropenem breakpoints for Streptococcus pneumoniae and Haemophilus influenzae in meningitis are 0.25/1 mg/L.
2 Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported as resistant.
3 Susceptibility of staphylococci to meropenem is inferred from the methicillin susceptibility.
4 Meropenem breakpoints in Neisseria meningitidis relates to meningitis only.
5 Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use for species not mentioned in the table and footnotes.
Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.

**Commonly susceptible species**

**Gram-positive aerobes**
- *Enterococcus faecalis*$
- *Staphylococcus aureus* (methicillin-susceptible)$^\dagger$
- *Staphylococcus* species (methicillin-susceptible) including *Staphylococcus epidermidis*
- *Streptococcus agalactiae* (Group B)
- *Streptococcus milleri* group (*S. anginosus, S. constellatus, and S. intermedius*)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (Group A)

**Gram-negative aerobes**
- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Moraxella morganii*
- *Neisseria meningitidis*
- *Proteus mirabilis*
- *Proteus vulgaris*
- *Serratia marcescens*
- *Gram-positive anaerobes*
- *Clostridium perfringens*
- *Peptostreptococcus asaccharolyticus*
- *Peptostreptococcus species* (including *P. micros, P. anaerobius, P. magnus*)

**Gram-negative anaerobes**
- *Bacteroides caccae*
- *Bacteroides fragilis* group
- *Prevotella bivia*
- *Prevotella disiens*

Species for which acquired resistance may be a problem

**Gram-positive aerobes**
- *Enterococcus faecium*$^\dagger$

**Gram-negative aerobes**
- *Acinetobacter species*
- *Burkholderia cepacia*
- *Pseudomonas aeruginosa*
Inherently resistant organisms
Gram-negative aerobes
Stenotrophomonas maltophilia
Legionella species
Other micro-organisms
Chlamydia pneumoniae
Chlamydia psittaci
Coxiella burnetii
Mycoplasma pneumoniae

Species that show natural intermediate susceptibility
\textsuperscript{\dagger}All methicillin-resistant staphylococci are resistant to meropenem
\textsuperscript{\dagger\dagger}Resistance rate \(\geq 50\%\) in one or more EU countries

5.2 Pharmacokinetic properties

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 \(\mu\)g/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 \(\mu\)g.h/ml. After infusion over 5 minutes Cmax values are 52 and 112 \(\mu\)g/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.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable Cmax and half-life to normal subjects but a greater volume of distribution 27 l.

Distribution
The average plasma protein binding of meropenem was approximately 2 % and was 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.

Metabolism
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.

Elimination
Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50 \textendash 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.

Renal insufficiency
Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see section 4.2).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher that in anuric patients.
Hepatic insufficiency
A study in patients with alcoholic cirrhosis shows no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Adult patients
Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Paediatrics
The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed Cmax values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months t1/2 1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2-5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for P. aeruginosa in 95 % of pre-term and 91 % of full term neonates.

Elderly
Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment (see section 4.2).

5.3 Preclinical safety data
Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and above and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

The IV LD50 of meropenem in rodents is greater that 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was increased evidence of abortions at 500 mg/kg in a preliminary study in monkeys.
There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium carbonate, anhydrous
6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years

After reconstitution:

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.

6.4 Special precautions for storage

Do not freeze the reconstituted solution.

6.5 Nature and contents of container

674 mg powder in a 20 ml type I colourless glass vial with butyl rubber (type I) closures and sealed with aluminium caps.

1348 mg powder in a 30 ml type I colourless glass vial with butyl rubber (type I) closures and sealed with aluminium caps.

The medicinal product is supplied in pack sizes of 1 or 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Injection

Meropenem to be used for bolus intravenous injection should be constituted with sterile water for injection to a final concentration of 50 mg/ml.

How to prepare this medicine

1. Wash your hands and dry them very well. Prepare a clean working area.

2. Remove the meropenem bottle (vial) from the packaging. Check the vial and the expiry date. Check that the vial is intact and has not been damaged.

3. Remove the coloured cap and clean the grey rubber stopper with an alcohol wipe. Allow the rubber stopper to dry.

4. Connect a new sterile needle to a new sterile syringe, without touching the ends.

5. Draw up the recommended amount of sterile ‘Water for Injections’ into the syringe. The amount of liquid that you need is shown in the table below:

<table>
<thead>
<tr>
<th>Dose of Meropenem</th>
<th>Amount of ‘Water for Injections’ needed for dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg (milligrams)</td>
<td>10 ml (milliliters)</td>
</tr>
<tr>
<td>1 g (gram)</td>
<td>20 ml</td>
</tr>
<tr>
<td>1.5 g</td>
<td>30 ml</td>
</tr>
<tr>
<td>2 g</td>
<td>40 ml</td>
</tr>
</tbody>
</table>

Please note: If your prescribed dose of meropenem is more than 1g, you will need to use more than 1 vial of meropenem. You can then draw the liquid in the vials into the one syringe.

6. Put the needle of the syringe through the centre of the grey rubber stopper and inject the recommended amount of Water for Injections into the vial or vials of meropenem.

7. Remove the needle from the vial and shake the vial well for about 5 seconds, or until all the powder has dissolved. Clean the grey rubber stopper once more with a new alcohol wipe and allow the rubber stopper to dry.
8. With the plunger of the syringe pushed fully into the syringe, put the needle back through the grey rubber stopper. You must then hold both the syringe and the vial and turn the vial upside down.

9. Keeping the end of the needle in the liquid, pull back the plunger and draw all the liquid in the vial into the syringe.

10. Remove the needle and syringe from the vial and throw the empty vial away in a safe place.

11. Hold the syringe upright, with the needle pointing upwards. Tap the syringe so that any bubbles in the liquid rise to the top of the syringe.

12. Remove any air in the syringe by gently pushing the plunger until all the air has gone.

13. If you are using meropenem at home, dispose of any needles and infusion lines that you have used in an appropriate way. If your doctor decides to stop your treatment, dispose of any unused meropenem in an appropriate way.

**Infusion**

For intravenous infusion meropenem vials may be directly constituted with 0.9% sodium chloride or 5% glucose solutions for infusion to a final concentration of 1 to 20 mg/ml.

For storage conditions of the reconstituted medicinal product, see section 6.3.

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.

The solutions should be inspected visually for particles prior to administration. Only clear pale yellow solution, free from visible particles should be used.

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3

Product Information Leaflet
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If you feel the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:
1. What Meropenem is and what it is used for
2. How to use Meropenem
3. Possible side effects
4. How to store Meropenem
5. Further information

1. WHAT MEROPENEM IS AND WHAT IT IS USED FOR

Meropenem belongs to a group of medicines called carbapenem antibiotics. It works by killing bacteria, which can cause serious infections.

- Infection affecting the lungs (pneumonia)
- Long and severely infected wounds (infections suffering from infection)
- Complicated urinary tract infection
- Complicated infections in the abdomen
- Infections that you cannot treat using other antibiotics
- Complicated skin and soft tissue infections
- Acute bacterial infection of the brain (meningitis)

Meropenem may be used in the management of abnormal patients with fever that is suspected to be due to a bacterial infection.

2. BEFORE YOU USE MEROPENEM

Do not use Meropenem:
- If you are allergic (hypersensitive) to meropenem or any of the other ingredients of Meropenem (listed in Section 6.1 of this information).
- If you are allergic (hypersensitive) to other antibiotics such as penicillins, cephalosporins, or carbapenems as you may be allergic to meropenem.

Take special care with Meropenem:
- Check with your doctor before using Meropenem.
- If you have health problems, such as liver or kidney problems.
- If you have had severe diarrhea after taking antibiotics.

You may develop a positive test (Geonium test) which indicates the presence of antibodies that may destroy red blood cells. Your doctor will discuss this with you. If you are not sure if any of the above applies to you, talk to your doctor or nurse before using Meropenem.

Using other medicines
Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines.

This is because Meropenem can affect the way some medicines work and some medicines can have an effect on Meropenem.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- Proton-pump inhibitors (used to treat heartburn)
- Sodium valproate (used to treat epilepsy).

Meropenem should not be used because it may decrease the effect of sodium valproate.

Pregnancy and breast-feeding
It is important that you tell your doctor if you are pregnant or are planning to become pregnant before receiving meropenem. It is possible to avoid the use of meropenem during pregnancy.

Your doctor will decide whether you should use Meropenem.

It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving meropenem. Small amounts of this medicine may pass into the breast milk and it may affect the baby. Therefore, your doctor will decide whether you should use Meropenem while breast-feeding.

Ask your doctor for advice before taking any medicine.

Driving and using machines
No studies on the effect on the ability to drive and use machines have been performed.

Important information about some of the ingredients of Meropenem
- Meropenem contains sodium. (Meropenem 500mg: This medicinal product contains approximately 2.09 mg of sodium per 500 mg of meropenem and sodium should be taken into consideration by patients on a controlled sodium diet.
- Meropenem 1.5g: This medicinal product contains approximately 4.09 mg of sodium per 1.5g of meropenem which should be taken into consideration by patients on a controlled sodium diet.

If you have a condition which requires you to monitor your sodium intake please inform your doctor or nurse.

3. HOW TO USE MEROPENEM

Adults
- The dose depends on the type of infection that you have and the dose that you need. Your doctor will decide on the dose that you need.
- The dose for adults is usually between 500mg (250mg and 250mg) and 1g every 8 hours. However, you may receive a dose less often if your kidneys do not work very well.

Children and adolescents
- The dose for children and adolescents is usually every 8 hours and will be decided on by your doctor or nurse.

- Meropenem will be given to you as an injection or infusion into a vein.
- Your doctor or nurse will normally give Meropenem by injection.
- However, if necessary, Meropenem can be given by Meropenem at home, in the presence of healthcare professionals.
- Meropenem can be given by injection at home if your doctor has told you how.
- Meropenem can be given by infusion at home if your doctor has told you how.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Meropenem can cause side effects, although not everybody gets them.

The frequency of possible side effects is defined below as follows:
- Very common (affects more than 1 in 10 people)
- Common (affects 1 in 10 to 100 people)
- Uncommon (affects 1 in 100 to 1000 people)
- Rare (affects less than 1 in 1000 people)
- Very rare (affects less than 1 in 10,000 people)

The side effects are:
- Headache
- Nausea
- Pain in the stomach
- Diarrhea
- Abdominal pain
- Changes in blood tests, including tests that show liver or kidney function.

If you stop using Meropenem
- Do not stop using Meropenem suddenly without asking your doctor or nurse.

5. POSSIBLE SIDE EFFECTS

- Changes in your blood: These include reduced numbers of platelets, increased numbers of red blood cells, increased numbers of white blood cells, decreased numbers of other white blood cells and increased numbers of other platelets (thrombocytopenia). Your doctor may do blood tests to check your blood counts.
- Increases in blood tests, including tests that show liver and kidney function.

If you stop using Meropenem
- Do not stop using Meropenem suddenly without asking your doctor or nurse.

6. POSSIBLE SIDE EFFECTS

- Changes in your blood: These include reduced numbers of platelets, increased numbers of red blood cells, increased numbers of white blood cells, decreased numbers of other white blood cells and increased numbers of other platelets (thrombocytopenia). Your doctor may do blood tests to check your blood counts.
- Increases in blood tests, including tests that show liver and kidney function.

If you stop using Meropenem
- Do not stop using Meropenem suddenly without asking your doctor or nurse.
Other possible side effects of unknown frequency
- Inflammation of the bowel with diarrhoea.
- Sore veins where Meropenem is injected.
- Other changes in your blood. The symptoms include: frequent infections, high temperature and sore throat.
- Your doctor may do blood tests from time to time.
- Sudden onset of a severe rash or blistering or peeling skin. This may be associated with a high fever and joint pains.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE MEROPENEM
Keep out of the reach and sight of children.
Do not use Meropenem after the expiry date which is stated on the container. The expiry date refers to the last day of the month.
Do not use Meropenem if deteriorated.
After reconstitution: 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.
Do not freeze the reconstituted solution.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Meropenem contains:
Each vial contains meropenem trihydrate equivalent: 500mg anhydrous meropenem.
or
Each vial contains meropenem trihydrate equivalent: 1g anhydrous meropenem.
The other ingredient is anhydrous sodium carbonate.
What Meropenem looks like and contents of the pack:
Meropenem is a white to light yellow crystalline pow for solution for injection or infusion in vial. Pack size of 1 or 10 vials.
Not all pack sizes may be marketed.
Marketing Authorisation Holder and Manufacturer
The marketing authorisation holder is:
Pharmatherm SA
6 Devrezeon str
153 51 Pirini
Greece
The manufacturer is:
Pharmatherm SA
6 Devrezeon str
153 51 Pirini
Greece
This leaflet was last approved in 02/2012.
The following information is intended for medical or healthcare professionals only:

Instructions for giving Meropenem to yourself or someone else at home

Some patients, parents and carers are trained to give Meropenem at home.

Warning —
You should only give this medicine to yourself or someone else at home after a doctor or nurse has trained you.

- The medicine must be mixed with another liquid (the diluent). Your doctor will tell you how much of the diluent to use.
- Use the medicine straight after preparing it. Do not freeze it.

How to prepare this medicine

1. Wash your hands and dry them very well. Prepare a clean working area.
2. Remove the Meropenem bottle (vial) from the packaging. Check the vial and the expiry date. Check that the vial is intact and has not been damaged.
3. Remove the coloured cap and clean the grey rubber stopper with an alcohol wipe. Allow the rubber stopper to dry.
4. Connect a new sterile needle to a new sterile syringe, without touching the ends.
5. Draw up the recommended amount of sterile “Water for Injections” into the syringe. The amount of liquid that you need is shown in the table below:

<table>
<thead>
<tr>
<th>Dose of Meropenem (milligrams)</th>
<th>Amount of “Water for Injections” needed for dilution (milliliters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500mg</td>
<td>10ml</td>
</tr>
<tr>
<td>1g (gram)</td>
<td>20ml</td>
</tr>
<tr>
<td>1.5g</td>
<td>30ml</td>
</tr>
<tr>
<td>2g</td>
<td>40ml</td>
</tr>
</tbody>
</table>

Please note:
If your prescribed dose of Meropenem is more than 1g, you will need to use more than 1 vial of Meropenem. You can then draw the liquid in the vials into the one syringe.

6. Put the needle of the syringe through the centre of the grey rubber stopper and inject the recommended amount of Water for Injections into the vial or vials of Meropenem.

7. Remove the needle from the vial and shake the vial well for about 5 seconds, or until all the powder has dissolved. Clean the grey rubber stopper once more with a new alcohol wipe and allow the rubber stopper to dry.

8. With the plunger of the syringe pushed fully into the syringe, put the needle back through the grey rubber stopper. You must then hold both the syringe and the vial and turn the vial upside down.

9. Keeping the end of the needle in the liquid, pull back the plunger and draw all the liquid in the vial into the syringe.

10. Remove the needle and syringe from the vial and throw the empty vial away in a safe place.

11. Hold the syringe upright with the needle pointing upwards. Tap the syringe so that any bubbles in the liquid rise to the top of the syringe.

12. Remove any air in the syringe by gently pushing the plunger until all the air has gone.

13. If you are using Meropenem at home, dispose of any needles and infusion lines that you have used in an appropriate way. If your doctor decides to stop your treatment, dispose of any unused Meropenem in an appropriate way.

Giving the injection

You can either give this medicine through a short cannula or venflon, or through a port or central line.

Giving Meropenem through a short cannula or venflon

1. Remove the needle from the syringe and throw the needle away carefully in your sharps bin.
2. Wipe the end of the short cannula or venflon with an alcohol wipe and allow it to dry. Open the cap on your cannula and connect the syringe.
3. Slowly push the plunger of the syringe to give the antibiotic steadily over about 5 minutes.
4. Once you have finished giving the antibiotic and the syringe is empty, remove the syringe and use a flush as recommended by your doctor or nurse.
5. Close the cap of your cannula and carefully throw the syringe away in your sharps bin.

Giving Meropenem through a port or central line

1. Remove the cap on the port or line, clean the end of the line with an alcohol wipe and allow it to dry.
2. Connect the syringe and slowly push the plunger on the syringe to give the antibiotic steadily over about 5 minutes.
3. Once you have finished giving the antibiotic, remove the syringe and use a flush as recommended by your doctor or nurse.
4. Place a new clean cap on your central line and carefully throw the syringe away in your sharps bin.

Giving Meropenem by intravenous infusion

Meropenem can be given by intravenous infusion over approximately 15 to 30 minutes. For intravenous infusion, Meropenem vials may be direct constituted with 0.9% sodium chloride or 5% glucose solutions for infusion to a final concentration of 1 to 20 mg/ml. The solution should be shaken before use. The solutions should be inspected visually for particles prior to administration. Only clear pale yellow solution, free from visible particles should be used.

Each vial is for single use only.
Module 4
Labelling

Meropenem 500mg powder for solution for injection or infusion - PL 17277/0207

Meropenem 500mg Powder for solution for injection or infusion
Each vial contains meropenem trihydrate equivalent to 500mg anhydrous meropenem

Meropenem 500mg Powder for solution for injection or infusion
Also contains: Anhydrous sodium carbonate
See leaflet for further information
Intravenous use
Read the package leaflet before use.
Keep out of the reach and sight
of children.

For single use only
After reconstitution:
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.
Do not freeze the reconstituted solution.

Meropenem 500mg Powder for solution for injection or infusion
Each vial contains meropenem trihydrate equivalent to 500mg anhydrous meropenem

Intravenous use. For single use only.
After reconstitution: Use within 1 hour.
Do not freeze.

MA Holder:
Pharmathen SA, 6 Dervenakion str,
153 51 Pallini, Attiki, Greece
Meropenem 1g powder for solution for injection or infusion - PL 17277/0208

Each vial contains meropenem trihydrate equivalent to 1g anhydrous meropenem.

Intravenous use. For single use only.
After reconstitution: Use within 1 hour. Do not freeze.

MA Holder: Pharmathen SA
6 Dervenakion str
153 51 Pallini, Attiki
Greece

Lot:
Exp:
Module 5

Scientific discussion during initial procedure

1 INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Pharmathen S.A. Marketing Authorisations for the medicinal products, Meropenem 500mg and 1g powder for solution for injection or infusion (PL 17277/0207-8, UK/H/4034/001-2/DC) on 08 December 2011. The products are prescription-only medicines.

These are generic applications for Meropenem 500mg and 1g powder for solution for injection or infusion, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The applications refer to the UK products, Meronem IV injection 500 mg/vial and 1 g/vial (PL 17901/0029-30), licensed to AstraZeneca UK Limited. The cross-referenced products were originally authorised to Zeneca Limited (PL 12619/0098-9) on 19 January 1995 and underwent Change of Ownership (CoA) procedures to the current AstraZeneca UK Limited licences on 11 May 2001. The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Pharmathen S.A. applied for Marketing Authorisations for Meropenem 500mg and 1g powder for solution for injection or infusion in Iceland, Ireland and Poland.

Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age:

- Pneumonia, including community acquired pneumonia and nosocomial 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. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the minimum inhibitory concentration (MIC) has been shown to best correlate with efficacy.
The medicinal products are presented as a sterile, white to light-yellow powder for solution for injection or infusion. The infusion is prepared by dissolving the powder in an appropriate infusion solution, as detailed in Section 6.6 of the SmPC. These medicines are not for self-administration; they will be administered to the patient by a qualified healthcare professional.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications cross-refer to products that have been licensed for over 10 years. Bioequivalence studies are not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Meropenem 500mg powder for solution for injection or infusion  
Meropenem 1g powder for solution for injection or infusion |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Meropenem (as meropenem trihydrate)</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code) | Antibacterials for systemic use, carbapenems  
(J01D H02) |
| Pharmaceutical form and strength(s) | Powder for solution for injection or infusion  
500mg and 1g |
| Reference numbers for the Decentralised Procedure | UK/H/4034/001-2/DC |
| Reference Member State | United Kingdom |
| Member States concerned | IE, IS, PL |
| Marketing Authorisation Number(s) | PL 17277/0207-8 |
| Name and address of the authorisation holder | Pharmathen S.A.,  
6 Dervenakion str.,  
153 51 Pallini, Greece |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCES

Meropenem trihydrate

Nomenclature:

INN: Meropenem trihydrate

Chemical names:

i) 1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[5-[(dimethylamino)carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo, trihydrate, [4R-[3(3S*,5S*),4α,5β,6β(R*)]]

ii) (4R,5S,6S)-3-[[3S,5S]-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-carboxylic acid, trihydrate

iii) (1R,5S,6S)-2-[[3S,5S]-5-(dimethylaminocarbonyl)pyrrolidin-3-ylthio]-6-[(R)-1-hydroxyethyl]-1-methylcarbapen-2-em-carboxylic acid

Structure:

Molecular formula: $C_{17}H_{25}N_{3}O_{5}S \cdot 3H_{2}O$ (trihydrate)

$C_{17}H_{23}N_{3}O_{5}S$ (anhydrous)

Molecular weight: 437.52 g/mol (trihydrate)

383.47 (anhydrous)

CAS No: 119478-56-7 (trihydrate)

96036-03-2 (anhydrous)

Physical form: A white to light yellow crystalline powder

Solubility: Sparingly soluble in water, very slightly soluble in alcohol, practically insoluble in ethanol and ether

The active substance, meropenem trihydrate, is not the subject of a European Pharmacopeia (Ph. Eur) monograph.

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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.
Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturers during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been applied.

**MEDICINAL PRODUCT**

**Description and Composition**

Meropenem 500mg and 1g powder for solution for injection or infusion are presented as a sterile, white to light-yellow powder. The medicinal products are supplied in glass vials containing 500 mg or 1 g meropenem (as meropenem trihydrate). The infusion is prepared by dissolving the powder in an appropriate infusion solution, as detailed in Section 6.6 of the SmPC.

Other ingredients consist of a single pharmaceutical excipient, namely anhydrous sodium carbonate. Appropriate justification for the inclusion of this excipient has been provided, which complies with its European Pharmacopoeia monograph. A satisfactory Certificate of Analysis has been provided.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to obtain stable, sterile, generic medicinal products, pharmaceutically equivalent to the reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

Comparative impurity profiles were provided for batches of the test and appropriate reference products.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.
Finished product specification

Finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Meropenem 500mg powder for solution for injection or infusion is supplied in packs of 1 or 10 x 20 ml, type I glass vials complete with rubber stoppers and aluminium seals. Meropenem 1g powder for solution for injection or infusion is supplied in packs of 1 or 10 x 30 ml, type I glass vials complete with rubber stoppers and aluminium seals. The vials are packaged, with the product information leaflet, into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 3 years for the unopened vials. 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 must not be frozen. For full details and instructions for reconstitution, dilution and infusion, refer to section 6.6 of the SmPC.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

The quality grounds for these applications are considered adequate. There are no objections to the approval of Meropenem 500mg and 1g powder for solution for injection or infusion from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS
Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of meropenem, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

There are no objections to approval of Meropenem 500mg and 1g powder for solution for injection or infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS
INDICATIONS
Meropenem is indicated for the treatment of the following infections in adults and children over 3 months of age (see SmPC sections 4.4 and 5.1):

- Pneumonia, including community acquired pneumonia and nosocomial 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. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The indications are consistent with those of the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY
The toxicology of meropenem is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
The clinical pharmacology of meropenem is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.
Clinical efficacy
No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview. The efficacy of meropenem is well-established from its extensive use in clinical practice.

Meropenem 500mg and 1g powder for solution for injection or infusion are to be administered as an aqueous intravenous solution and contain the same active substance, in the same concentrations, as the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited). Thus, in accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98), Section 5.1.6 Parenteral solutions, the applicant is not required to submit a bioequivalence study.

Clinical safety
No new safety data have been submitted and none are required for these types of application. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of meropenem is well-known.

CLINICAL OVERVIEW
A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:
An article 30 referral for Meronem produced harmonised product information texts.

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those of the UK reference product and are acceptable.

Product Information Leaflet (PIL)
The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling is satisfactory.

CONCLUSIONS
Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Meropenem 500mg and 1g powder for solution for injection or infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

No new data are submitted and none are required for these types of application. Efficacy is reviewed in the clinical overview.

The applicant’s Meropenem 500mg and 1g powder for solution for injection or infusion have been demonstrated to be generic versions of the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those for the UK reference products and are satisfactory.

The final PIL is in line with the SmPCs and is satisfactory. 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, as amended. 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.

The approved labelling artwork complies with statutory requirements.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Meropenem 500mg and 1g powder for solution for injection or infusion and the UK reference products, Meronem IV injection 500 mg/vial and 1 g/vial (AstraZeneca UK Limited), are interchangeable. Extensive clinical experience with meropenem is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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