

Summary of Product Characteristics

1.0 Name of the Medicinal Product

Penem-1g (**Meropenem for Injection USP 1000 mg**)

2.0 Qualitative and Quantitative Composition

Each Vial Contains:

Sterile Meropenem USP

Eq. to Anhydrous Meropenem 1000 mg

Also contains Sterile Sodium Carbonate (Sodium 90.2 mg) USP added as buffer

3.0 Pharmaceutical Form

Dry Powder for Injection

4. Clinical Particulars:

4.1 Therapeutic Indications:

Meronem is indicated for the treatment of the following infections in adults and children aged 3 months and older.

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Meronem may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection

4.2 Posology and method of administration:

Posology

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 infections due to less susceptible bacterial species (e.g. Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp.), or very severe infections.

Adults and Adolescents

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	500 mg - 1 gm

Broncho-pulmonary infections in cystic fibrosis	2 gm
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. 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 administration of these dose adjustments for a unit dose of 2 g.

Method for administration

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. 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

4.4 Special warning and precaution 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.

Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. resistance

Resistance to penems of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions

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

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial 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.

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/sodium valproate/valpromide 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. Paediatric population Interaction studies have only been performed in adults.

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

Breast feeding

Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast-feeding women unless the potential benefit for the mother justifies the potential risk to the baby

4.7 Effects on the ability to drive and use machines:

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that headache, paraesthesia and convulsions have been reported for meropenem.

4.8 Undesirable effects:

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting

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 Particulars:

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems,

ATC code: J01DH02

Mechanism 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).

5.2 Pharmacokinetic

properties Absorption

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 C_{max} 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 C_{max} 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.

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.

Biotransformation

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 –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

5.3 Pre-clinical Safety:

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 than 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 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:

Penem 1 g: Sterile sodium carbonate

6.2 Incompatibilities:

Nil

6.3 Shelf Life:

24 months.

6.4 Special Precautions for storage:

Store below 30°C temperature. Do not allow to freeze

6.5 Nature and contents of container:

20 ml tubular clear glass vial USP Type I sealed with grey bromo butyl rubber stopper and magenta colored flip off seal. (1 x1 Vial)

6.6 Special precautions for disposal and other handling

No Special Precautions for disposal and other handling

7. Marketing Authorization Holder:

Syner-Med Pharmaceuticals (Kenya)
Ltd. Gayatri House, P.O. Box No.:
52096-00200 ICD Road, Off. Mombasa
Road, Nairobi, Kenya Telephone: +254
733676310
E-Mail: regulatory@syner-medkenya.com

8. Marketing Authorization Number: -

H2010/20520/303

9. Date of first Authorization /renewal of the authorization:

6th May 2010

10. Date of revision of text:

14th August 2026