Size-110x220mm

MEROPENEM

MPEN 1000

1 g Powder for Injection (I.V.)
Antibacterial (Carbapenem)

FORMULATION:
Each vial contains:
Sterile Meropenem Trihydrate USP
Eq. to Anhydrous Meropenem 1g
Each ampoule contains:
Sterile Water for Injection.....10mL

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems.

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.

PRODUCT DESCRIPTION:
Off white powder filled in clear glass sealed vials.
Meropenem for injection is a sterile, pyrogen-free, synthetic, **ultra-broadspectrum**, **Carbapenem antibiotic** for intravenous administration. It is Chemically (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-2-carboxylic acid, trihydrate. Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria.

PHARMACOKINETICS:
After intravenous injection of meropenem 0.5g and 1g over 5 minutes, peak plasma concentrations of about 50 and 112 micrograms/mL respectively are attained. The same doses infused over 30 minutes produce peak plasma concentrations of 23 and 49 micrograms/mL, respectively.
Meropenem has a plasma elimination half-life of about 1 hour; this may be prolonged in patients with renal impairment and is also slightly prolonged in children. Meropenem is widely distributed in body tissues and fluids including the CSF and bile. It is about 2% bound to plasma proteins. It is more stable to renal dehydropeptidase I than imipenem and is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% of a dose is recovered unchanged in the urine over a 12-hour period and urinary concentrations above 10 micrograms/mL are maintained for up to 5 hours after a 500-mg dose. Meropenem is reported to have one metabolite (ICI-213689), which is inactive and is excreted in the urine.
Meropenem is removed by haemodialysis.

MECHANISM OF ACTION:
Meropenem is a broad-spectrum carbapenem antibiotic. It is active against Gram-positive and Gram-negative bacteria. The bactericidal activity of Meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of Escherichia coli and Pseudomonas aeruginosa; and PBPs 1, 2 and 4 of Staphylococcus aureus.

Meropenem has significant stability to hydrolysis by beta-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria. Meropenem has significant stability to hydrolysis by beta-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive (except methicillin-resistant staphylococci (MRSA) and Gram-negative bacteria. In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa.

INDICATIONS:
It is used in the treatment of susceptible infections, including intra-abdominal infections, meningitis, respiratory tract infections (including cystic fibrosis patients), septicaemia, skin infections, urinary tract infections, and infections in immunocompromised patients.

DOSAGE AND ADMINISTRATION:
Route of Administration: For I.V. use only
Meropenem is given intravenously as the trihydrate, but doses are expressed in terms of the amount of anhydrous meropenem; 1.14 g of meropenem trihydrate is approximately equivalent to 1 g of anhydrous meropenem. It is given by slow injection over 3 to 5 minutes or by infusion over 15 to 30 minutes in a usual adult dose of 0.5 to 1 g every 8 hours, increased to 2 g every 8 hours for meningitis; doses of up to 2 g every 8 hours have also been used in cystic fibrosis.

In Renal Impairment: Children over 3 months of age and weighing less than 50 kg may be given 10 to 20 mg/kg every 8 hours, increased to 40 mg/kg every 8 hours for meningitis. Doses of 25 to 40 mg/kg every 8 hours have been used in children aged 4 to 18 years with cystic fibrosis.

DIRECTION FOR RECONSTITUTION:
For Intravenous Administration: Constitute Meropenem 1 g with Sterile Water for Injection provided with this pack. The reconstituted solution should be used immediately after preparation.

ADVERSE DRUG REACTIONS:
Meropenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits this enzyme, is not required. Meropenem may have less potential to induce seizures than imipenem.

CONTRAINDICATIONS:
Meropenem is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or Beta-lactamase inhibitors.

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.

Enterobacteriaceae, Pseudomonas aeruginosa and *Acinetobacter spp* resistance.

Resistance to penems of Enterobacteriaceae, Pseudomonas aeruginosa, 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
As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported.
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. 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
Seizures have infrequently been reported during treatment with carbapenems, including meropenem.

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

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.

Direct antiglobulin test (Coombs test) seroconversion
A positive direct or indirect Coombs test may develop during treatment with meropenem.

Concomitant use with valproic acid/sodium valproate/valpromide
The concomitant use of meropenem and valproic acid/sodium valproate/valpromide is not recommended.

Paediatric population
Meropenem is licensed for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.
This medicinal product contains 90 mg sodium per dose, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum daily dose of this product is equivalent to $\geq$ 27% of the WHO recommended maximum daily intake for sodium.
Meropenem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

DRUG INTERACTIONS:
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.

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 Normalized Ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

Paediatric population
Interaction studies have only been performed in adults.

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

Breastfeeding
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.

OVERDOSE AND TREATMENT:
Relative overdose may be possible in patients with renal impairment if the dose is not adjusted. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile, 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.

STORAGE CONDITION:
Store at temperatures not exceeding 30^{0}C. Keep out of reach of children.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Patient should seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY:
USP Type III glass vial x 20 mL + Ampoule Sterile Water for Injection x 10 mL (diluent) (Box of 1's)

DRP-10484
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