PACKAGE INSERT TEMPLATE FOR MEROPENEM POWDER FOR INTRAVENOUS INJECTION & INFUSION

Brand or Product Name
[Product name] Powder for IV Injection & Infusion 500mg
[Product name] Powder for IV Infusion & Infusion 1000mg

Name and Strength of Active Substance(s)
Meropenem trihydrate…mg equivalent to 500mg meropenem
Meropenem trihydrate…mg equivalent to 1000mg meropenem

Product Description
[Visual description of the appearance of the product (eg colour, odour etc)
eg White to pale yellow crystalline powder. Upon reconstitution, meropenem powder yields a clear solution]

Pharmacodynamics

Meropenem is a carbapenem antibiotic for parenteral use, that is relatively stable to human dehydropeptidase-1 (DHP-1) and therefore, does not require the addition of an inhibitor of DHP-1.
Meropenem exerts bactericidal activity by inhibiting cell wall synthesis by penetrating the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding–protein (PBP) targets. Its strongest affinity is toward PBPs 2, 3, and 4 of Escherichia coli and Pseudomonas aeruginosa, and PBPs 1, 2, and 4 of Staphylococcus aureus. Bactericidal concentrations are typically one to two times the bacteriostatic concentrations; the exception is Listeria monocytogenes, against which lethal activity has not been observed. Similar to imipenem, the antibacterial action of meropenem is related to binding of the drug to penicillin binding proteins (PBPs) of gram-positive and gram-negative organisms. The high resistance of meropenem to most bacterial beta-lactamases and good penetration of the drug through the outer membrane also contribute significantly to antimicrobial activity. Meropenem may be less of an inducer of beta-lactamases than imipenem.

Pharmacokinetics

Absorption
Peak Concentration: dependent on dose, renal function, and administration technique
The time to peak concentration following intravenous administration is approximately 1 hour (range: 0.5 - 1.5 hours) after the start of the infusion

Distribution

Plasma protein binding of meropenem is approximately 2%.
Meropenem achieves concentrations that match or exceed those required to inhibit most susceptible bacteria in most body fluids and tissues including cerebrospinal fluid. Peak concentrations in body fluids were mostly achieved in 1 hour following intravenous infusion
The volume of distribution is 12 to 20 L

Metabolism
Extrarenal, 20% to 25% Increases up to 50% in patients with creatinine clearance of less than 20 mL/minute . There is one metabolite, which is inactive, ICI-213689

Elimination
Approximately 70% of a meropenem dose administered intravenously is recovered unchanged in the urine over 12 hours. The clearance of meropenem from plasma correlates with the creatinine clearance. There is no accumulation of repeated doses of meropenem 500 mg every 8 hours or 1 gram every 6 hours in patients with normal renal function. Dose adjustments are necessary in patients with renal impairment

Elimination Half-life
- Adults and children age 2 years and older: 1 hour
- Children age 3 months to 2 years: 1.5 hours
- Preterm neonates (27 to 32 weeks gestational age, 21 days mean postnatal age): 3.4 hours
- Impaired renal function: 3.4 to 20 hours or longer

Indication

Meropenem is indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem.
- Pneumonias and Nosocomial pneumonias
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections, such as endometritis and pelvic inflammatory disease.
- Bacterial Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

Meropenem has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

Recommended Dosage
The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient.
The recommended daily dosage is as follows:-
500 mg IV every 8 hours in the treatment of pneumonia, UTI and gynaecological infections such as endometritis.
1 g IV every 8 hours in the treatment of hospital acquired pneumonias, peritonitis, presumed infections in febrile neutropenic patients, septicaemia.
In meningitis the recommended dosage is 2g every 8 hours.
As with other antibiotics, particular caution is recommended in using meropenem as monotherapy in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infection.
Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infection.

Dosage Schedule for Adults with Impaired Renal Function
Dosage should be reduced in patients with creatinine clearance less than 51 ml/min, as scheduled below:

Creatinine Clearance (ml/min)	**Dose (based on unit doses of 500mg, 1g, 2g)**	**Frequency**
26-50	one unit dose	every 12 hours
10-25	one-half unit dose	every 12 hours
<10	one-half unit dose	every 24 hours

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

Children
For children over 3 months and up to 12 years of age the recommended dose is 10 - 20 mg/kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient. In children over 50 kg weight, adult dosage should be used.

In meningitis the recommended dose is 40 mg/kg every 8 hours.

Febrile episodes in neutropenic patients-the dose should be 20mg/kg every 8 hours.

There is no experience in children with renal impairment.
***Meropenem can be given either as an intravenous bolus injection (over approx. 5 minutes) or by intravenous infusion (over approx. 15 to 30 minutes).*

Mode of Administration
Intravenous injection and infusion

Contraindications

- anaphylactic reaction to beta-lactam antibiotics
- hypersensitivity to meropenem or any component of the product or other drugs in the same class (carbapenems)

Warnings and Precautions

There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins. As with all beta-lactam antibiotics, rare hypersensitivity reactions have been reported. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. Meropenem should be used with caution in patients with such a history. If an allergic reaction to meropenem occurs, the drug should be discontinued and appropriate measures taken.

Use of meropenem in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels.

As with other antibiotics, overgrowth of non-susceptible organisms may occur and, therefore, continuous monitoring of each patient is necessary.

Use in infections caused by methicillin resistant staphylococci is not recommended.

Rarely, pseudomembranous colitis has been reported on meropenem as with practically all antibiotics and may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastro-intestinal complaints, particularly colitis.

It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea in association with the use of meropenem. Although studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis, other causes should be considered.

The co-administration of meropenem with potentially nephrotoxic drugs should be considered with caution.

Meropenem may reduce serum valproic acid levels. Sub-therapeutic levels may be reached in some patients.

*Paediatric use :*Efficacy and tolerability in infants under 3 months old have not been established; therefore, meropenem is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.

Effects on Ability to Drive and Use Machines
No data is available, but it is not anticipated that meropenem will affect the ability to drive and use machines.

Interactions with Other Medicaments

- Concurrent use of meropenem and valproic acid may result in decreased valproic acid plasma concentrations and loss of anticonvulsant effect.
- Concurrent use of meropenem and probenecid may result in increased plasma concentrations of meropenem
- Concurrent use of live typhoid vaccine and antibiotics may result in a decreased immunological response to the typhoid vaccine.

Statement on Usage During Pregnancy and Lactation

Pregnancy
The safety of Meropenem in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing foetus. Meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician.

Lactation
Meropenem is detectable at very low concentrations in animal breast milk. Meropenem should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

Adverse Effects / Undesirable Effects

- Immunologic Effects: rarely, systemic allergic reactions (hypersensitivity) which may include angioedema and manifestations of anaphylaxis.
- Dermatologic Effects: Thrombophlebitis, injection site pain & inflammation, rash, pruritus, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis
- Gastro-intestinal Effects: abdominal pain, nausea, vomiting, diarrhoea.
- Hematologic Effects: Reversible thrombocythaemia, eosinophilia, thrombocytopenia, leucopenia and neutropenia (including very rare cases of agranulocytosis), haemolytic anaemia, bleeding

- Hepatic Effects : Increases in serum concentrations of bilirubin, transaminases, alkaline phosphatase and lactic dehydrogenase alone or in combination
- Central nervous system Effects: headache, paraesthesiae, seizure(convulsions)
- Other: Oral and vaginal candidosis.

Overdose and Treatment

Treatment is symptomatic and supportive. There is no known antidote.
Rapid renal elimination will occur in patients without renal impairment.
Haemodialysis will remove meropenem and its metabolite in patients with renal impairment.

Incompatibilities
[To add appropriate information based on formulation]

Instructions for Use
[To add appropriate information and graphic]

Storage Conditions
[Store below …. ℃]

Dosage Forms and Packaging Available
[Packaging type & pack size eg 10 ml type I clear glass vial, capped with a butyl rubber stopper/box]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]