INSERT MEROSAN
(29 SEP '20) - Exp. Malaysia
Depan

Controlled Medicine

MEROSAN®

Sterile powder for injection

Meropenem for Injection USP

MEROSAN 0.5 g Sterile powder for injection
Each vial contains:
Meropenem Trihydrate equivalent to 500 mg of Anhydrous Meropenem

MEROSAN 1 g Sterile powder for injection
Each vial contains:
Meropenem Trihydrate equivalent to 1 g of Anhydrous Meropenem

Specification: **USP**

PRODUCT DESCRIPTION
White to pale yellow powder, has characteristic odor; and clear, colorless to pale yellow solution with characteristic odor after reconstituted with water for injection.

PHARMACODYNAMICS
Meropenem is a carbapenem antibiotic for parenteral use which 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

INDICATIONS
MEROSAN Sterile Powder for Injection 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.

MEROSAN Sterile Powder for Injection is efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections

CONTRAINDICATIONS
- Anaphylactic reaction to beta-lactam antibiotics.
- Hypersensitivity to meropenem or any component of the product or other drugs in the same class (carbapenems).

ADVERSE EFFECTS
- Immunologic Effects: rarely, systemic allergic reactions (hypersensitivity) which may include angioedema and manifestations of anaphylaxis.
- Dermatologic Effects: Thrombophlebitis, injection site pain and 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 candidiasis.

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.
In the event of an overdose, meropenem should be discontinued and general supportive treatment given until renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdose.

WARNING AND PRECAUTIONS
- There is some clinical and laboratory evidence of partial cross-allergenicity between other carba-penems 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 hyper-sensitivity 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 trans-aminase and bilirubin levels.
- As with other antibiotics, overgrowth of non-sus-ceptible organisms may occur and, therefore, continous 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 com-plaints, particularly colitis.
- It is important to consider the diagnosis of pseudo-membranous 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.
- Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with **MEROSAN** Sterile Powder for Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, **MEROSAN** Sterile Powder for Injection must be discontinued immediately and appropriate alternative therapy instituted.

INTERACTIONS WITH OTHER MEDICAMENTS
- Concurrent use of meropenem and valproic acid may result in decreased valproic acid plasma concen-trations and loss of anticonvulsant effect.
- Concurrent use of meropenem and probenecid may result in increased plasma concentrations of mero-penem.
- Concurrent use of live typhoid vaccine and antibiotics may result in a decreased immunological response to the typhoid vaccine.

Country:	Packaging:	Dimension:	Material:	Color:	Scale:
Malaysia	Insert	209 x 193 mm (double side printing)	HVS paper 60 g	BLACK	100%

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Belakang

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.

EFFECTS ON 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 **MEROSAN**.

RECOMMENDED DOSE

Adults

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 I.V. every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis.
- 1 g I.V. every 8 hours in the treatment of hospital acquired pneumonias, peritonitis, presumed infections in febrile neutropenic patients, septicaemia.
- In meningitis the recommended dosage is 2 g every 8 hours.
- 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*.
- Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infection.
- There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.

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. There are limited data to support the application of these dose adjustments for a unit dose of 2 g.

Creatinine clearance (mL/min)	Dose (based on unit doses of 500 mg, 1 g, 2 g)	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

MEROSAN Powder for Injection is cleared by haemodialysis and haemofiltration; if continued treatment with Meropenem I.V. is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of **MEROSAN** Powder for Injection in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency.

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 20 mg/kg every 8 hours.

There is no experience in children with renal impairment.

There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.

Method of Administration

MEROSAN Powder for Injection can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available pre-sentations.

MEROSAN Powder for Injection to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 mL per 250 mg Meropenem). This provides an approximate concentration of 50 mg/mL. Constituted solutions are clear, and colourless or pale yellow.

For intravenous bolus injection administration, this product should be constituted with water for injections as shown in following table:

Vial content	Amount of diluent added (mL)	Appoximate withdrawable volume (mL)	Appoximate average concentration (mg/mL)
500 mg	10	10	50
1 g	20	20	50

MEROSAN for I.V. infusion may be directly constituted with compatible infusion fluids below:

1) Constituted with water for injections
2) Solutions (1 - 20 mg/ml) prepared with:

Sodium Chloride 0.9%, Glucose 5%, Glucose 10%, Glucose 5% and Sodium Chloride 0.9%, Glucose 5% and Sodium Chloride 0.45%, Glucose 5% and Sodium Chloride 0.225%, Ringer Lactate and Glucose 5%, Ringer Lactate, Mannitol 2.5%

Alternatively, an injection vial may be constituted, then the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid in table above.

It is recommended to use freshly prepared solutions of Meropenem for I.V. injection and infusion.
Constituted solution are clear and colorless or pale yellow.

Shake constituted solution before use.

DOSAGE FORMS AND PACKAGING AVAILABLE

MEROSAN 0.5 g Sterile Powder for Injection
Box of 1 vial @ 0.5 g.
Lic. No. : DKL0722244144A1
MAL No.: MAL16105028AZ

MEROSAN 1 g Sterile Powder for Injection
Box of 1 vial @ 1 g.
Lic. No. : DKL0722244144B1
MAL No.: MAL16105029AZ

SHELF LIFE AND STORAGE CONDITION

Before Reconstitution:

Store dry powder at temperature below 30°C. Do not freeze. The shelf life of **MEROSAN** Sterile Powder for Injection is 24 months.

After Reconstitution:

a. Intravenous bolus injection administration
Reconstituted solution in water for injection is stable for 2 hours at temperature 15° - 25°C or for 12 hours in a refrigerator (2° - 8°C). Discard any unused solutions after these periods.

b. Intravenous infusion administration
Constituted solutions maintain satisfactory potency at 15° - 25°C or under refrigeration (2° - 8°C) as shown in the stability table below. Discard any unused solutions after these periods.

Diluent	Hours stable	
	15° - 25°C	2° - 8°C
Constituted with water for injections	2	12
Solutions (1 - 20 mg/mL) prepared with:		
- Sodium Chloride 0.9%	4	24
- Glucose 5%	1	4
- Glucose 10%	1	2
- Glucose 5% and Sodium Chloride 0.9%	1	2
- Glucose 5% and Sodium Chloride 0.45%	2	4
- Glucose 5% and Sodium Chloride 0.225%	2	4
- Ringer Lactate and Glucose 5%	1	4
- Ringer Lactate	4	12
- Mannitol 2.5%	2	16

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in the table above.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARIPADA KANAK-KANAK

Name & Address of Manufacturer:
PT SANBE FARMA
Jalan Mahar Martanegara No. 162 (Jl. Leuwigajah No. 162)
RT.01 RW. 12 Kelurahan Baros, Kecamatan Cimahi Tengah,
Kota Cimahi, Indonesia

Name & Address of Product Registration Holder:
Medispec (M) Sdn. Bhd.
55 & 57, Lorong Sempadan 2 (Off Boundary Road),
11400 Ayer Itam, Pulau Pinang, Malaysia

Date of Revision of Package Insert:
07/10/2021

* BF 446 - EMY3

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Malaysia	Insert	209 x 193 mm (double side printing)	HVS paper 60 g	BLACK	100%