PT PFIZER INDONESIA
Local Product Document

Generic Name: Meropenem
Trade Name: MERONEM®
CDS Effective Date: October 31, 2018
Supersedes: January 10, 2018

Qualitative and quantitative composition

MERONEM® is presented as a sterile white powder containing meropenem; 500 mg or 1 g as the trihydrate blended with anhydrous sodium carbonate for constitution. MERONEM® injection contains 208 mg sodium carbonate for each gram of meropenem (anhydrous potency).

Vial for I.V. injection or infusion	**MERONEM® 500 mg**	**MERONEM® 1 g**
Active ingredient:		
Meropenem (as the trihydrate)	570 mg	1.14 g
Equivalent to anhydrous meropenem	500 mg	1 g
Excipient:		
Anhydrous sodium carbonate	104 mg	208 mg

For each gram of meropenem (anhydrous potency) the vial contains 90 mg (3.9 mmol) of sodium.

Pharmaceutical form
Powder for constitution for intravenous administration.

Therapeutic indications
MERONEM® 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
- Skin and skin structure infections
- Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in adult patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

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

There is no experience in paediatric patients with neutropenia or primary or secondary immunodeficiency.

Posology and method of administration

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 IV every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis, skin and skin structure infections.

1 g IV every 8 hours in the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients, septicaemia.

In meningitis the recommended dosage is 2 g every 8 hours.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa,* a dose of at least 1 g every 8 hours in adults (maximum approved dose is 6 g daily given in 3 divided doses) and a dose of at least 20 mg/kg every 8 hours in children (maximum approved dose is 120 mg/kg daily given in 3 divided doses) are recommended.

Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infection.

MERONEM® should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes. There is limited safety data available to support the administration of a 2 g bolus dose.

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 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

MERONEM® is cleared by haemodialysis and haemofiltration; if continued treatment with MERONEM® is necessary, the unit dose based on the infection type and severity is recommended at the completion of the haemodialysis procedure to re-institute effective treatment.

There is no experience with peritoneal dialysis.

Dosage in adults with hepatic insufficiency

No dosage adjustment is necessary in patients with hepatic impairment.

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, the known or suspected susceptibility of the pathogen(s) 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. There is no experience in children with renal impairment.

MERONEM® should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes. There is limited safety data available to support the administration of a 40 mg/kg bolus dose.

Constitution and compatibility
MERONEM® to be used for bolus intravenous injection should be constituted with sterile water for injections (10 mL per 500 mg). This provides an approximate available concentration of 50 mg/mL. Constituted solutions are clear or pale yellow.

For intravenous infusion MERONEM® vials may be directly constituted with a compatible infusion fluid (as listed in *Special precautions for storage*) and then further diluted with the compatible infusion fluid, as needed.

Freshly prepared solutions of MERONEM® should be used whenever possible. However, constituted solutions of MERONEM® maintain satisfactory potency at room temperature (15-25°C) or under refrigeration (4°C) as shown in *Special precautions for storage*.

MERONEM® should not be mixed with or physically added to solutions containing other drugs. Solutions of MERONEM® should not be frozen.

Contraindications
MERONEM® is contraindicated in patients who have demonstrated hypersensitivity to this product.

Special warnings and precautions for use
Patients who have a history of hypersensitivity to carbapenems, penicillins or other β-lactam antibiotics may also be hypersensitive to MERONEM®. As with all β-lactam antibiotics rare hypersensitivity reactions (serious and occasionally fatal) have been reported (see Undesirable effects).

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving MERONEM® (see Undesirable effect). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and alternative treatment should be considered.

As with other antibiotics, overgrowth of non-susceptible organisms may occur and repeated evaluation of each patient is necessary.

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

Rarely, pseudomembranous colitis has been reported on MERONEM® 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 MERONEM®. 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 concomitant use of valproic acid/sodium valproate and MERONEM® is not recommended. MERONEM® may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients (see *Interaction with other medicinal products and other forms of interaction*).

Paediatric use

Efficacy and tolerability in infants under 3 months old have not been established; therefore, MERONEM® is not recommended for use below this age.

Use in patients with renal insufficiency: Refer to dosage recommendations for MERONEM®.

Use in patients with liver disease: Patients with pre-existing liver disorders should have liver function monitored during treatment with MERONEM®.

A positive direct or indirect Coombs test may develop.

Interaction with other medicinal products and other forms of interaction

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion, with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of MERONEM® dosed without probenecid are adequate, the co-administration of probenecid with MERONEM® is not recommended. The potential effect of MERONEM® on the protein binding of other drugs or metabolism has not been studied. However, the protein binding of MERONEM® 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 MERONEM® in patients stabilised on valproic acid is not considered to be manageable and therefore should be avoided (see *Special warnings and precautions for use*).

MERONEM® has been administered concomitantly with other medications without adverse pharmacological interactions. However, no specific drug interactions studies other than probenecid were conducted.

Pregnancy and lactation

Pregnancy

The safety of MERONEM® in human pregnancy has not been established although animal studies have not shown an adverse effect on the developing foetus. MERONEM® should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

Lactation

Meropenem has been reported to be excreted in human milk. MERONEM® should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

Effect on ability to drive or operate machinery

No studies 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 MERONEM®.

Undesirable effects

MERONEM® is generally well tolerated. Adverse reactions rarely lead to cessation of treatment. Serious adverse reactions are rare.

The following adverse reactions have been identified following clinical studies and post-marketing experience with MERONEM®.

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
Infections and infestations		Oral and vaginal candidiasis			
Blood and lymphatic system disorders	Thrombocythaemia	Thrombocytopenia, Neutropenia, Leucopenia, Eosinophilia	Agranulocytosis*	Haemolytic anaemia*	
Immune system disorders				Manifestations of anaphylaxis*	Angioedema*
Psychiatric disorders			Delirium*		
Nervous system disorders	Headache	Paraesthesia	Convulsions		

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea				Pseudomembranous colitis*
Hepatobiliary disorders	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Gamma-glutamyltransferase increased	Blood bilirubin increased			
Skin and subcutaneous tissue disorders	Rash, Pruritus	Urticaria		Toxic epidermal necrolysis*, Stevens Johnson syndrome*, Erythema multiforme*	Drug Reaction with Eosinophilia and Systemic Symptoms*, Acute generalised exanthematous pustulosis*
General disorders and administration site conditions	Inflammation, Pain	Thrombophlebitis			

*ADR identified post-marketing.

Overdose

Intentional overdosing of MERONEM® is unlikely, although overdosing could occur particularly in patients with renal impairment. Limited post-marketing experience indicates that if adverse events occur following over dosage, they are consistent with the adverse event profile described in *Undesirable effects*, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In normal individuals rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

Pharmacological properties

Pharmacodynamic properties

Meropenem is a carbapenem antibiotic for parenteral use, that is relatively stable to human dehydropeptidase-1(DHP-1). It is structurally similar to imipenem.

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all serine β -lactamases and its marked affinity for the Penicillin Binding Proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. The bactericidal concentrations are generally within one doubling dilution of the minimum inhibitory concentrations (MICs).

Meropenem is stable in susceptibility tests and these tests can be performed using normal routine methods. *In vitro* tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect against Gram-positive and Gram-negative organisms.

Mechanisms of resistance

Bacterial resistance to meropenem may result from one or more factors: (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 β-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

The susceptibility to meropenem of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

The antibacterial spectrum of meropenem includes the following species, based on clinical experience and therapeutic guidelines.

Commonly susceptible species: Gram-positive aerobes

Enterococcus faecalis (note that *E. faecalis* can naturally display intermediate susceptibility), *Staphylococcus aureus* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSA are resistant to meropenem), *Staphylococcus* species including *Staphylococcus epidermidis* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSE are resistant to meropenem), *Streptococcus agalactiae* (Group B streptococcus), *Streptococcus milleri* group (*S. anginosus, S. constellatus,* and *S. intermedius*), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (Group A streptococcus)

Commonly susceptible species: Gram-negative aerobes

Citrobacter freundii, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus vulgaris*, *Serratia marcescens*

Commonly susceptible species: Gram-positive anaerobes

Clostridium perfringens, *Peptoniphilus asaccharolyticus*, *Peptostreptococcus* species (including *P. micros*, *P anaerobius*, *P. magnus*)

Commonly susceptible species: Gram-negative anaerobes
Bacteroides caccae, *Bacteroides fragilis, Prevotella bivia*, *Prevotella disiens*

Species for which acquired resistance may be a problem: Gram-positive aerobes
Enterococcus faecium (*E. faecium* can naturally display intermediate susceptibility even without acquired resistance mechanisms.

Species for which acquired resistance may be a problem: Gram-negative aerobes
Acinetobacter species, *Burkholderia cepacia*, *Pseudomonas aeruginosa*

Inherently resistant organisms: Gram-negative aerobes
Stenotrophomonas maltophilia, *Legionella* species

Other inherently resistant organisms
Chlamydophila pneumoniae, *Chlamydophila psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae*

The published medical microbiology literature describes *in-vitro* meropenem-susceptibilities of many other bacterial species. However the clinical significance of such in-vitro findings is uncertain. Advice on the clinical significance of in-vitro findings should be obtained from local infectious diseases and clinical microbiology experts and local professional guidelines.

Meropenem is active *in vitro* against many strains resistant to other β-lactam antibiotics. This is explained in part by enhanced stability to β-lactamases. Activity *in vitro* against strains resistant to unrelated classes of antibiotics such as aminoglycosides or quinolones is common.

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.

Stenotrophomonas maltophilia, Enterococcus faecium and methicillin-resistant staphylococci have been found to be resistant to meropenem.

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 and the mean clearance is 239 mL/min at 500 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.

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. 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 β-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.

Renal insufficiency
Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

Hepatic insufficiency
A study in patients with alcoholic cirrhosis has shown no effect of liver disease on the pharmacokinetics of meropenem after repeated doses.

Paediatrics
Studies in children have shown that the pharmacokinetics of MERONEM IV in children is similar to those in adults. The elimination half-life for meropenem was approximately 1.5 to 2.3 hours in children under the age of 2 years and the pharmacokinetics is linear over the dose range of 10 to 40 mg/kg.

Elderly
Pharmacokinetic studies in the 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 with normal renal function or creatinine clearance values above 50 mL/min (see *Posology and method of administration*).

Preclinical safety data
Animal studies indicate that meropenem is well tolerated by the kidney. In animal studies meropenem has shown nephrotoxic effects, only at high dose levels (500 mg/kg).

Meropenem is generally well tolerated by the CNS. Effects were seen only at very high doses of 2000 mg/kg and above.

The IV LD_{50} 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 small decrease in red cell parameters and an increase in liver weight in dogs treated with doses of 500 mg/kg.

There was no evidence of mutagenic potential in the 5 tests conducted and no evidence of reproductive and teratogenic toxicity in studies at the highest possible doses in rats and monkeys; the no effect dose level of a (small) reduction in F_1 body weight in rats was 120 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.

Pharmaceutical particulars

List of excipients
Anhydrous sodium carbonate.

Incompatibilities
MERONEM® is compatible with the infusion fluids listed in *Special precautions for storage.*
MERONEM® should not be mixed with or physically added to solutions containing other drugs.

Special precautions for storage
Do not store above 30°C.
Do not freeze.

A solution for bolus injection is prepared by dissolving the drug product MERONEM® in water for injection to a final concentration of 50 mg/mL Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 16 hours under refrigerated conditions (2-8ºC).

A solution for infusion is prepared by dissolving the drug product MERONEM® in either 0.9% sodium chloride solution for infusion or 5% glucose (dextrose) solution for infusion to a final concentration of 1 to 20 mg/mL. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 15 hours under refrigerated conditions (2-8ºC). Constituted solutions of MERONEM® in 5% glucose (dextrose) solution should be used immediately.

The constituted solutions should not be frozen.

From a microbiological point of view, unless the method of opening/constitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Instructions for use/handling

Refer to *Posology and method of administration* and *Special precautions for storage*. Shake constituted solution before use.

All vials are for single use only.

Standard aseptic technique should be employed during constitution and administration.

Supply
MERONEM® (500 mg): vial in boxes of 10 (Reg. No.: DKI1814500644A1)
MERONEM® (1.0 g): vial in boxes of 10 (Reg. No.: DKI1814500644B1)

HARUS DENGAN RESEP DOKTER

Manufactured by:
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