# Mapenem

MAPENEM (500 MG INJECTION), MAPENEM (1 G INJECTION)

**PRODUCT NAME**

MAPENEM (500 MG INJECTION) (Powder for solution for injection or infusion)
MAPENEM (1 G INJECTION) (Powder for solution for injection or infusion)

**NAME AND STRENGTH OF ACTIVE SUBSTANCE AND EXCIPIENT**

**MAPENEM (500 MG INJECTION)**

Each vial contains
Meropenem trihydrate equivalent to Meropenem 500 mg and 104 mg of anhydrous sodium carbonate.
For each 500 mg of Meropenem (anhydrous potency), the vial contains sodium 45 mg (1.95 millimole).

**MAPENEM (1 G INJECTION)**

Each vial contains
Meropenem trihydrate equivalent to Meropenem 1 g and 208 mg of anhydrous sodium carbonate.
For each 1 g of Meropenem (anhydrous potency), the vial contains sodium 90 mg (3.9 millimole).

**DOSAGE FORM**

Sterile powder for injection or infusion

**PRODUCT DESCRIPTION**

MAPENEM INJECTION is presented as a white to off-yellow crystalline powder. Constituted solutions are clear colorless to yellowish and no visible matter.

**PHARMACODYNAMICS**

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).

**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.

**Mechanism of resistance**

Bacterial resistance to meropenem may result from: (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 beta-lactamases that can hydrolyse carbapenems.
Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.
There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

**Breakpoints**

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

**EUCAST clinical MIC breakpoints for meropenem (2013-02-11, v 3.1)**

| Organism | Susceptible (S) (mg/l) | Resistant (R) (mg/l) |
|---|---|---|
| *Enterobacteriaceae* | ≤ 2 | > 8 |
| *Pseudomonas* spp. | ≤ 2 | > 8 |
| *Acinetobacter* spp. | ≤ 2 | > 8 |
| *Streptococcus groups* A, B, C and G | note 6 | note 6 |
| *Streptococcus pneumoniae*[1] | ≤ 2 | > 2 |
| *Viridans* group *streptococci*[2] | ≤ 2 | > 2 |
| *Enterococcus* spp. | -- | -- |
| *Staphylococcus* spp. | note 3 | note 3 |
| *Haemophilus influenzae*[1, 2] and *Moraxella catarrhalis*[2] | ≤ 2 | > 2 |
| *Neisseria meningitidis*[2,4] | ≤ 0.25 | > 0.25 |
| Gram-positive anaerobes except *Clostridium difficile* | ≤ 2 | > 8 |
| Gram-negative anaerobes | ≤ 2 | > 8 |
| *Listeria monocytogenes* | ≤ 0.25 | > 0.25 |
| Non-species related breakpoints[5] | ≤ 2 | > 8 |

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).
[2] Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.
[3] Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.
[4] Breakpoints relate to meningitis only.
[5] Non-species related breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.
[6] The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.

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.
The following table of pathogens listed is derived from clinical experience and therapeutic guidelines.

**Commonly susceptible species**

**Gram-positive aerobes**
*Enterococcus faecalis*[§], *Staphylococcus aureus* (methicillin-susceptible)[£], *Staphylococcus* species (methicillin-susceptible) including *Staphylococcus epidermidis*, *Streptococcus agalactiae* (Group B), *Streptococcus milleri* group (*S. anginosus*, *S. constellatus*, and *S. intermedius*), *Streptococcus pneumonia*, *Streptococcus pyogenes* (Group A)

**Gram-negative aerobes**
*Citrobacter freudii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenza*, *Klebsiella oxytaca*, *Klebsiella pneumonia*, *Morganella morganii*, *Neisseria meningitides*, *Proteus mirabilis*, *Proteus vulgaris*, *Serratia marcescens*

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

**Gram-negative anaerobes**
*Bacteroides caccae*, *Bacteroides fragilis* group, *Prevotella bivia*, *Prevotella disiens*

**Species for which acquired resistance may be a problem**

**Gram-positive aerobes**
*Enterococcus faecium*[£†]

**Gram-negative aerobes**
*Acinetobacter* species, *Burkholderia cepacia*, *Pseudomonas aeruginosa*

**Inherently resistant organisms**

**Gram-negative aerobes**
*Stenotrophomonas maltophilia*, *Legionella* species

**Other micro-organisms**
*Chlamydophila pneumonia*, *Chlamydophila psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae*

[§] Species that show natural intermediate susceptibility
[£] All methicillin-resistant staphylococci are resistant to meropenem
[†] Resistance rate ≥ 50% in one or more EU countries.

Glanders and melioidosis: Use of meropenem in humans is based on *in vitro B.mallei* and *B. pseudomallei* susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis.

**PHARMACOKINETICS**

**Absorption**

A 30-minute intravenous infusion of a single dose of meropenem in patients results in peak plasma levels of approximately 11 µg/mL for the 250 mg dose, 23 µg/mL for the 500 mg dose and 49 µg/mL for the 1g dose.
However, there is no absolute pharmacokinetic proportionality with the administered dose both as regards $C_{max}$ and AUC. Furthermore, a reduction in plasma clearance from 239 to 205 mL/min for the range of dosage 500 mg to 2 g has been observed.
A 5-minute intravenous bolus injection of meropenem IV in patients results in peak plasma levels of approximately 52 µg/mL for the 500 mg dose and 112 µg/mL for the 1g dose. After an IV dose of 500 mg, plasma levels of meropenem decline to values of 1 µg/mL or less, 6 hours after administration.
When multiple doses are administered at 8 hourly intervals to patients with normal renal function, accumulation of meropenem does not occur.
In patients with normal renal function, meropenem's elimination half-life is approximately 1 hour.

**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.

**Metabolism**

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite. 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.

**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, usedvas monotherapy or in combination with anti-viral or anti-fungal agents.

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

**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 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.
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 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 |

Meropenem IV is cleared by haemodialysis and haemofiltration; if continued treatment with Meropenem IV 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 Meropenem IV in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency (See "Warning and Precautions").

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.

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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.
There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.
***Meropenem can be given either as an intravenous bolus injection (over approx. 5 minutes) or by intravenous infusion (over approx. 15 to 30 minutes).*

**ROUTE OF ADMINISTRATION**
Intravenous injection and infusion

**CONTRAINDICATION**
Hypersensitivity to Meropenem, any component of the formulation or hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).

**WARNING AND PRECAUTIONS**
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.

Hypersensitivity reactions
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 Mapenem Injection, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Mapenem Injection must be discontinued immediately and appropriate alternative therapy instituted.

*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.

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 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.
Meropenem contains sodium.

Paediatric use
Efficacy and tolerability in infants under 3 months old have not been established; therefore, Meropenem IV is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.
Keep all medicines away from children.

**INTERACTIONS WITH OTHER MEDICAMENTS**
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 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.

**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**
Meropenem injection is generally well tolerated. Adverse reactions rarely lead to cessation of treatment. Serious adverse reactions are rare. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1**

| System Organ Class | Frequency | Event |
|---|---|---|
| Infections and infestations | Uncommon | oral and vaginal candidiasis |
| Blood and lymphatic system disorders | Common | thrombocythaemia |
| | Uncommon | eosinophilia, thrombocytopenia, leucopenia, neutropenia |
| | Uncommon | agranulocytosis, haemolytic anaemia |
| Immune system disorders | Uncommon | angioedema, anaphylaxis |
| Nervous system disorders | Common | headache |
| | Uncommon | paraesthesiae |
| | Rare | convulsions |
| Gastrointestinal disorders | Common | diarrhoea, vomiting, nausea, abdominal pain |
| | Uncommon | antibiotic-associated colitis |
| Hepatobiliary disorders | Common | transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased. |
| | Uncommon | blood bilirubin increased |
| Skin and subcutaneous tissue disorders | Common | rash, pruritis |
| | Uncommon | urticaria |
| | Uncommon | toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme. |
| Renal and urinary disorders | Uncommon | blood creatinine increased, blood urea increased |
| General disorders and administration site conditions | Common | inflammation, pain |
| | Uncommon | thrombophlebitis |
| | Uncommon | pain at the injection site |

**Reporting of Suspected Adverse Reactions**
You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my
[Consumers →Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)]

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINE**
No studies on the effects 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, paraesthesiae and convulsions have been reported for meropenem.

**SYMPTOMS AND TREATMENT OF OVERDOSE**
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 described in section Side Effecs, 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.

**INCOMPATIBILITIES**
This medicinal product must not be mixed with other medicinal products except those mentioned in section *INSTRUCTIONS FOR USE*, compatible infusion fluids.

**INSTRUCTIONS FOR USE**

**IV bolus injection**
For IV bolus injection, 10 or 20 ml of sterile water for injection should be added to a vial labeled as containing 500 mg or 1 g respectively. The resulting solution will contain Meropenem approximately 50 mg/mL. The solution of Meropenem is clear and colorless or yellowish. (Stability after reconstitution; see table of Stability after Reconstitution).
The IV bolus injection should be given slowly over a period of 5 minutes.
Freshly prepared solution of Mapenem for IV injection and infusion is recommended to use. Unused portion of each vial should be discarded.
The solution of Meropenem should be inspected visually for particulate matter and discoloration prior to administration.

**IV infusion**
Preparation for IV infusion, Meropenem is dissolved in approximately 50-200 ml of one of the following appropriate infusion fluid: 5% dextrose in water and 0.9% sodium chloride solution. The resulting solution will contain Meropenem approximately 1-20 mg/mL (see table of Stability after Reconstitution).
The IV infusion should be infused by slow over a period of 15-30 minutes.
Freshly prepared solution of Mapenem for IV injection and infusion is recommended to use. Unused portion of each vial should be discarded.
The solution of Meropenem should be inspected visually for particulate matter and discoloration prior to administration.

**Stability after Reconstitution**

**IV bolus injection**

| Solvent for reconstituted | Keep in Room temperature (20-25°C) | Keep in Refrigerated (2-8°C) |
|---|---|---|
| Sterile water for injection 20 mL (50 mg/mL) | 1 hour | 8 hours |

**IV infusion**

| Solvent for reconstituted | Keep in Room temperature (20-25°C) | Keep in Refrigerated (2-8°C) |
|---|---|---|
| 0.9% Sodium chloride intravenous infusion (NSS) 50 mL (1-20 mg/mL) | 3 hours | 24 hours |
| 5% Dextrose in water (D5W) 50 mL (1-20 mg/mL) | Should be used immediately | |

**STORAGE CONDITIONS**
Keep out of reach of children.
Powder for injection: Store below 30°C
Solution of Meropenem should not be frozen.
Reconstituted solution: Store at recommended condition as specified in the table: Stability after Reconstitution

**SHELF LIFE**
Unopened: 2 years

**DOSAGE FORMS AND PACKAGING AVAILABLE**
Mapenem 500 mg X 20 mL (Type I clear glass vial with rubber closure and flip off aluminium cap)
Mapenem 1 g X 30 mL (Type I clear glass vial with rubber closure and flip off aluminium cap)

**DATE OF REVISION OF PI**
Date of revision: 14/08/2020

**Manufacturer:- SIAM BHEASACH CO., LTD.**
123 Soi Chokechairuammitr, Vibhavadi-Rangsit Road, Chomphon, Chatuchak, Bangkok 10900 and 9 Soi Chokechairuammitr 3, Vibhavadi-Rangsit Road, Dindang, Dindang, Bangkok 10400, Thailand.
**Product Registration Holder, Importer:- SPG PHARMA (MALAYSIA) SDN BHD**
Suite 1701, Block A, Damansara Intan e-Business Park, No. 1, Jalan SS20/27, 47400 Petaling Jaya, Selangor Darul Ehsan, Malaysia.

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