# Meropenem-AFT

***Meropenem 500 mg / 1 g powder for intravenous injection or infusion***

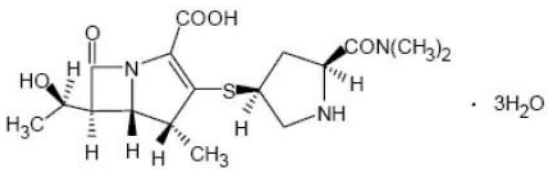
AFT Pharmaceuticals Ltd

## NAME OF THE MEDICINE

Meropenem, as meropenem trihydrate.

## DESCRIPTION

Structural Formula:




CAS Number: 119478-56-7 meropenem trihydrate.

Meropenem-AFT powder for intravenous injection or infusion is presented as a sterile, white to off-white powder containing meropenem trihydrate equivalent to meropenem, 500 mg or 1 g, blended with sodium carbonate anhydrous. Meropenem-AFT powder for intravenous injection or infusion contains 208 mg sodium carbonate anhydrous for each gram of meropenem (anhydrous potency). Constituted solutions are both clear and colourless to pale yellow.

| Meropenem-AFT powder for intravenous injection or infusion | 500 mg | 1 g |
|---|---|---|
| *Active Ingredient* | | |
| Meropenem (as the trihydrate) | 570.5 mg | 1.14 g |
| Equivalent to anhydrous meropenem | 500 mg | 1 g |
| *Excipient* | | |
| Sodium carbonate anhydrous | 104 mg | 208 mg |

## PHARMACOLOGY

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

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. Bactericidal concentrations are commonly the same as 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.

Meropenem is usually active, *in vitro* and in clinical infections, against the strains of bacteria shown below:

**Gram-positive aerobes**

*Enterococcus faecalis*, *Staphylococcus aureus* (penicillinase negative and positive), Staphylococci-coagulase-negative including *Staphylococcus epidermidis*, streptococci including *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus mitis*, *Streptococcus milleri*, *Streptococcus sanguis*, *Streptococcus viridans*.

**Gram-negative aerobes**

*Acinetobacter anitratus*, *Citrobacter* spp., including *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, and other *Enterobacter* spp., *Escherichia coli*, *Haemophilus influenzae* (including β-lactamase positive strains), *Moraxella (Branhamella) catarrhalis*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, and other *Klebsiella* spp., *Morganella morganii*, *Proteus mirabilis*, *Serratia* spp.

**Anaerobic bacteria**

*Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, and other *Bacteroides* spp., *Clostridium* spp. including *C. perfringens*, *Eubacterium lentum*, *Fusobacterium* spp., *Mobiluncus curtisii*, *Peptostreptococcus* spp., *Peptococcus* spp.

Some strains of *Pseudomonas aeruginosa* are susceptible to meropenem *in vitro* and in clinical infections.

*Enterococcus faecium*, *Stenotrophomonas (Xanthomonas) maltophilia*, and methicillin resistant staphylococci have been found to be resistant to meropenem.

**Pharmacokinetics**

A 30 minute intravenous infusion of a single dose of meropenem in normal volunteers results in peak plasma levels of approximately 11 µg/mL for the 250 mg dose, 23 µg/mL for the 500 mg dose, 49 µg/mL for the 1 g dose and 115 µg/mL following the 2 g dose.

A 5 minute intravenous bolus injection of meropenem in normal volunteers results in peak plasma levels of approximately 52 µg/mL for the 500 mg dose and 112 µg/mL for the 1 g dose.

Intravenous infusions over 2 minutes, 3 minutes and 5 minutes of a 1 g dose of meropenem were compared in a three-way crossover trial. These durations of infusion resulted in peak plasma levels of 110, 91 and 94 µg/mL, respectively.

After an intravenous 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 subjects with normal renal function, accumulation of meropenem does not occur.

In subjects with normal renal function, meropenem's elimination half-life is approximately one hour.

Plasma protein binding of meropenem is approximately 2%.

Approximately 70% of the intravenous administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours at the 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

The only metabolite of meropenem is microbiologically inactive.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Studies in children have shown that the pharmacokinetics of meropenem in children are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in children under the age of 2 years.

The pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

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.

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem which correlated with age-associated reduction in creatinine clearance.

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

## INDICATIONS

Meropenem is indicated for treatment of the following infections, in adults and children (aged 3 months and over), when the causative organisms are known or suspected to be resistant to commonly used antibiotics:

- Community acquired lower respiratory tract infection
- Hospital acquired lower respiratory tract infection
- Complicated urinary tract infection
- Febrile neutropenia
- Intra-abdominal and gynaecological (poly microbial) infections
- Complicated skin and skin structure infections
- Meningitis
- Septicaemia

## CONTRAINDICATIONS

Meropenem is contraindicated in patients who have demonstrated hypersensitivity to this product.

## PRECAUTIONS

Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving therapy with β-lactams. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity when treated with another β-lactam. Before initiating treatment with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, or other β-lactam antibiotics. If an allergic reaction occurs to meropenem then discontinue the drug. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

As with other β-lactam antibiotics, strains of *Pseudomonas aeruginosa* may develop resistance on treatment with meropenem. Development of resistance has been reported in pseudomonal hospital acquired lower respiratory tract infections. In such cases, meropenem should be used with caution and repeat sensitivity testing is recommended.

Pseudomembranous colitis has been observed 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 gastrointestinal complaints, particularly colitis. It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea when using an antibiotic. 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. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered.

Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (lomotil) may prolong and/or worsen the condition and should not be used.

Neurological sequelae were reported following treatment of severe meningitis with meropenem. In clinical trials these adverse events were reported in 23 of 148 patients treated with meropenem and in 17 of 144 patients treated with comparator antibiotics.

A positive or indirect Coombs' test may develop.

The concomitant use of valproic acid/sodium valproate and meropenem is not recommended (see *Interactions with other drugs* section).

**Carcinogenicity, mutagenicity and impairment of fertility**

The carcinogenic potential of meropenem has not been investigated. Meropenem, with and without metabolic activation as appropriate, was not genotoxic in assays for gene mutations (*Salmonella typhimurium, E. coli* and Chinese hamster ovary cells) and chromosomal damage (mouse micronucleus assay and human lymphocytes *in vitro*).

Fertility was not impaired in rats with exposures (based on AUC) slightly greater than those observed in patients at the recommended intravenous dose.

**Use in pregnancy – Category B2**

Reproduction studies conducted with meropenem in rats have shown no embryotoxicity or teratogenicity at plasma exposures (based on AUC values) approximately equal to those observed in patients at the recommended intravenous dose. In a teratology study in cynomolgus monkeys given daily intravenous injections meropenem showed no evidence of teratogenicity at dose levels up to 360 mg/kg/day.

There are however, no adequate or well controlled trials of meropenem in pregnant women. Because reproduction studies are not always predictive of human response, meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

**Use in 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.

**Use in children**

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

**Use in patients with renal insufficiency**

See *Dosage and administration*.

**Use in patients with liver disease**

Patients with pre-existing liver disorders should have liver function monitored during treatment with meropenem.

**Interactions with other drugs**

Meropenem has been administered concomitantly with many other medications without apparent adverse interaction. However, no specific drug interaction studies other than with probenecid were conducted.

***Probenecid***

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. As the potency and duration of action of

meropenem dosed without probenecid are adequate the co-administration of probenecid with meropenem is not recommended. The potential effect of meropenem on the protein binding of other drugs or metabolism has not been studied. However, the protein binding is so low (approximately 2%) that no interactions with other compounds would be expected on the basis of this mechanism.

***Valproic acid/sodium valproate***

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 meropenem in patients stabilised on valproic acid/sodium valproate is not considered to be manageable and therefore should be avoided (see *Precautions* section).

**Effects on ability to drive and use machines**

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, paraesthesiae and convulsions have been reported for meropenem.

## ADVERSE EFFECTS

Meropenem is generally well tolerated.

In clinical trials, adverse events lead to cessation of treatment in less than 1% of patients. Serious adverse events are rare.

| **Common events** | |
|---|---|
| *Local intravenous injection site reactions* | Inflammation, thrombophlebitis, pain. |
| *Gastrointestinal disorders* | Nausea, vomiting, diarrhoea |
| *Blood* | Reversible thrombocythaemia. |
| *Nervous system disorders* | Headache |
| *Skin & subcutaneous tissue disorders* | Rash, pruritus |
| *Liver function* | Reversible increases in serum transaminases, bilirubin, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported. |
| **Adverse reactions reported at a frequency < 1%** | |
| *Systemic allergic reactions* | Systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis. |
| *Skin & subcutaneous tissue disorders* | Urticaria (uncommon). Severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed. |
| *Gastrointestinal disorders* | Pseudomembranous colitis. Jaundice and hepatic failure have been reported but a causal link with meropenem has not been established. |
| *Blood & lymphatic system disorder* | Uncommon - Eosinophilia, leucopenia, thrombocytopenia and neutropenia; Rare - agranulocytosis; Very rare - haemolytic anaemia.<br>A positive direct or indirect Coombs' test may develop. |
| *Cardiovascular* | Cardiac failure has been reported but a causal link with meropenem has not been established. |
| *Nervous system disorders* | Uncommon – paraesthesiae; Rare - convulsions. Delirium and hallucinations have been reported but a causal link with meropenem has not been established. |
| *Respiratory* | Pneumonia and respiratory failure have been reported but a causal link with meropenem has not been established. |
| *Whole body* | Fever and septicaemia have been reported but a causal link with meropenem has not been established. |
| *Other* | Oral and vaginal candidiasis (uncommon). |

## DOSAGE AND ADMINISTRATION

**Adults**

***Usual dose***

500 mg to 1 g by intravenous administration 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.

***Exceptions***

1. Febrile episodes in neutropenic patients - the dose should be 1 g every 8 hours.
2. Meningitis - the dose should be 2 g every 8 hours.

As with other antibiotics, caution may be required 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.

Meropenem-AFT should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (see *Method of administration*).

***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 to 50 | One unit dose | Every 12 hours |
| 10 to 25 | One-half unit dose | Every 12 hours |
| < 10 | One-half unit dose | Every 24 hours |

Meropenem is cleared by haemodialysis. If continued treatment with Meropenem-AFT 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 peritoneal dialysis.

***Use in adults with hepatic insufficiency***

No dosage adjustment is necessary in patients with impaired hepatic metabolism.

**Elderly patients**

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

**Children**

For infants and children over 3 months and up to 12 years of age the recommended intravenous dose is 10 to 40 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.

***Exceptions***

1. Febrile episodes in neutropenic patients - the dose should be 20 mg/kg every 8 hours.
2. Meningitis - the dose should be 40 mg/kg every 8 hours.

Meropenem-AFT should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes.

There is no experience in children with renal impairment.

**Method of administration**

Meropenem-AFT to be used for bolus intravenous injection should be constituted with sterile Water for Injections (10 mL per 500 mg meropenem). This provides an approximate available concentration of 50 mg/mL. Constituted solutions are both clear and colourless to pale yellow.

Meropenem-AFT for intravenous infusion may be directly constituted with a compatible infusion fluid and then further diluted (50 to 200 mL) with the compatible infusion fluid.

Shake constituted solution before use. All vials are for single use only. Standard aseptic technique should be employed during constitution and administration.

**Compatibility and stability**

*Intravenous bolus injection administration*

A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/mL. The solution must be used immediately after reconstitution.

*Intravenous infusion administration*

A solution for infusion is prepared by dissolving the drug product 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. The solution must be used immediately after reconstitution.

Solutions of Meropenem-AFT should not be frozen.

## OVERDOSAGE

The pharmacological properties and mode of administration make it unlikely that intentional overdose will occur. Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Treatment of overdosage should be symptomatic. In normal individuals rapid renal elimination will occur. In subjects with renal impairment haemodialysis will remove meropenem and its metabolite.

## PRESENTATION AND STORAGE CONDITIONS

Meropenem-AFT powders for intravenous injection or infusion packs contain 10 vials of meropenem trihydrate / sodium carbonate anhydrous blend as sterile powder:

**15 mL vial**

Meropenem trihydrate equivalent to meropenem 500 mg, sodium carbonate anhydrous 104 mg as buffer.

**20 mL vial**

Meropenem trihydrate equivalent to meropenem 1 g, sodium carbonate anhydrous 208 mg as buffer.

**Storage**

Store below 30°C. Protect from light.
See Compatibility and stability for storage of prepared solutions.

**Shelf life**

The expiry date can be found on outer carton.
See Compatibility and stability for shelf life of prepared solutions.

**Name and address of the product owner**

AFT Pharmaceuticals Ltd
Level 1, 129 Hurstmere Rd, Takapuna, Auckland 0622, New Zealand

**Product registrant in Singapore:**
Apex Pharma Marketing Pte Ltd.,
4 Loyang Way 1, #02-00, Singapore 508708

**Poison Schedule**
Prescription Only Medicine

**Singapore Registration Numbers:**

500 mg vial SIN14857P
1 g vial SIN14858P

**Date of Approval**

Date of Approval: 05/10/2015

Date of most recent amendment: March 2024