

Meropenem-AFT 500 mg Powder for Solution for Injection or Infusion

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1 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem-AFT Powder for Solution for Injection or Infusion contains meropenem trihydrate equivalent to meropenem, 500 mg or 1 g, blended with sodium carbonate. Meropenem-AFT 500 mg vial contains approximately 45 mg (2 mmol) of sodium and 1000 mg vial contains approximately 90 mg (4 mmol) of sodium.

2 PHARMCEUTICAL FORM

White to light yellow crystalline powder for injection.

After reconstitution and dilution: Colourless to yellow solution

3 CLINICAL PARTICULARS

3.1 THERAPEUTIC INDICATIONS

Meropenem-AFT 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.

3.2 DOSE 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.

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 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

Meropenem is cleared by haemodialysis and haemofiltration; if continued treatment with meropenem 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 intravenous meropenem 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

Meropenem-AFT 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 presentations.

Meropenem-AFT 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 **colorless to yellow solutions**.

Meropenem-AFT for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL).

3.3 CONTRAINDICATIONS

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

3.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins. Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions (SCAR)) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with Meropenem-AFT, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, Meropenem-AFT must be discontinued immediately and appropriate alternative therapy instituted.

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

Use of Meropenem-AFT 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 intravenous 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-AFT. 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-AFT with potentially nephrotoxic drugs should be considered with caution.

The concomitant use of valproic acid/sodium valproate and Meropenem-AFT is not recommended. Meropenem-AFT may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

Paediatric use

Efficacy and tolerability in infants under 3 months old have not been established; therefore, Meropenem-AFT 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.

3.5 INTERACTIONS WITH OTHER MEDICINES 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 intravenous meropenem dosed without probenecid are adequate, the co-administration of probenecid with Meropenem-AFT is not recommended.

The potential effect of intravenous meropenem on the protein binding of other drugs or metabolism has not been studied. The protein binding of intravenous meropenem is low (approximately 2%) and, therefore, no interactions with other compounds based on displacement from plasma proteins would be expected.

Meropenem-AFT may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

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 intravenous meropenem in patients stabilised on valproic acid is not considered to be manageable and therefore should be avoided.

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

3.6 PREGNANCY AND LACTATION

Pregnancy

The safety of intravenous meropenem in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing foetus. The only adverse effect observed in animal reproductive studies was an increased incidence of abortions in monkeys at 13 times the expected exposure in man. Meropenem-AFT 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 has been reported to be excreted in human milk. Meropenem-AFT should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

3.7 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.

3.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Meropenem-AFT 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 with intravenous meropenem. Their frequency is presented in Table 1 Frequency of Adverse Reactions (data derived from clinical trial data sources) using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level. Frequencies of occurrence of undesirable effects are defined as: very common ($\geq 1/10$; $\geq 10\%$); common ($\geq 1/100$ to $< 1/10$; $\geq 1\%$ to $< 10\%$); uncommon ($\geq 1/1,000$ to $< 1/100$; $\geq 0.1\%$ to $< 1\%$); rare ($\geq 1/10,000$ to $< 1/1,000$; $\geq 0.01\%$ to $< 0.1\%$); very rare ($< 1/10,000$; $< 0.01\%$).

Table 1 Frequency of Adverse Reactions (data derived from clinical trial data sources)¹

System organ class	Frequency	Reaction
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	Thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia
Nervous system disorders	Common	Headache
	Uncommon	Paraesthesiae
	Rare	Convulsions
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea
Hepatobiliary disorders	Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis

1 1999 Norrby SR and Gildon KM. Safety profile of Meropenem: a review of nearly 5000 patients treated with Meropenem.; Scand J Infect Dis 1999;31: 3-10 and the Integrated Summary of Safety 1993.

The following adverse reactions have been identified from post-marketing clinical trials and spontaneous reports. Their frequency is presented in Table 2: Reporting Rate of Adverse Reactions (data derived from a combination of post-marketing clinical trial and spontaneous sources) using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred level. Frequencies of occurrence of undesirable effects are defined as: very common ($\geq 1/10$; $\geq 10\%$); common ($\geq 1/100$ to $< 1/10$; $\geq 1\%$ to $< 10\%$); uncommon ($\geq 1/1,000$ to $< 1/100$; $\geq 0.1\%$ to $< 1\%$); rare ($\geq 1/10,000$ to $< 1/1,000$; $\geq 0.01\%$ to $< 0.1\%$); very rare ($< 1/10,000$; $< 0.01\%$), not known (cannot be estimated from the available data).

Table 2 Reporting Rate of Adverse Reactions (data derived from a combination of post-marketing clinical trial and spontaneous sources)

System organ class	Frequency	Reaction
Blood and lymphatic system disorders	Rare	agranulocytosis
	Very rare	haemolytic anaemia
Immune system disorders	Very rare	angioedema, manifestations of anaphylaxis
Psychiatric disorders	Rare	Delirium
Gastrointestinal disorders	Very rare	pseudomembraneous colitis
Skin and subcutaneous tissue disorders	Very rare	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme
	Not known	drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome), acute generalised exanthematous pustulosis (AGEP)

3.9 OVERDOSE

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.

4 PHARMACOLOGICAL PROPERTIES

4.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems

ATC code: J01DH02

Mode of action

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to multiple 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.

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 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
<i>Pseudomonas</i> spp.	≤ 2	> 8
<i>Acinetobacter</i> spp.	≤ 2	> 8
Streptococcus groups A, B, C and G	Note 6	Note 6
<i>Streptococcus pneumoniae</i> ¹	≤ 2	> 2
Viridans group streptococci ²	≤ 2	> 2
<i>Enterococcus</i> spp.	---	---
<i>Staphylococcus</i> spp.	Note 3	Note 3
<i>Haemophilus influenzae</i> ^{1,2} and <i>Moraxella catarrhalis</i> ²	≤ 2	> 2
<i>Neisseria meningitidis</i> ^{2,4}	≤ 0.25	> 0.25
Gram-positive anaerobes except <i>Clostridium difficile</i>	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
<i>Listeria monocytogenes</i>	≤ 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 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 ceftazidime 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 pneumoniae

Streptococcus pyogenes (Group A)

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

Gram-positive anaerobes

Clostridium perfringens

Peptoniphilus asaccharolyticus

Peptostreptococcus species (including *P. micros*, *P. anaerobius*, *P. magnus*)

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^{\$}

Gram-negative aerobes

Acinetobacter species

Burkholderia cepacia

Pseudomonas aeruginosa

Inherently resistant organisms

Gram-negative aerobes

Stenotrophomonas maltophilia

Legionella species

Other micro-organisms

Chlamydophila pneumoniae

Chlamydophila psittaci

Coxiella burnetii

Mycoplasma pneumoniae

^{\$}Species that show natural intermediate susceptibility

[£]All methicillin-resistant staphylococci are resistant to meropenem

4.2 PHARMACOKINETIC PROPERTIES

A 30 minute intravenous infusion of a single dose of Meronem in healthy volunteers 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 Meronem IV in healthy volunteers 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 subjects with normal renal function, accumulation of meropenem does not occur.

In subjects with normal renal function, meropenem's elimination half-life is approximately 1 hour.

Plasma protein binding of meropenem is approximately 2%.

Approximately 70% of the 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 after the administration of a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1g 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.

The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months $t_{1/2}$ 1.6 hours). The mean meropenem clearance values were 5.8 mL/min/kg (6-12 years), 6.2 mL/min/kg (2-5 years), 5.3 mL/min/kg (6-23 months) and 4.3 mL/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter-individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full-term neonates.

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.

5 PHARMACEUTICAL PARTICULARS

5.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

5.2 INCOMPATIBILITIES

Meropenem-AFT should not be mixed with or physically added to solutions containing other medicines.

5.3 SHELF LIFE

Unopened vial: 36 months.

5.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial: Store below 30°C. Do not freeze.

Constitution and compatibility

Meropenem-AFT to be used for bolus I.V. 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 colorless to yellow solutions.

Meropenem-AFT for I.V. infusion is prepared by dissolving the drug product Meropenem-AFT 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.

Pharmaceutical precautions

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

Stability after constitution and dilution

To reduce microbiological hazard, solutions of meropenem should be administered immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Solutions of Meropenem-AFT should not be frozen.

5.5 NATURE AND CONTENTS OF CONTAINER

Meropenem-AFT 500 mg and 1000 mg are supplied in 20 mL and 30 mL Type I glass vials, respectively covered with brominated butyl rubber stopper.

5.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6 PRODUCT REGISTRATION HOLDER

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7 REVISION DATE

August 2024

The minimum font size in this PI is 11 (Cambria font).