MERO-AFT (meropenem as trihydrate)

Powder for injection

1 NAME OF THE MEDICINE

Mero-AFT powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mero-AFT powder for intravenous injection or infusion contains meropenem trihydrate equivalent to meropenem, 500 mg or 1 g, blended with sodium carbonate.

Excipients with known effects: Mero-AFT powder for intravenous injection or infusion contains 208 mg sodium carbonate for each gram of meropenem. One vial of 500 mg contains 45 mg of sodium and one vial of 1 g contains 90 mg of sodium.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMCEUTICAL FORM

White to light yellow crystalline powder for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mero-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
- 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.

Meropenem 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.

4.2 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, 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.

There is limited safety data available to support a dose of above 2 g three times daily (or every 8 hours).

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

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

Mero-AFT is cleared by haemodialysis and haemofiltration; if continued treatment with Mero-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 the use of Mero-AFT in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency (see “Special warnings and precautions for use”).

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.

There is no experience in children with renal impairment.

Method of Administration

Mero-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.

There is limited safety data available to support the administration of a 40 mg/kg bolus dose.

There is limited safety data available to support the administration of a 2 g bolus dose.

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

Mero-AFT for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL) (see "Incompatibilities and Special precautions for storage").

4.3 CONTRAINDICATIONS

Mero-AFT is contraindicated in patients who have demonstrated hypersensitivity to this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported (see "Contraindications" and "Undesirable effects").

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken.

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 generalised exanthematous

pustulosis (AGEP) have been reported in patients receiving meropenem (See "Undesirable effects"). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

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 (see "Undesirable effects"). 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 (see "Undesirable effects").

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see "Undesirable effects").

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 (see "Posology and method of administration").

A positive direct or indirect Coombs test may develop during treatment with meropenem.

The concomitant use of valproic acid/sodium valproate and Mero-AFT is not recommended. Mero-AFT may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients (see "Interactions with other medicinal products and other forms of interaction").

Mero-AFT contains sodium.

Paediatric use

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 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. The protein binding of meropenem is low (approximately 2%) and,

therefore, no interactions with other compounds based on displacement from plasma proteins would be expected.

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 is not considered to be manageable and therefore should be avoided (see "Special warnings and precautions for use").

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

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.

4.6 FERTILITY, 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. Mero-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. Mero-AFT should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

4.7 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, paraesthesia, and convulsions have been reported for meropenem.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions have been identified following clinical studies with 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 (≥1/10; ≥10%); common (≥1/100 to

<1/10; ≥1% to <10%); uncommon (≥1/1,000 to <1/100; ≥0.1% to <1%); rare (≥1/10,000 to <1/1,000; ≥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, abdominal pain
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
	Not known	pain at the injection site

[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 (≥1/10; ≥10%); common (≥1/100 to <1/10; ≥1% to <10%); uncommon (≥1/1,000 to <1/100; ≥0.1% to <1%); rare (≥1/10,000 to <1/1,000; ≥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), acute generalised exanthematous pustulosis

4.9 OVERDOSE

Accidental overdosage could occur during therapy, particularly in patients with renal impairment. Limited post-marketing experience indicates that adverse events following over dosage are consistent with the adverse event profile described in the undesirable effects section. Treatment of overdosage should be symptomatic. In normal individuals, rapid renal elimination will occur; in subjects with renal impairment, haemodialysis will remove meropenem IV and its metabolite.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mero-AFT is a carbapenem antibiotic for parenteral use, that is relatively stable to human dehydropeptidase-1 (DHP-1) and therefore, does not require the addition of an inhibitor of DHP-1.

Mero-AFT 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 □-lactamases and its high affinity for multiple Penicillin Binding Proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. Minimum bactericidal concentrations (MBC) are commonly the same as the minimum inhibitory concentrations (MIC). For 76% of the bacteria tested, the MBC:MIC ratios were 2 or less.

Mero-AFT 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.

A single set of meropenem susceptibility criteria are recommended based on pharmacokinetics and correlation of clinical and microbiological outcomes with zone diameter and minimum inhibitory concentrations (MIC) of the infecting organisms.

Categorisation	**Method of assessment**	
	Zone Diameter (mm)	**MIC breakpoints (mg/L)**
Susceptible	≥ 14	≤ 4
Intermediate	12 to 13	8
Resistant	≤ 11	≥ 16

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 β-lactamases that can hydrolyse carbapenems.

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

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 antibacterial 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.	--	--

Organism	Susceptible (S) (mg/L)	Resistant (R) (mg/L)
Staphylococcus spp.[2]	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 meropenem is inferred from the methicillin 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.

Antibacterial spectrum

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.

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)

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*

Anaerobic bacteria

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

Bacteroides caccae, *Bacteroides fragilis* group, *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; note that in some European countries the frequency of resistance among *E. faecium* is greater than 50% of isolates)

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 pneumonia*

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 and imipenem have a similar profile of clinical utility and activity against multi-resistant bacteria. However, meropenem is intrinsically more potent against *Pseudomonas aeruginosa* and may be active *in vitro* against imipenem-resistant strains.

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.

5.2 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 (11-27 L) 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 C_{max} 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. 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. *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

Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 mL/min), 5 fold in severe impairment (CrCL 4-23 mL/min) and 10 fold in haemodialysis patients (CrCL <2 mL/min) when compared to healthy subjects (CrCL >80 mL/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment (see “Posology and method of administration”).

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency

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

Adult patients

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

Paediatrics

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 t1/2 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.

Elderly

Pharmacokinetic studies in healthy 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, except in cases of moderate to severe renal impairment (see “Posology and method of administration”).

5.3 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).

Effects on the CNS; convulsions in rats and vomiting in dogs, were seen only at high doses (>2000 mg/kg).

For an IV dose the LD_{50} in rodents is greater than 2000 mg/kg. In repeat dose studies (up to 6 months) 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 F1 body weight in rat 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium carbonate

6.2 INCOMPATIBILITIES

Mero-AFT should not be mixed with or added to other drugs.

Mero-AFT is compatible with the infusion fluids listed under "Special precautions for storage".

6.3 SHELF LIFE

Please refer to the expiry date on the outer carton.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Constitution and compatibility

Mero-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 both clear and colourless to pale yellow.

Mero-AFT for I.V. infusion may be directly constituted with either 0.9% sodium chloride solution for infusion or 5% glucose (dextrose) solution for infusion and then further diluted (50 to 200 mL) with the compatible infusion fluid (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.

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

Stability after constitution and dilution

After reconstitution

For bolus IV injection: Reconstitute with water for injection and use immediately at 25 °C. The reconstituted solution can be stored at 2-8 °C for 30 minutes.

For IV infusion:

Reconstitute with 0.9% sodium chloride. Store at 25 °C for 1 hour or 2-8 °C for 5 hours.

Reconstitute with 5% glucose: Use immediately at 25 °C or store at 2-8 °C for 2 hours.

Solutions of Mero-AFT should not be frozen.

6.5 NATURE AND CONTENTS OF CONTAINER

Mero-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. 10 vials are packed in a carton.

7 PRODUCT OWNER

AFT Pharmaceuticals Ltd.

129 Hurstmere Road, Takapuna, Auckland, New Zealand

8 DATE OF REVISION

April 2024