NEW ZEALAND DATA SHEET

1 NAME OF THE MEDICINE

Meropenem-AFT Meropenem trihydrate powder for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Meropenem-AFT 500 mg

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.

Meropenem-AFT 1 g

Each vial contains meropenem trihydrate equivalent to 1 g anhydrous meropenem.

Excipients:

Each 500 mg vial contains 104 mg sodium carbonate. Each 1 g vial contains 208 mg sodium carbonate.

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

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

A white to light yellow powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Meropenem-AFT is indicated for the treatment, in adults and children, of the following infections caused by single or multiple susceptible bacteria and as empiric therapy prior to the identification of the causative organisms (see sections 4.4 and 5.1):

- Lower Respiratory Tract Infections
- Urinary Tract Infections, including complicated infections
- Intra-abdominal Infections
- Gynecological Infections, including postpartum infections
- Skin and Skin Structure Infections
- Meningitis
- Septicaemia
- Empiric treatment, including initial monotherapy, for presumed bacterial infections in host- compromised, neutropenic patients

Because of its broad spectrum of bactericidal activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, meropenem is effective for the treatment of polymicrobial infections.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and Adolescents

Dosage range is 1.5 g – 6 g daily in three divided doses.

Usual dose

500 mg to 1 g by intravenous administration every 8 hours depending on type and severity of infection, the known or expected 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.

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

Renal impairment

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 or 1 g or 2 g every 8 hours)**	**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 and haemofiltration. If continued treatment with meropenem is necessary, the unit dose (based on the type and severity of infection) is recommended at the completion of the haemodialysis procedure to reinstitute effective treatment.

Hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see section 4.4).

Dose in elderly patients

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

Paediatric population

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.

There is no experience in children with renal impairment.

Meropenem is usually given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2, 6.3, and 6.6). There are limited safety data available to support the administration of a 40 mg/kg bolus dose.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

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 medicine. Serious hypersensitivity reactions may require adrenaline and other emergency measures.

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of meropenem. If signs or symptoms of rhabdomyolysis are observed, meropenem should be discontinued and appropriate therapy initiated.

Overgrowth of non-susceptible organisms

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

Resistance

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.

Antibiotic-associated colitis

Rarely, pseudomembranous colitis has been reported with meropenem injection 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 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 medicine 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. Medicines 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

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.

Concomitant use with valproic acid/sodium valproate

The concomitant use of valproic acid/sodium valproate and meropenem is not recommended. Meropenem-AFT may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients (see Section 4.5 Interactions with other medicines and other forms of interactions).

Skin and subcutaneous tissue disorders

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 injection (see Section 4.8 Adverse effects (undesirable effects)). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

Use in hepatic impairment

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

Use in renal impairment

See Section 4.2 Dose and method of administration.

Use in the elderly

See Sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties.

Paediatric use

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

Effects on laboratory tests

A positive or indirect Coombs test may develop.

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 of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. As 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 medicines 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.

Meropenem has been administered concomitantly with many other medications without apparent adverse interaction. Meropenem may reduce serum valproic acid levels.

Subtherapeutic levels may be reached in some patients. However, no specific drug interaction studies other than with probenecid were conducted.

Decreases in serum valproic acid levels that may fall below the therapeutic range, have been reported in patients co-administered sodium valproate with carbapenem agents, including meropenem. The significant reductions in serum valproic acid levels (60-100%) have been reported within two days of carbapenem administration and may lead to inadequate seizure control. Due to the rapid onset and the extent of the decrease in serum levels, co-administration of carbopenem agents in patients stabilised on sodium valproate is not considered to be manageable and should therefore be avoided (see section 4.4).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of meropenem in human pregnancy has not been established, although animal studies have not shown an adverse effect on the developing foetus. Meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus (see section 5.3).

Lactation

Meropenem is detectable at very low concentration animal breast milk. Meropenem 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

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	
General disorders and administration site conditions	Inflammation, thrombophlebitis, pain
Gastrointestinal disorders	Nausea, vomiting, diarrhoea
Blood and lymphatic system disorders	Thrombocythaemia
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Rash, pruritus
Hepatobiliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, and blood bilirubin increased alone or in combination have been reported.

Adverse reactions reported at a frequency <1%	
Immune system disorders	Systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.
Skin and subcutaneous tissue disorders	Uncommon – Urticaria Severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed. Not known – Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome), acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Not known – Rhabdomyolysis

Gastrointestinal disorders	Pseudomembranous colitis. Jaundice and hepatic failure have been reported but a causal link with meropenem has not been established.
Blood and lymphatic system disorders	Uncommon – Eosinophilia, leucopenia, thrombocytopenia and neutropenia Rare – agranulocytosis Very rare – haemolytic anaemia A positive direct or indirect Coombs test may develop.
Cardiac disorders	Cardiac failure has been reported but a causal link with meropenem has not been established.
Nervous system disorders	Uncommon – paraesthesia, convulsions
Psychiatric disorders	Delirium and hallucinations have been reported but a causal link with meropenem has not been established.
Respiratory, thoracic and mediastinal disorders	Pneumonia and respiratory failure have been reported but a causal link with meropenem has not been established.
Renal and urinary disorders	Renal impairment.
Whole body	Fever and sepsis have been reported but a causal link with meropenem has not been established.
Infections and infestations	Uncommon – Oral candidiasis and vaginal candidiasis.

Description of selected adverse reactions

Kounis Syndrome

Kounis syndrome (acute coronary syndrome associated with an allergic reaction) has been reported with other beta-lactam antibiotics.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Intentional overdosing of meropenem is unlikely, although overdosing could occur during therapy particularly in patients with renal impairment. Limited post-marketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile described in section 4.8, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered. In normal individuals rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, carbapenems

ATC code: J01DH02

Mechanism of action

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

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

Meropenem is stable in susceptibility tests and these tests can be performed using the normal routine systems. *In vitro* tests show that meropenem can act synergistically with various antibiotics.

It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect against Gram-positive and Gram-negative organisms.

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 b-lactamases that can hydrolyse carbapenems.

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

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

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 × 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g × 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

[6] The b-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 freudii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
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 $\$\dagger$

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
[†] 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.

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 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. 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 b-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 (Cr_{CL} 33-74 ml/min), 5 fold in severe impairment (Cr_{CL} 4-23 ml/min) and 10 fold in haemodialysis patients (Cr_{CL} < 2 ml/min) when compared to healthy subjects (Cr_{CL} > 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 section 4.2).

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 shows 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 $t_{1/2}$ 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.

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 section 4.2).

5.3 PRECLINICAL SAFETY DATA

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above.

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

The IV LD_{50} of meropenem in rodents is greater than 2000 mg/kg. In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters and increase in liver weight in dogs at 500mg/kg.

There was no evidence of mutagenic potential in the 5 tests conducted and no evidence of reproductive toxicity including teratogenic potential in studies at the highest possible level in rats and monkeys. (The no effect dose level of a small reduction in F1 body weight in rats was 120 mg/kg).

There was increased evidence of abortions at 500 mg/kg in a preliminary study in monkeys.

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 intramuscular formulation caused reversible injection site necrosis.

The sole metabolite of meropenem had a similar low profile of toxicity in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Meropenem-AFT, 500 mg: anhydrous sodium carbonate

Meropenem-AFT, 1 g: anhydrous sodium carbonate

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE

3 years

After reconstitution:

To reduce microbiological hazard, solutions of meropenem should be administered immediately after preparation. The constituted solutions should not be frozen.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store over 30 °C.

Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

White to light yellow powder in clear glass vial sealed with rubber stopper and flip off cap, containing meropenem 500 mg (equivalent to meropenem trihydrate 570 mg) or 1 g (equivalent to meropenem trihydrate 1.14 g).

Available in packs of 10 vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Injection

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

Infusion

Meropenem-AFT for intravenous infusion may be directly constituted with 0.9 % sodium chloride or 5% dextrose solutions for infusion and then further diluted (50 to 200 mL), as needed.

Each vial is for single use only.

Standard aseptic techniques should be used for solution preparation and administration. The solution should be shaken before use.

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

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.
PO Box 33-0232
Takapuna Auckland
Email: customer.service@aftpharm.com
Phone: 0800 423 823

9 DATE OF FIRST APPROVAL

10 March 2016

10 DATE OF REVISION OF TEXT

13 September 2024

Summary table of changes

Section changed	Summary of new information
4.4, 4.8	Revised in-line with Australian PI of reference product.