PROFESSIONAL INFORMATION

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

MEROPENEM 500 mg FRESENIUS – sterile powder for solution for injection or infusion

MEROPENEM 1 000 mg FRESENIUS – sterile powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MEROPENEM 500 mg FRESENIUS:

Each 20 mL vial or 100 mL bottle contains meropenem trihydrate 570 mg, equivalent to 500 mg anhydrous meropenem.

MEROPENEM 1 000 mg FRESENIUS:

Each 20 mL vial or 100 mL bottle contains meropenem trihydrate 1 140 mg, equivalent to 1 000 mg anhydrous meropenem.

Excipients with known effect:

MEROPENEM 500 mg FRESENIUS contains approximately 104 mg sodium carbonate which equates to approximately 45,13 mg sodium per vial/bottle, equivalent to 2,3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

MEROPENEM 1 000 mg FRESENIUS contains approximately 208 mg sodium carbonate which equates to approximately 90,25 mg of sodium per vial/bottle, equivalent to 4,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white to light yellow, sterile crystalline powder for solution for injection or infusion.

pH of the product after reconstitution is 7,3 to 8,3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MEROPENEM FRESENIUS is indicated for treatment of the following infections, caused by single or multiple susceptible bacteria and as empiric therapy prior to the identification of the causative organisms:

Acute exacerbation of chronic bronchitis and pneumonia due to:

Staphylococcus aureus (methicillin susceptible strains only)*, Streptococcus pneumoniae, Streptococcus* spp*., Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae*, *Pseudomonas aeruginosa, Moraxella (Branhamella) catarrhalis, Klebsiella* spp*, Enterobacter cloacae, Enterobacter* spp., *Acinetobacter* spp.

Pneumonia in children due to:

Staphylococcus aureus (methicillin susceptible strains only)*, Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa*

Urinary tract infections in adults and children, including complicating infections due to:

Enterobacter cloacae, Escherichia coli, Morganella morganii, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Citrobacter freundii

Pelvic inflammatory disease (including tubo-ovarian abscess) and endometritis due to:

Enterococcus faecalis, Staphylococcus aureus (methicillin susceptible strains only)*,* coagulase-negative *Staphylococcus* spp. (methicillin susceptible strains only)*, Streptococcus agalactiae* Group B*, Streptococcus viridans, Streptococcus* spp.,

*Escherichia coli, Neisseria gonorrhoeae, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Proteus mirabili*s, *Acinetobacter anitratus, Acinetobacter lwoffii, Gardnerella vaginalis, Bacteroides fragilis* group, *Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus*

Skin and skin structure infections in adults due to:

Staphylococcus aureus (methicillin susceptible strains only), coagulase-negative *Staphylococcus* spp*, Streptococcus pyogenes (*Group A), *Streptococcus agalactiae, Streptococcus viridans, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Peptostreptococcus* spp.

Meningitis in adults and children due to:

Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides

Septicaemia in adults and children due to:

Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumonia

Empiric treatment, including initial monotherapy, for presumed bacterial infections in host-compromised neutropenic patients due to:

Streptococcus epidermidis, Streptococcus mitis, Streptococcus sanguinis, Escherichia coli

Intra-abdominal abscess and peritonitis due to:

Streptococcus milleri, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Bacteroides fragilis group (including

Bacteroides distasonis, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus), Clostridium perfringens, *Streptococcus mitior*

Polymicrobial infections

Note:

In the treatment of infections caused by *Pseudomonas aeruginosa,* an aminoglycoside should be administered concomitantly.

4.2 Posology and method of administration

Posology

Adult dosage schedule (normal renal function)

Intravenous administration:

Usually, 500 mg to 1 000 mg is administered every 8 hours, based on the type or severity of the infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient. See section 4.1 for types of infections and *in vivo* susceptible organisms.

Exceptions:

1. Febrile episodes in neutropenic patients – the dose should be 1 000 mg every 8 hours.
2. Meningitis – the dose should be 2 000 mg every 8 hours.

Caution may be required in using beta-lactam antibiotics in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections.

Concomitant use of an aminoglycoside is recommended.

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

Dosage schedule for adults with impaired renal function

The dosage should be reduced in patients with creatinine clearance less than 51 mL/minute, as scheduled below.

Creatinine clearance (m	**Dose (based on "unit" dose range of 000 mg every 8 hours – see above)**	**Frequency**
26 – 50	one unit dose	every 12 hours
10 -25	half the unit dose	every 12 hours
< 10	half the unit dose	every 24 hours

Dosage for the treatment of adults on haemodialysis:

MEROPENEM FRESENIUS is cleared from the circulation during haemodialysis. If continued treatment with MEROPENEM FRESENIUS is necessary, the required dose should be used at completion of the haemodialysis cycle to re-institute effective treatment. There is no experience with peritoneal dialysis.

Adults with hepatic insufficiency

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

Elderly

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

Paediatric population

Safety and efficacy in babies under 3 months have not been established.

Infants and children from 3 months to 12 years: 10 – 40 mg/kg every 8 hours, depending on the type and severity of the infection, the suspected susceptibility of the pathogens and condition of the patient.

Children > 50 kg: The dosage as indicated for adults should be used.

EXCEPTION:

Meningitis: 40 mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of administration

MEROPENEM FRESENIUS should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15-30 minutes after dissolving the sterile powder.

For instructions on reconstitution of MEROPENEM FRESENIUS before administration, see section 6.6. For further dilution for infusion, see section 6.6 (see instructions for compatibility and stability in sections 6.2, 6.3 and 6.6).

The reconstituted solution for infusion is a clear, colourless to pale yellow solution, free from visible particulate matter.

4.3 Contraindications

- Hypersensitivity to meropenem or any component of MEROPENEM FRESENIUS.
- History of hypersensitivity to carbapenems, penicillins, cephalosporins or other beta-lactam antibiotics.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

The selection of MEROPENEM FRESENIUS to treat an individual patient should consider the appropriateness of using a carbapenem antibacterial medicine based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial medicines and the risk of selecting for carbapenem-resistant bacteria.

See section 5.1.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem (see section 4.3). Before initiating therapy with MEROPENEM FRESENIUS, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, MEROPENEM FRESENIUS 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 section 4.8). If signs and symptoms suggestive of these reactions appear, MEROPENEM FRESENIUS should be withdrawn immediately and an alternative treatment should be considered.

Antibiotic-associated colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial medicines, 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 FRESENIUS (see section 4.8). Discontinuation of therapy with MEROPENEM FRESENIUS and the administration of specific treatment for *Clostridium difficile* should be considered. Medicines that inhibit peristalsis should not be given.

Seizures

Seizures have infrequently been reported during treatment with carbapenems, including MEROPENEM FRESENIUS (see section 4.8).

Hepatic function monitoring

Hepatic function should be closely monitored during treatment with MEROPENEM FRESENIUS due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).

Patients with pre-existing liver disorders should have their liver function monitored during treatment with meropenem. There is no dose adjustment necessary (see section 4.2).

Direct antiglobulin test (Coombs test) seroconversion

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

Concomitant use with valproic acid/sodium valproate/valpromide

The concomitant use of MEROPENEM FRESENIUS and valproic acid/sodium valproate/valpromide is not recommended (see section 4.5).

Paediatric population

Efficacy and tolerability in infants under 3 months of age have not been established, therefore, MEROPENEM FRESENIUS is only approved for children over 3 months of age.

MEROPENEM FRESENIUS contains sodium

MEROPENEM 500 mg FRESENIUS contains approximately 2,0 mmol of sodium per 500 mg dose which should be taken into consideration by patients on a controlled sodium diet.

MEROPENEM 1 000 mg FRESENIUS contains approximately 4,0 mmol of sodium per 1 000 mg dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

No specific medicine interaction studies other than probenecid were conducted. 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 that no interactions with other compounds would be expected based on this mechanism.

Probenecid

Probenecid competes with MEROPENEM FRESENIUS for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. Caution is required if probenecid is co-administered with MEROPENEM FRESENIUS.

Valproate/valproic acid

Decreases in blood levels of valproic acid have been reported when it is co-administered with carbapenem medicines (including MEROPENEM FRESENIUS) resulting in a 60-100 % decrease in valproic acid levels in about two days. Subtherapeutic levels may be reached. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with MEROPENEM FRESENIUS is not considered to be manageable and therefore should be avoided (see section 4.4).

Oral anti-coagulants

Simultaneous administration of MEROPENEM FRESENIUS 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 medicines, including warfarin, in patients who are concomitantly receiving antibacterial medicines. 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnant women has not been established. MEROPENEM FRESENIUS should therefore not be used during pregnancy.

Breastfeeding

Meropenem (contained in MEROPENEM FRESENIUS) is detectable in small quantities in human breast milk. MEROPENEM FRESENIUS should not be used in breastfeeding mothers, or mothers should not breastfeed their babies if treatment with MEROPENEM FRESENIUS is deemed essential for them.

4.7 Effects on ability to drive and use machines

When driving or operating machines, it should be considered that headache, paraesthesia and convulsions have been reported for meropenem.

4.8 Undesirable effects

Summary of the safety profile

Meropenem-related adverse reactions most frequently reported were diarrhoea, rash, nausea/vomiting and injection site inflammation. The most frequently reported meropenem-related laboratory adverse events were thrombocytosis and increased hepatic enzymes.

Tabulated summary of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency: frequent; less frequent; and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Event
Infections and infestations	Less frequent	oral and vaginal candidiasis
Blood and lymphatic	Frequent	thrombocytaemia
system disorders	Less frequent	agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia, leukopenia, eosinophilia
Immune system disorders	Less frequent	anaphylaxis (see sections 4.3 and 4.4), angioedema
Psychiatric disorders	Less frequent	delirium
Nervous system disorders	Frequent	headache
	Less frequent	paraesthesia, convulsions (see section 4.4)
Gastrointestinal disorders	Frequent	diarrhoea, abdominal pain, vomiting, nausea
	Less frequent	antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Frequent	increases in serum transaminases, blood alkaline phosphatase, blood lactate dehydrogenase
	Less frequent	blood bilirubin increased
Skin and subcutaneous	Frequent	rash, pruritus

tissue disorders	Less frequent	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme (see section 4.4), urticaria, petechiae, purpura, diaphoresis, flushing
	Not known	drug reaction with eosinophilia and systemic symptoms(DRESS), acute generalised exanthematous pustulosis (AGEP), toxic epidermal n (see section 4.4)
Renal and urinary disorders	Less frequent	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Frequent	inflammation, pain
	Less frequent	thrombophlebitis, pain at the injection site

Paediatric population

MEROPENEM FRESENIUS is approved for children over 3 months of age. There is no evidence of an increased risk of adverse reactions in children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address:

safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

In patients with renal impairment relative overdosage is possible if the dose is not adjusted as described in section 4.2.

Treatment is symptomatic and supportive. Patients with normal renal function should have rapid renal elimination.

In patients with renal impairment, haemodialysis will remove MEROPENEM FRESENIUS and its metabolite.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Meropenem is a carbapenem antibiotic for intravenous administration that is stable to human dehydropeptidase-1 (DHP-1). It is structurally similar to imipenem.

Meropenem acts bactericidal by interfering with vital bacterial cell wall synthesis. Bactericidal concentrations are generally the same as the minimum inhibitory concentrations (MICs).

Meropenem has a high degree of stability to almost all beta-lactamases produced by Gram-positive and Gram-negative bacteria. Meropenem is stable in susceptibility test systems.

Susceptibility tests can be performed using routine method.

In vitro, meropenem can act synergistically with various antibiotics.

Meropenem may be active *in vitro* against imipenem-resistant strains of *Pseudomonas aeruginosa.*

A post-antibiotic effect has been demonstrated *in vitro* and *in vivo.*

For *in vivo* efficacy information, refer to section 4.1.

Microbial resistance

All methicillin-resistant staphylococci are resistant to meropenem.

Resistance to penems of *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter* spp. varies across regions. Prescribers are advised to consider the local prevalence of resistance in these bacteria to penems.

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

[†] Resistance rate ≥ 50 % in one or more EU countries.

5.2 Pharmacokinetic properties

Absorption

Meropenem is not absorbed orally; the formulation is administered by intravenous infusion.

After a 30-minute intravenous infusion of 500 mg and 1 000 mg meropenem, the peak plasma concentrations of meropenem respectively averages 23 µg/mL and 49 µg/mL.

After a 5-minute bolus injection of 500 mg and 1 000 mg meropenem, the peak plasma concentrations of meropenem respectively averages 52 µg/mL and 112 µg/mL.

Intravenous infusions of 1 000 mg meropenem over 2 minutes, 3 minutes, and 5 minutes result in peak plasma concentrations of 110, 91 and 94 micrograms/mL, respectively.

When multiple doses are administered at 8 hourly intervals to patients with normal renal function, accumulation of meropenem does not occur.

When multiple doses are administered to patients at 8 hourly intervals, the concentrations at steady-state are approximately 20 % higher than after a single dose.

Distribution

Meropenem penetrates well into most body fluids and tissues, including the cerebrospinal fluid (CSF) of patients with bacterial meningitis; achieving concentrations that exceed those required to inhibit most bacteria.

The plasma protein binding of meropenem is approximately 2 %.

Biotransformation and elimination

In patients with normal renal function, meropenem's elimination half-life is approximately 1 hour. For children, see "*Paediatric patients"* below.

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

Meropenem is mostly excreted unchanged. There is one metabolite, which is microbiologically inactive.

Elimination is renal, with approximately 70 % of an administered dose recovered in the urine as unchanged meropenem over 12 hours.

Specific patient groups

Renal insufficiency:

The plasma clearance of meropenem correlates with the creatinine clearance. Dose adjustment is required for patients with moderate to severely impaired renal function (see section 4.2).

Hepatic insufficiency:

Hepatic impairment does not seem to affect the pharmacokinetics of meropenem in patients with impaired liver function.

Paediatric patients:

The pharmacokinetics of meropenem in children are essentially like those in adults. The elimination half-life of meropenem is approximately 1,5 hours in children under the age of 2 years. The pharmacokinetics are linear over the dose range of 10-40 mg/kg (see section 4.2).

Elderly patients:

Elderly patients with age-related reduction in creatinine clearance, requires a reduction of dosage (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MEROPENEM 500 mg FRESENIUS:

anhydrous sodium carbonate.

MEROPENEM 1 000 mg FRESENIUS:

anhydrous sodium carbonate.

6.2 Incompatibilities

MEROPENEM FRESENIUS must not be mixed with or physically added to other medicines except those mentioned in section 6.6.

6.3 Shelf life

Dry powder in 20 mL vial: 48 months

Dry powder in 100 mL bottle: 36 months

After reconstitution:

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the MEROPENEM FRESENIUS in water for injection to a final concentration of 50 mg/mL. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25 °C or 12 hours under refrigerated conditions (2 – 8 °C). Chemical and physical in-use stability for a prepared solution for infusion using 5 % dextrose solution has been demonstrated for 1 hour at 25 °C or for 8 hours at 2 - 8 °C.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

Intravenous infusion administration

A solution for infusion is prepared by dissolving the MEROPENEM FRESENIUS in either 0,9 % sodium chloride solution for infusion or 5 % dextrose solution for infusion to a final concentration of 1 to 20 mg/mL. Chemical and physical in-use stability for a prepared solution for infusion using 0,9 % sodium chloride solution has been demonstrated for 3 hours at up to 25 °C or 24 hours under refrigerated conditions (2 – 8 °C).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the product should be used immediately.

If not used immediately in-use storage times and conditions are the responsibility of the user.

Reconstituted solution of the product in 5 % dextrose solution should be used immediately.

6.4 Special precautions for storage

Dry powder

Store the dry powder at or below 25 °C and protect from light. Keep the vial/bottle in the outer container until required for use.

Reconstituted Solution

The product must be used immediately after first opening.

Do not freeze the reconstituted solution.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

MEROPENEM 500 mg FRESENIUS:

20 mL Type III colourless glass vials or 100 mL Type II colourless glass bottles, closed with bromobutyl rubber stoppers and sealed with 20 mm or 32 mm flip-off plastic-aluminium caps.

MEROPENEM 1 000 mg FRESENIUS:

20 mL Type III colourless glass vials or 100 mL Type II colourless glass bottles, closed with bromobutyl rubber stoppers and sealed with 20 mm or 32 mm flip-off plastic-aluminium caps.

Pack sizes of 1 or 10 vials/bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Injection

MEROPENEM FRESENIUS, used as bolus intravenous injection, should be constituted with sterile water for injection, 10 mL per 500 mg and 20 mL per 1 000 mg of meropenem. This provides an approximate concentration of 50 mg/mL. Prepared solutions are clear, colourless or pale yellow, without visible particles.

Infusion

For intravenous infusion MEROPENEM FRESENIUS vials/bottles may be directly reconstituted with 0,9 % sodium chloride or 5 % dextrose solutions for infusion to a final volume of 50 – 200 mL. Do not mix MEROPENEM FRESENIUS with other medicines. Standard aseptic techniques should be used for solution preparation and administration.

Shake the solution before use and inspect visually for clarity and absence of particles.

Freshly prepared solutions should be used (see section 6.3).

Each vial/bottle is for single use only.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi SA (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Midrand, 1685

SOUTH AFRICA

Tel: (011) 545 0000

8 REGISTRATION NUMBERS

MEROPENEM 500 mg FRESENIUS: 48/20.1.1/0293

MEROPENEM 1 000 mg FRESENIUS: 48/20.1.1/0294

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 06 July 2021

10 DATE OF REVISION OF THE TEXT

28 November 2023