SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MERONEM® 500 Powder for solution for injection or infusion

MERONEM® 1 000 Powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MERONEM 500

Meropenem (as trihydrate) 570 mg, equivalent to meropenem anhydrous 500 mg/vial.

MERONEM 1 000

Meropenem (as trihydrate) 1 140 mg, equivalent to meropenem anhydrous 1 000 mg/vial.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion

Clear glass vial containing a white to light yellow powder.

Reconstituted solution

The solution is clear and varies from colourless to yellow depending on the concentration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MERONEM 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 mirabilis, 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. (methicillin-susceptible strains only), *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 meningitidis*
- Septicaemia in adults and children due to: *Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae*

- 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

4.2 Posology and method of administration

Posology

Intravenous administration

Adults

Usual dose

500 mg to 1 g by intravenous administration every 8 hours depending on the type and severity of infection, the known or suspected susceptibility of the pathogen(s), and the condition of the patient.

Exceptions

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

MERONEM should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 – 30 minutes (see section 6.6 for constitution details).

Special populations

Use in elderly patients

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

Dosage schedule for adults with impaired renal function

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

Creatinine clearance (mL/min)	*Dose (based on "unit" dose range of 500 mg to 2 g every 8 hours – see above)*	*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

MERONEM is cleared by haemodialysis, if continued treatment with MERONEM is necessary, the unit dose based on the infection type and severity is recommended at the completion of the haemodialysis procedure to reinstitute effective treatment.

There is no experience with peritoneal dialysis.

Use in adults with hepatic insufficiency

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

Paediatric population

For infants and children over 3 months and up to 12 years of age the IV dose is 10 – 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

Meningitis – the dose should be 40 mg/kg every 8 hours.

MERONEM should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15 – 30 minutes (see section 6.6 for constitution details).

There is no experience in children with renal impairment.

Method of administration

For bolus intravenous injection or intravenous infusion.

For instructions on reconstitution and dilution of MERONEM before administration, see section 6.6.

4.3 Contraindications

MERONEM is contraindicated:

- in patients who have demonstrated hypersensitivity to meropenem or to any of the excipients of MERONEM (listed in section 6.1).
- Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to MERONEM. As with all beta-lactam antibiotics hypersensitivity reactions have been reported (see section 4.8).

4.4 Special warnings and precautions for use

Overgrowth of non-susceptible organisms may occur and repeated evaluation of each patient is necessary. Infrequently, *pseudomembranous colitis* has been reported on MERONEM, therefore, it is important to consider its diagnosis in patients who develop diarrhoea in association with MERONEM use.

A positive direct or indirect Coombs test may develop.

Special populations

Use in patients with liver disease

Patients with pre-existing liver disorders must have liver function monitored during treatment with MERONEM.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

MERONEM may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients.

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of MERONEM dosed without probenecid are adequate the co-administration of probenecid with MERONEM is not recommended.

The potential effect of MERONEM on the protein binding of other drugs or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected.

MERONEM has been administered concomitantly with many other medications without apparent adverse interaction. MERONEM may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients. However, no specific data regarding other potential drug interactions are available.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of MERONEM in human pregnancy has not been established.

Breastfeeding

Meropenem is detectable at very low concentrations in animal breast milk. MERONEM should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines

No data are available, but it is not anticipated that MERONEM will affect the ability to drive or use machines.

4.8 Undesirable effects

Frequency	**System Organ Class**	**Event**
Common (≥ 1 % and < 10 %)	Blood and lymphatic system disorders	Thrombocythaemia
	Gastrointestinal disorders	Nausea, vomiting, diarrhoea
	Hepatobiliary disorders	Increases in serum, transaminases, bilirubin, alkaline phosphatase, lactic dehydrogenase
	General disorders and administration site conditions	Inflammation, thrombophlebitis, pain
Uncommon (≥ 0,1 % and < 1 %)	Blood and lymphatic system disorders	Eosinophilia, thrombocytopenia
	Nervous system disorders	Headache, paraesthesia
	Skin and subcutaneous tissue disorders	Rash, urticaria, pruritus

Rare (≥ 0,01 % and < 0,1 %)	Blood and lymphatic system disorders	Leucopenia, neutropenia, agranulocytosis
	Nervous system disorders	Convulsions*
	General and administration site disorders	Oral and vaginal candidiasis
Very rare (< 0,01 %)	Blood and lymphatic system disorders	Haemolytic anaemia
	Immune system disorders	Angioedema, manifestations of anaphylaxis
	Gastrointestinal disorders	Pseudomembranous colitis
	Skin and subcutaneous tissue disorders	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

*Convulsions have been observed in a temporal association with the administration of MERONEM; a causal relationship with MERONEM has not been established.

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Intentional overdosing of MERONEM is unlikely, although overdosing could occur 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.

In subjects with renal impairment, haemodialysis will remove MERONEM and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

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 action by interfering with vital bacterial cell wall synthesis. Bactericidal concentrations are commonly 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 methods.

In vitro, meropenem can act synergistically with various antibiotics.

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

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

5.2 Pharmacokinetic properties

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

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

Intravenous infusions of 1 g of meropenem over 2 minutes, 3 minutes and 5 minutes resulted in peak plasma levels of 110, 91 and 94 micrograms/mL, respectively.

After an IV dose of 500 mg, plasma levels of meropenem decline to values of 1 microgram/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 IV 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 micrograms/mL are maintained for up to 5 hours at the 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

There is 1 metabolite, which 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.

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

Special populations

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 renal insufficiency have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

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

Paediatric population

Studies in children have shown that the pharmacokinetics of meropenem in children are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1,5 hours in children under the age of 2 years. The pharmacokinetics are linear over the dose range of 10 – 40 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate

6.2 Incompatibilities

MERONEM should not be mixed with or physically added to solutions containing other medicines except those mentioned in section 6.6.

6.3 Shelf life

48 months.

After reconstitution:

Intravenous bolus injection administration

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) (see section 6.6).

Intravenous infusion administration

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) (see section 6.6).

Constituted solutions of MERONEM IV should not be frozen.

6.4 Special precautions for storage

Store at or below 30 °C.

For storage of the reconstituted solution(s), see section 6.3.

6.5 Nature and contents of container

MERONEM 500: 20 mL vial in single packs or packs containing 10 vials.

MERONEM 1 000: 30 mL vial in single packs or packs containing 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility and constitution

Injection

MERONEM to be used for bolus intravenous injection should be constituted with sterile water for injection (5 mL/250 mg; 10 mL/500 mg and 20 mL/1 000 mg). This provides an approximate available concentration of 50 mg/mL. Constituted solutions are clear or pale yellow.

Infusion

For intravenous infusion MERONEM vials may be directly constituted with a compatible infusion fluid (with 0,9 % sodium chloride or 5 % dextrose solutions) and then further diluted with the compatible infusion fluid, 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.

Dilution and stability

Intravenous bolus injection administration

A solution for bolus injection is prepared by dissolving the medicine 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) (see section 6.3).

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbiological contamination, the medicine 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 medicine 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) (see section 6.3).

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

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

MERONEM 500: 29/20.1.1/0340

MERONEM 1 000: 29/20.1.1/0341

9. DATE OF FIRST AUTHORISATION

MERONEM 500: 08 February 1996

MERONEM 1 000: 08 February 1996

10. DATE OF REVISION OF THE TEXT

17 December 2021

BOTSWANA: S2

MERONEM 500 – Reg. No.: BOT0801239

MERONEM 1 000 – Reg. No.: BOT0801325

NAMIBIA: NS2

MERONEM 500 – Reg. No.: 04/20.1.1/1764

MERONEM 1 000 – Reg. No.: 04/20.1.1/1763