**SCHEDULING STATUS:** S4

## 1. NAME OF THE MEDICINAL PRODUCT

**MESPEC 500 mg** (powder for injection)

**MESPEC 1000 mg** (powder for injection)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**MESPEC 500 mg**:

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

**MESPEC 1000 mg**:

Each vial contains meropenem trihydrate equivalent to 1 000 mg anhydrous meropenem.

Sugar free

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

**MESPEC 500 mg**:

*Powder:*

White to pale yellow crystalline powder filled in clear glass vial stoppered with grey rubber stopper and sealed with aluminium seal having taxim blue colour PP disc.

*Reconstituted solution:*

Clear colourless to yellow colour solution.

**MESPEC** 1 000 mg:

*Powder:*

White to pale yellow crystalline powder filled in clear glass vial stoppered with grey rubber stopper and sealed with aluminium seal having white colour PP disc.

*Reconstituted solution:*

Clear colourless to yellow colour solution.

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

## 4. CLINICAL PARTICULARS

4.1 Therapeutic indications

**MESPEC** 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*),* S*treptococcus 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 Iwoffii, 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 1000 mg 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. See section 4.1 for types of infections and *in vivo* susceptible organisms.

*Instruction for inserting the needle into the rubber stopper:*

In order to avoid a coring phenomenon of the plug, when inserting the needle into the rubber stopper, it is recommended to use a needle with a 21-gauge or smaller diameter needle for the reconstitution of the product. The needle should be inserted only at the center of the rubber stopper and in a vertical direction.

*Exceptions:*

(1) Febrile episodes in neutropenic patients - the dose should be 1 000 mg every 8 hours.

(2) Meningitis - the dose should be 2000 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. Concornitant use of an aminoglycoside is recommended.

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

**MESPEC** should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15-30 minutes (see "*Constitution, compatibility, and stability*" section for constitution details).

*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 2000 mg 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 |

**MESPEC** is cleared by haemodialysis, if continued treatment with **MESPEC** is necessary, the unit dose based on the infection type and severity is recommended at the completion of the haemodialysis procedure to re-institute 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.

*Elderly:*

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

*Paediatric population:*

Children under 3 months of age

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

Children from 3 months to 11 years of age and up to 50 kg body weight

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.

Children over 50 kg body weight

The adult dosage should be used.

There is no experience in children with renal impairment.

*Exceptions:*

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

**MESPEC** should be given as an IV bolus over approximately 5 minutes or by intravenous infusion over approximately 15-30 minutes (see "*Constitution, compatibility, and stability*" section for constitution details).

*Constitution, compatibility and stability:*

**MESPEC** 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 colourless to a yellow colour solution.

For intravenous infusion **MESPEC** IV vials may be directly constituted with a compatible infusion fluid (as listed below) and then further diluted with the compatible infusion fluid, as needed.

Freshly prepared solutions of **MESPEC** IV should be used whenever possible. However,

constituted solutions of **MESPEC** IV, as supplied in injection and infusion vials, and constituted as noted above maintain satisfactory potency at room temperature (15-25 °C) or under refrigeration (4 °C) as shown in the following table:

**MESPEC** should not be mixed with or physically added to solutions containing other medicines.

| Diluent | Hours stable at 15-25 °C | Hours stable at 4 °C |
|---|---|---|
| Vials constituted with water for injection for bolus injection | 8 | 48 |
| Infusions (1-20 mg/ml) prepared with: 0,9 % sodium chloride | 3 | 24 |
| 5 % dextrose | 1 | 1 |

Solutions of **MESPEC** should not be frozen.

Method of Administration

For intravenous use only.

### 4.3 Contraindications

**MESPEC** is contra-indicated in

- Patients who have demonstrated hypersensitivity to meropenem or to any of the excipients listed in section 6.1.
- Patients who have a history of hypersensitivity to carbapenems, penicillins, cephalosporins or other beta-Lactam antibiotics, may also be hypersensitive to **MESPEC** and is contra-indicated in patients.

### 4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship

The selection of **MESPEC** 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.

*Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp resistance*

Resistance to penems of *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter* spp. varies across the world. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported with meropenem (see sections 4.8).

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.

*Antibiotic-associated colitis*

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial 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 [PRODUCT NAME], (see section 4.8). Discontinuation of therapy with [PRODUCT NAME], and the administration of specific treatment for *Clostridium difficile* should be considered.

Medicinal products that inhibit peristalsis should not be given.

Skin reactions

*"Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and*

*acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected. beta-lactam antibiotics should be discontinued.*

*Seizures*

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

*Hepatic function monitoring*

Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) (see section 4.8).
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 section 4.2).

*Direct antiglobulin test (Coombs test) seroconversion*

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

*Concomitant use with valproic acid/sodium valproate/valpromide.*

The concomitant use of **MESPEC** 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", [PRODUCT NAME], may only be used in children over 3 months of age.

*Contains sodium*

**MESPEC** contains 104 mg and 208 mg sodium per dose in the 500 mg and 1 000 mg respectively, equivalent to 5.2 % and 10.4 % respectively of the WHO recommended maximum daily intake for sodium.

Meropenem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

**4.5 Interaction with other medicinal products and other forms of interaction**

No specific medicinal product interaction studies other than probenecid were conducted.

Probenecid competes with **MESPEC** 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 [PRODUCT NAME]. Caution is required if probenecid is co-administered with [PRODUCT NAME].

The potential effect of **MESPEC** on the protein binding of other medicinal products or metabolism has not been studied. However, the protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.

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 valproic acid/sodium valproate/valpromide with carbapenem agents is not considered to be manageable and therefore should be avoided (see section 4.4).

*Oral anti-coagulants*

Simultaneous administration of **MESPEC** 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 normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after coadministration of antibiotics with an oral anti-coagulant agent.

*Paediatric population*

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

There are no or limited amount of data from the use of **MESPEC** in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

The safety in pregnant women has not been established. [PN] should therefore not be used during pregnancy.

Breastfeeding

Small amounts of **MESPEC** have been reported to be excreted in human milk. **MESPEC** should not be used in breastfeeding women unless the potential benefit for the mother justifies the potential risk to the baby.

**4.7 Effects on ability to drive and use machines**

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**

Summary of the safety profile

In a review of patients treated with meropenem, the most frequently reported meropenem related adverse reactions were diarrhoea, nausea/vomiting and injection site inflammation. The most commonly reported meropenem related laboratory adverse events were thrombocytosis and increased hepatic enzymes.

Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1:

| System Organ Class | Frequency | Event |
|---|---|---|
| Infections and infestations | Less frequent | oral and vaginal candidiasis |
| Blood and lymphatic system disorders | Frequent | thrombocythaemia |
| | Less frequent | eosinophilia, thrombocytopenia, leucopenia, neutropenia, |
| Immune system disorders | Less frequent | Angioedema ,anaphylaxis |
| Nervous system disorders | Frequent | headache |
| | Less frequent | paraesthesiae |
| | Less frequent | convulsions (see section 4.4) |
| Gastrointestinal disorders | Frequent | diarrhoea, vomiting, nausea, |
| | Less frequent | antibiotic-associated |
| Hepatobiliary disorders | Less frequent | Transaminases increased, blood alkaline phosphatase increased, blood |
| | Less frequent | blood bilirubin increased |
| Skin and subcutaneous tissue disorders | Frequent | rash, pruritis |
| | Less frequent | Urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme. |
| | Frequency unknown | Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome)<br>Acute generalized exanthematous pustulosis (AGEP)<br>toxic epidermal necrolysis (TEN) |

| | | |
|---|---|---|
| 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

**MESPEC** may be used in children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.

**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. Healthcare provders are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse DrugReactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section 4.2. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile described in section 4.8 . Treatment symptomatic and supportive.

In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH02

Mechanism of action

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).

There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterials agents when the mechanism involved include impermeability and/or an efflux pump(s).

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.

*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 pneumonia

All methicillin-resistant staphylococci are resistant to meropenem

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.

A 30- minute intravenous infusion of a single dose of 500 mg and 1 000 mg meropenem in normal volunteers results in peak plasma levels of approximately 11µg/mL for the 250 mg dose, 23 µg/mL for the 500 mg dose, 49 µg/mL for the 1000 mg dose, and 115 µg/mL following the 2000 mg dose. A 5- minute intravenous bolus injection of meronem in normal volunteers resulted in peak plasma levels of approximately 52 µg/mL for 500 mg dose and 112 µg/mL for the 1 000 mg dose respectively Intravenous infusions of 1 000 mg of meropenem over 2 minutes, 3 minutes and 5 minutes resulted in peak plasma levels of 110, 91and 94 µg/mL, respectively.

After an intravenous dose of 500 mg, plasma levels of meropenem decline to values of µg/mL or less 6 hours after administration.

When multiple doses are administered at 8 hourly intervals to subject's 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 %.

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 µg/mL are maintained for up to 5 hours at the 500 mg dose. No accumulation of rneropenem in plasma or urine was observed with regimen's using 500 mg administered every 8 hours or 1 000 mg administered every 6 hours in volunteers with normal renal function.
When multiple doses are administered 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 cerebro- spinal fluid (CSF) of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

The plasma protein binding of meropenem is approximately 2 %.

Biotransformation

There is one metabolite which is microbiologically inactive

Elimination

Meropenem is mostly excreted unchanged by the kidneys. The
elimination half-life is approximately 1 hour in patients with normal
renal function. The pharmacokinetics are linear over the dose range
of 10 to 40 mg/kg.

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

*Hepatic insufficiency:*

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

*Elderly*:

Elderly patients with age-related reduction in creatinine clearance, requires a reduction of dosage

Paediatric population

The pharmacokinetics of meropenem in children are essentially similar to those in adults. The elimination half-life for 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.

5.3 Preclinical safety data

There was no evidence reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

## 6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of **MESPEC** are sodium carbonate as a solubilizer and buffering agent.

### 6.2 Incompatibilities

**MESPEC** is to be administered either by intravenous bolus or intravenous infusion.

For intravenous bolus administration, the **MESPEC** must be constituted with Sterile Water for Injection which gives a final concentration of 50 mg/ml. The reconstituted solution

may be stored at room temperature for 3 hrs at 25°C(15-25ºC) and 4 hrs at 2-8ºC.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Keep the vial in the carton until required for use.

Do not use **MESPEC** if you observe any discoloration upon storage.

### 6.5 Nature and contents of container

**MESPEC 500 mg**:

Powder for injection is filled in 30 ml clear glass tubular vial type-I stoppered with grey rubber stoppers and sealed with aluminium seal having taxim blue colour PP disc.

Pack size: 1's: Printed cardboard carton containing one vial only.

**MESPEC 1000 mg**:

Powder for injection is filled in 40 ml clear glass tubular vial type-I stoppered with grey rubber stoppers and sealed with aluminium seal having white colour PP disc.

Pack size: 1's: Printed cardboard carton containing one vial only.

### 6.6 Special precautions for disposal and other handling

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

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12

Johannesburg

South Africa

## 8. REGISTRATION NUMBER

**MESPEC 500 mg:** 49/20.1.1/1222

**MESPEC 1000 mg:** 49/20.1.1/1223

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2021

## 10. DATE OF REVISION OF THE TEXT

23 November 2023