PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MEROJECT 500 mg powder for injection

MEROJECT 1 g powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

MEROJECT 500 mg: Each vial contains 500 mg meropenem anhydrous (as trihydrate).

MEROJECT 1 g: Each vial contains 1000 mg meropenem anhydrous (as trihydrate).

Sodium content:

MEROJECT 500 mg: 45 mg/sodium/vial

MEROJECT 1 g: 90 mg/sodium/vial

MEROJECT contains sodium which should be taken into consideration by patients on a controlled sodium diet.

MEROJECT is sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to light yellow crystalline sterile powder for injection. The reconstituted solution is a clear colourless solution practically free from particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEROJECT is indicated for the 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, Pseudomonas aeruginosa, Morganella morganii, Proteus mirabilis, Serratia marcescens, Citrobacter freundii.
- **Pelvic Inflammatory Disease (including tubo-ovarian abscess) and endometritis due**

to:

Staphylococcus aureus (methicillin-susceptible strains only), *Staphylococcus epidermidis*, *Streptococcus haemolyticus*, *Staphylococcus* spp. (coagulase negative), *Streptococcus agalactiae* Group B, *Pseudomonas aeruginosa, Streptococcus beta-haemolytic, Streptococcus faecalis, Staphylococcus gamma haemolyticus,* Group D Streptococcus (enterococcus and non-enterocossus*), Streptococcus viridans, Acinetobacter anitratus, Acinetobacter lwoffii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Gardnerella vaginalis, Klebsiella pneumoniae, Neisseria gonorrhoeae, Proteus mirabilis, Enterococcus faecalis, Bacteroides fragilis group, Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus*

- **Skin and skin structure infections in adults due to:**

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

Staphylococcus aureus, Micrococcus spp., Streptococcus sanguis, Streptococcus epidermidis, Streptococcus mitis, Escherichia coli, Pseudomonas aeruginosa.

- **Intra-abdominal abscess and peritonitis due to:**

  Streptococcus milleri, Streptococcus mitior, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides ovatus, Bacteroides distasonis, Bacteroides thetaiotaomicron, Bacteroides vulgatus, Klebsiella oxytoca, Clostridium perfringens.

- **Polymicrobial infections**

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

4.2 Posology and method of administration

<u>Posology</u>:

Adults:

Usual dose: Administration of 500 mg to 1 g by intravenous infusion every 8 hours.

Dose Exceptions:

a) Dose of 1 g every 8 hours for febrile episodes in neutropenic patients.

b) Dose of 2 g every 8 hours for meningitis.

In critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections, concomitant use of an aminoglycoside is recommended, and regular sensitivity testing is recommended.

Impaired renal function – Adult dosage schedule:

In adult patients with creatinine clearance below 51 m/min the dosage of MEROJECT should be reduced as follows:

Creatinine Clearance (ml/min)	**Dose**
26 – 50	1 g every 12 hours
10 - 25	500 mg every 12 hours
< 10	500 mg every 24 hours

Meropenem is cleared by haemodialysis. If continued use with MEROJECT 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.

Impaired hepatic function:

MEROJECT dosage need not be adjusted in patients with impaired hepatic function.

Elderly:

MEROJECT dosage need not be adjusted for the elderly with normal renal function or creatinine clearance values above 50 ml/min.

Children:

No data on meropenem is available for children.

In children over 50 kg weight, the adult dosage schedule should be used.

Children older than three months and up to 12 years are to be administered an intravenous dose of 10 to 40 mg/kg every 8 hours, depending on the type and severity of the infection, the condition of the patient and known susceptibility of the organism(s).

Exceptions:

Meningitis: An 8 hourly 40 mg/kg dose should be given.

There is no experience in children with renal impairment.

Preparation of MEROJECT:

Rapid intravenous injection:

Water for injection (5 ml/250 mg: 10 ml for 500 mg and 20 ml for 1 g MEROJECT respectively). This provides an approximate available concentration of 50 mg/ml. Constituted solutions are clear or pale yellow.

Intravenous infusion:

The MEROJECT vial may be reconstituted as above or with a compatible infusion fluid (see section 6.3) and the resultant solution added to an infusion container.

Solutions of MEROJECT should not be frozen.

Method of administration:

MEROJECT is intended for intravenous injection administered by intravenous infusion over 15 to 30 minutes or by rapid intravenous injection of 3 to 5 minutes every 8 hours.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

4.3 Contraindications:

MEROJECT is contraindicated in:

- Patients with hypersensitivity to meropenem or any of the other ingredients of MEROJECT.

- Patients hypersensitive (allergic) to carbapenems, penicillins or other beta-lactam antibacterials (e.g., cephalosporins, imipenem) may be hypersensitive to meropenem.
- Pregnancy and lactation **(see section 4.6).**

4.4 Special warnings and special precautions use:

Safety and efficacy have not been established in children less than 3 months old and MEROJECT is not recommended for children younger than 3 months (**see section 4.2**).

Antibiotic-associated colitis and pseudomembranous colitis have been reported with MEROJECT 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. Discontinuation of therapy with MEROJECT and the administration of specific treatment for *Clostridium difficile* should be considered.

Serious and occasionally fatal hypersensitivity reactions have been reported **(see** sections 4.3 and 4.8).

Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to MEROJECT.

Before initiating therapy with MEROJECT, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

If a severe allergic reaction occurs, MEROJECT should be discontinued, and appropriate measures taken.

MEROJECT should be given with caution to patients with renal impairment, and the dose reduced appropriately.

Care is necessary is in patients with CNS disorders such as epilepsy as seizures have been reported during the treatment with carbapenems, although MEROJECT may have less potential to induce seizures than imipenem.

Liver function monitoring is essential in patients with pre-existing liver disorders during treatment with MEROJECT due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis) and vanishing bile duct syndrome. There is no dose adjustment necessary.

A positive direct or indirect antiglobulin (Coombs) test may develop.

The concomitant use of MEROJECT (powder for injection) and valproic acid/sodium valproate/valpromide is not recommended (**see** section 4.5).

4.4 Interaction with other medicines and other forms of interaction

Probenecid inhibits the renal excretion of MEROJECT thereby increasing its plasma concentrations and prolonging the elimination half-life.

As the potency and duration of action of MEROJECT dosed without probenecid are adequate, the co-administration of probenecid with MEROJECT is not recommended.

Valproic acid plasma levels may be reduced by meropenem 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).

Simultaneous administration of MEROJECT with warfarin may augment its anti-coagulant

effects. It is recommended that the INR should be monitored frequently during and shortly after co-administration of MEROJECT with an oral anti-coagulant agent such as warfarin.

4.6 Fertility, pregnancy and lactation

The safety of MEROJECT has not been established during pregnancy and the use of MEROJECT is not recommended (see section 4.3).

The use of MEROJECT is not recommended during breastfeeding.

4.7 Effects on ability to drive and use machines:

Although no data is available, MEROJECT is not expected to affect the ability to drive or operate machinery.

4.8 Undesirable effects

Tabulated list of adverse effects

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Oral and vaginal candidiasis, pharyngitis

Blood and the lymphatic system disorders	*Frequent:* *Less frequent:*	Thrombocythaemia Eosinophilia, neutropenia, leukopenia, agranulocytosis thrombocytopenia lymphadenopathy, haemolytic anaemia, positive direct or indirect antiglobulin test may develop
Immune system disorders	Less frequent	Angioedema, manifestations of anaphylaxis
Metabolism and nutrition disorders	*Less frequent:*	Hypoglycaemia
Nervous system disorders	*Less frequent:*	Headache, paraesthesia, convulsions
Vascular disorders	*Frequency unknown:*	Peripheral vascular disorder
Respiratory, thoracic and mediastinal disorders:	*Less frequent:*	Epistaxis, apnoea

Gastrointestinal disorders	*Frequent:* *Less frequent:*	Nausea, vomiting, constipation, diarrhoea, abdominal pain Pseudomembranous colitis
Hepato-biliary disorders	*Frequent:*	Increases in serum transaminases, bilirubin, alkaline phosphatase, lactic dehydrogenase
Skin and subcutaneous tissue disorders	*Less frequent:*	Rash, pruritus, urticarial, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders	*Less frequent:*	Increased blood creatinine, increased blood urea
General disorders and administrative site conditions	*Frequent:*	Inflammation, pain, thrombophlebitis

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

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

4.9 Overdose

Renal impairment may lead to accidental overdosage of MEROJECT if the dose is not adjusted as described in **Section 4.2**. The treatment is symptomatic and supportive and haemodialysis to be implemented in patients with renal impairment to remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibiotic

ATC code: J01DH02

Pharmacological classification: A20.1.1 Broad spectrum antibiotics

Mechanism of action:

Meropenem is a carbapenem antibiotic which interferes with vital bacterial cell wall synthesis through binding to penicillin-binding proteins (PBPs) to exert its bacterial action. Meropenem has a high degree of stability to hydrolysis by almost all beta-latamases produced by gram-positive and gram-negative bacteria.

Meropenem has been shown *in vitro* to act synergistically with various antibiotics. A post-antibiotic effect has been demonstrated for meropenem *in vitro* and *in vivo.*

In vitro sensitivity does not necessarily imply clinical sensitivity.

Inherently resistant organisms:

Gram-negative aerobes:

Stenotrophomonas maltophilia, Legionella species

Other micro-organisms:

Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii

Mycoplasma pneumoniae

5.2 Pharmacokinetic properties:

Absorption

Meropenem is well distributed in most body fluids and tissues with a low (2 %) protein binding. Peak serum concentration after a 30 minute intravenous infusion of a single-dose of meropenem in normal volunteers reaches 23 µ/ml for the 500 mg dose, 49 µ/ml for the 1 g dose.

Peak serum concentration after a 5 minute intravenous bolus injection of meropenem in normal volunteer results' reaches of approximately 52 µ/ml for the 500 mg dose and 112 µ/ml for the 1 g dose.

When multiple doses are administered at 8 hourly intervals to subjects with normal renal function accumulation of meropenem dose do not occur.

Metabolism

Meropenem is metabolised by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite.

Elimination:

Approximately 70 % of an administered dose is recovered in the urine as unchanged meropenem over 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.

Urinary concentrations of meropenem in excess of 10 µ/ml are maintained for up to 5 hours at the 500 mg dose.

The plasma elimination half-life of meropenem may be prolonged in patients with renal impairment.

Meropenem is primarily excreted unchanged, with one inactive metabolite having been identified.

Special Populations

Renal insufficiency

Renal impairment results in higher plasma AUC and longer half-life for meropenem. The AUC of the microbiologically inactive metabolite considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with 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.

Elderly:

Pharmacokinetic studies in the elderly have shown a reduction in plasma clearance of meropenem which correlated with age-associated reduction in creatinine clearance.

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 after a single administration and above and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg.

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 in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium carbonate

6.2 Incompatibilities

Compatibility of MEROJECT with other medicines has not been established and should not be mixed with other medicines except those mentioned in section 6.3.

6.3 Shelf life

Powder:

48 months

Reconstituted solution:

Diluent	**Storage temperature 25˚C**	**Storage temperature 4 ˚C**
Water for injection	2 h	12 h
Sodium chloride 0,9 %	4 h	24 h
Dextrose 5 %	1 h	4 h
Dextrose 10 %	1 h	2 h
Dextrose 5 % and Sodium chloride 0,225 %	2 h	4 h
Dextrose 5 % and Sodium chloride 0,9 %	1 h	4 h

Dextrose 5 % and Potassium chloride 0,15%	1 h	6 h
Mannitol 2,5 %	2 h	16 h
Mannitol 10 %	1 h	8 h
Normosol M in Dextrose 5 %	1 h	8 h
Dextrose 5 % and Sodium bicarbonate 0,02 %	1 h	6 h

6.4 Special precautions for storage

Powder:

Store at or below 25 °C. Do not freeze.

Keep in the outer carton until required for use
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

MEROJECT 500 mg: 20 ml clear colourless Type I glass vials with Type I grey butyl rubber closures and grey aluminium secure caps with a plastic flip-top cover, available in pack size of one vial.

MEROJECT 1 g: 30 ml clear colourless Type I glass vials with Type I grey butyl rubber closures and grey aluminium secure caps with a plastic flip-top cover, available in pack size of one and ten vials.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Single use only. Discard any unused portion.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa
Tel: 021 707 7000

8. REGISTRATION NUMBERS

MEROJECT 500 mg:

A42/20.1.1/0280

MEROJECT 1 g:

A42/20.1.1/0281

9. DATE OF FIRST AUTHORISATION

07 December 2012

10. DATE OF REVISION OF THE TEXT

16 February 2022

NAMIBIA:

MEROJECT 500 mg:

NS3 13/20.1.1/0238

MEROJECT 1 g:

NS3 13/20.1.1/0239

MOZAMBIQUE:

MEROJECT 500:

J5669

MEROJECT 1000:

J5668