Prescribing Information (Summary of Product Characteristics)

1. Name of the medicinal product

HEKOPENEM 1g (Meropenam for Injection USP 1g)

2. Qualitative and Quantitative composition

Each vial contains:

Meropenem Trihydrate (Sterile) USP

equivalent to Anhydrous Meropenem. 1 g

Sodium Carbonate (Sterile) added as buffer

(Sodium content- 90.2 mg)

FOR I.V. Use Only

3. Pharmaceutical form

Dry Injection

A white to off-white crystalline powder filled in clear colourless glass vial, sealed with flip off-seal.

4. Clinical Particulars

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenemsATC code: J01DH02

1. Therapeutic indications

HEKOPENEM 1g is indicated for the treatment of the following infections in adults andchildren aged 3 months and older:

- Severe pneumonia, including hospital and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis

Meropenem may be used in the management of neutropenic patients with fever that is sus-pected to be due to a bacterial infection.

Meropenem may be used in the treatment of patients with bacteraemia that occurs in asso-ciation with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterialagents.

2. Posology and method of administration

Posology

The dose of meropenem administered and the duration of treatment should take into ac- count the type of infection to be treated, including its severity, and the clinical response.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species (e.g. Entero- bacteriaceae, Pseudomonas aeruginosa, Acinetobacter spp.), or very severe infections.

Adults and Adolescents

Infection	**Dose to be administered every 8hours**
Severe pneumonia including hospital and venti- lator-associated pneumonia.	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g
Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration ofa 2 g dose in adults as an intravenous bolus injection.

Renal impairment

The dose for adults and adolescents should be adjusted when creatinine clearance is less than 51 ml/min, as shown below. There are limited data to support the administration of these dose adjustments for a unit dose of 2 g.

r e a t i n i n e clearance(ml/min)	**Dose**(based on “unit” dose range of 500 mg or 1 g or 2 g, see table above)	**Frequency**
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

Meropenem is cleared by haemodialysis and haemofiltration. The required dose should be administered after completion of the haemodialysis cycle.

There are no established dose recommendations for patients receiving peritoneal dialysis.Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment

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

Children under 3 months of age

The safety and efficacy of meropenem in children under 3 months of age have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regimen.

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

Infection	**Dose to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated pneumonia.	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

Children over 50 kg body weight

The adult dose should be administered.

There is no experience in children with renal impairment.

Method of administration

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, meropenem doses of up to 20 mg/kg may be given as an intravenous bolus over approximately 5 minutes. There are limited safety data available to support the ad- ministration of a 40 mg/kg dose in children as an intravenous bolus injection.

3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hypersensitivity to any other carbapenem antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any othertype of betalactam antibacterial agent (e.g. penicillins or cephalosporins).

4. Special warnings and precautions for use

The selection of meropenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as se- verity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.

Antibiotic-associated colitis

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial 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 meropenem Discontinuation of therapy with meropenem and the administration of specific treatment for Clostridium difficile should be considered

Seizures

Seizures have infrequently been reported during treatment with carbapenems, includingmeropenem.

Hepatic function monitoring

Hepatic function should be closely monitored during treatment with meropenem due tothe risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis.

Use in patients with liver disease: patients with pre-existing liver disorders should haveliver function monitored during treatment with meropenem.

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 meropenem and valproic acid/sodium valproate/valpromide is not recommended.

5. Interaction with other medicinal products and other forms of interaction

Probenecid competes with Meropenem for active tubular secretion and thus inhibits the re- nal excretion of Meropenem with the effect of increasing the elimination half-life and plas- ma concentration of Meropenem.

Decreases in blood levels of Valproic acid have been reported when it is co-administeredwith Carbapenem agents resulting in a 60-100 % decrease in Valproic acid levels in about two days.

Oral anti-coagulants

Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant ef- fects. There have been many reports of increases in the anti-coagulant effects of orally ad- ministered anti-coagulant agents, including warfarin in patients who are concomitantly re- ceiving antibacterial agents. The risk may vary with the underlying infection, age and gen- eral status of the patient so that the contribution of the antibiotic to the increase in INR (in- ternational normalised ratio) is difficult to assess. It is recommended that the INR should bemonitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

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6. Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of meropenem in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductivetoxicity.

As a precautionary measure, it is preferable to avoid the use of meropenem during pregnancy.

Breastfeeding

Small amounts of meropenem have been reported to be excreted in human milk. Meropenem should not be used in breast-feeding women unless the potential benefit for the mother justi- fies the potential risk to the baby.

7. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that head-ache, paraesthesia and convulsions have been reported for meropenem.

8. Undesirable effects

Summary of the safety profile

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3 %), rash (1.4 %), nausea/vomiting (1.4 %) and injection site inflammation (1.1 %). The most commonly re- ported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and in- creased hepatic enzymes (1.5-4.3 %).

Tabulated risk of adverse reactions

In the table below all adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000) 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	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anaemia
Immune system disorders	Uncommon	angioedema, anaphylaxis.
Nervous system disorders	Common	headache
	Uncommon	paraesthesiae
	Rare	Convulsions.
Gastrointestinal disorders	Common	diarrhoea, vomiting, nausea, abdominal pain
	Uncommon	antibiotic-associated colitis
Hepatobiliary disorders	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.
	Uncommon	blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritis
	Uncommon	urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme.
	Not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS

		Syndrome)
Renal and urinary dis-orders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration siteconditions	Common	inflammation, pain
	Uncommon	Thrombophlebitis, pain at the injection site

Paediatric population

Meropenem is licensed for children over 3 months of age. There is no evidence of an in- creased 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.

9. Overdose

In case of accidental overdosage treatment should be symptomatic and supportive.

5. Pharmacological properties

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).

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 (11-27 l) and the mean clearance is 287 ml/minat 250 mg falling to 205 ml/min at 2 g.

Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean Cmax 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 Cmax 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 oc-cur.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for in- tra-abdominal infections showed a comparable Cmax and half-life to normal subjects buta greater volume of distribution 27 l.

Distribution

The average plasma protein binding of meropenem was approximately 2 % and was in- dependent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. 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.

Biotransformation

Meropenem is metabolised by hydrolysis of the beta-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.

3. Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evi dence 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 LD50 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

1. List of Excipients

Diluent: Sterile water for injection (diluent)

2. Incompatibilities

It is a well-developed established product. No incompatibility data is available.

3. Shelf Life

24 months form the date of manufacturing

4. Special Precautions for Storage

Store at a temperature below 30^0C. Protect from light & moisture.

5. Nature and Contents of container

1 g. sterile powder for injection filled in 30ml glass vial (USP Type-I) duly labeled and sealed with flip-off seal, along with two plastic ampoule of 10ml SWFI in a tray, packedin printed monocarton with insert.

6. Special precautions for disposal and other handling

Injection

Meropenem to be used for bolus intravenous injection should be constituted with sterilewater for injection.

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. The solutions should be inspected visually for particles and discolouration prior to administration. Only clear colourless to yellow solution, free from particles should be used.

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

7. Mode of selling

Prescription Only Medicine

7. Marketing Authorization Holder

UNGUJA PHARMACY LIMITED
Plot 10, Block 19, Max Mbwana Street Kariakoo Area,
P.O.Box 2657,
Dar –Es-Salaam
Tanzania

8. Marketing Authorization Number

TAN 22 HM 0401

9. Date of First Authorization/Renewal of Authorization

21/09/2022

10. Date of Revision of the Text

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