

## Summary Product Characteristics (SPC)

### 1. Name of the medicinal product

MEROZ 500MG

### 2. Qualitative and quantitative composition

Each vial contains meropenem trihydrate equivalent to 500 mg anhydrous meropenem.  
Excipients with known effect: Each 500 mg vial contains 45.1 mg of Sodium As Sodium Carbonate For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

**Dosage form:** Dry powder for injection

**Description:** Colorless to white or light-yellow crystals or crystalline powder.

## 4 Clinical particulars

### 4.1 Therapeutic indications

Meropenem is indicated for the treatment of the following infections in adults and children 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 suspected to be due to a bacterial infection.

Treatment of patients with bacteraemia that occurs in association 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 antibacterial agents.

## 4.2 Posology and method of administration

### Posology

The dose of meropenem administered and the duration of treatment should take into account 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. Enterobacteriaceae *Pseudomonas aeruginosa* or *Acinetobacter* spp.) or very severe infections.

Additional considerations for dosing are needed when treating patients with renal insufficiency.

### Adults and adolescents

| Infection                                                                | Dose to be administered every 8 hours |
|--------------------------------------------------------------------------|---------------------------------------|
| Severe pneumonia including hospital and ventilator-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 of a 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.

| <b>Creatinine clearance (ml/min)</b> | <b>Dose</b><br>(based on “unit” dose range of 500 mg or 1 g or 2 g, see table above) | <b>Frequency</b> |
|--------------------------------------|--------------------------------------------------------------------------------------|------------------|
| 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.

#### **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 administration of a 40 mg/kg dose in children as an intravenous bolus injection.

For instructions on reconstitution of the medicinal product before administration.

Meropenem is a white to pale yellow crystalline powder for solution for injection or infusion in vial.

Product after reconstitution is clear colourless to yellow solution

## **4.3 Contraindications**

Hypersensitivity to any other carbapenem antibacterial agent.

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

#### **4.4 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 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 European Union. Prescribers are advised to take into account the local prevalence of resistance in these bacteria to penems.

##### **Hypersensitivity reactions**

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported.

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.

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.

If signs and symptoms suggestive of these reactions appear, meropenem 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 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. Medicinal products that inhibit peristalsis should not be given.

## **Seizures**

Seizures have infrequently been reported during treatment with carbapenems, including meropenem.

## **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).

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.

## **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.

This medicinal product contains 90 mg sodium per dose, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The maximum daily dose of this product is equivalent to  $\geq 27\%$  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 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. Caution is required if probenecid is co-administered with meropenem.

The potential effect of meropenem 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.

#### **Oral anti-coagulants**

Simultaneous administration of antibiotics 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 co-administration of antibiotics with an oral anti-coagulant agent.

#### **Paediatric population**

Interaction studies have only been performed in adults.

### **4.6 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 reproductive toxicity.

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

#### **Lactation**

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 justifies the potential risk to the baby.

### **4.7 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 reported meropenem-related laboratory adverse events were thrombocytosis (1.6 %) and increased 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  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                                                                               |
| Psychiatric disorders                  | Rare      | Delirium                                                                                              |
| 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  | toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme urticaria                   |
|                                        | Not known | Drug Reaction with Eosinophilia and Systemic Symptoms, acute generalised exanthematous pustulosis     |
| Renal and urinary disorders            | Uncommon  | blood creatinine increased, blood urea increased                                                      |
|                                        | Common    | inflammation, pain                                                                                    |

|                                                      |          |                                              |
|------------------------------------------------------|----------|----------------------------------------------|
| General disorders and administration site conditions | 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 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.

## **4.8 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, are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.

In individuals with normal renal function, rapid renal elimination will occur.

Haemodialysis will remove meropenem and its metabolite.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org> ,

## **5 Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group (ATC code): 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).

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship

Similar to other beta-lactam antibacterial agents, the time that meropenem concentrations exceed the MIC ( $T > MIC$ ) has been shown to best correlate with efficacy. In preclinical models meropenem demonstrated activity when plasma concentrations exceeded the MIC of the infecting organisms for approximately 40 % of the dosing interval. This target has

not been established clinically.

#### Mechanism of resistance

Bacterial resistance to meropenem may result from: (1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) (2) reduced affinity of the target PBPs (3) increased expression of efflux pump components, and (4) production of beta-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in the European Union.

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).

#### Breakpoints

| Organism                                                                                   | Susceptible (S)<br>(mg/l) | Resistant (R)<br>(mg/l) |
|--------------------------------------------------------------------------------------------|---------------------------|-------------------------|
| <i>Enterobacteriaceae</i>                                                                  | ≤ 2                       | > 8                     |
| <i>Pseudomonas</i> spp.                                                                    | ≤ 2                       | > 8                     |
| <i>Acinetobacter</i> spp.                                                                  | ≤ 2                       | > 8                     |
| <i>Streptococcus</i> groups A, B, C, G                                                     | note 6                    | note 6                  |
| <i>Streptococcus pneumoniae</i> <sup>1</sup>                                               | ≤ 2                       | > 2                     |
| <i>Viridans</i> group <i>streptococci</i> <sup>2</sup>                                     | ≤ 2                       | > 2                     |
| <i>Enterococcus</i> spp.                                                                   | --                        | --                      |
| <i>Staphylococcus</i> spp.                                                                 | note 3                    | note 3                  |
| <i>Haemophilus influenzae</i> <sup>1,2</sup> and <i>Moraxella catarrhalis</i> <sup>2</sup> | ≤ 2                       | > 2                     |
| <i>Neisseria meningitidis</i> <sup>2,4</sup>                                               | ≤ 0.25                    | > 0.25                  |
| Gram-positive anaerobes except <i>Clostridium difficile</i>                                | ≤ 2                       | > 8                     |
| Gram-negative anaerobes                                                                    | ≤ 2                       | > 8                     |
| <i>Listeria monocytogenes</i>                                                              | ≤ 0.25                    | > 0.25                  |
| Non-species related breakpoints <sup>5</sup>                                               | ≤ 2                       | > 8                     |

<sup>1</sup> Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

<sup>2</sup> Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

<sup>3</sup> Susceptibility of staphylococci to carbapenems is inferred from the cefoxitin susceptibility.

<sup>4</sup> Breakpoints relate to meningitis only.

<sup>5</sup> Non-species related breakpoints have been determined mainly from PK/PD data and are independent of the MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Non species related breakpoints are based on the following dosages: EUCAST breakpoints apply to meropenem 1000 mg x 3 daily administered intravenously over 30 minutes as the lowest dose. 2 g x 3 daily was taken into consideration for severe infections and in setting the I/R breakpoint.

<sup>6</sup> The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.

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.

### Commonly susceptible species

|                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------|
| <b>Gram-positive aerobes</b>                                                                                    |
| <i>Enterococcus faecalis</i> <sup>§</sup>                                                                       |
| <i>Staphylococcus aureus</i> (methicillin-susceptible) <sup>£</sup>                                             |
| <i>Staphylococcus species</i> (methicillin-susceptible) including <i>Staphylococcus epidermidis</i>             |
| <i>Streptococcus agalactiae</i> (Group B)                                                                       |
| <i>Streptococcus milleri</i> group ( <i>S. anginosus</i> , <i>S. constellatus</i> , and <i>S. intermedius</i> ) |
| <i>Streptococcus pneumoniae</i>                                                                                 |
| <i>Streptococcus pyogenes</i> (Group A)                                                                         |
| <b>Gram-negative aerobes</b>                                                                                    |
| <i>Citrobacter freundii</i>                                                                                     |
| <i>Citrobacter koseri</i>                                                                                       |
| <i>Enterobacter aerogenes</i>                                                                                   |
| <i>Enterobacter cloacae</i>                                                                                     |

|                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Escherichia coli</i><br><i>Haemophilus influenzae</i><br><i>Klebsiella oxytoca</i><br><i>Klebsiella pneumoniae</i><br><i>Morganella morganii</i><br><i>Neisseria meningitidis</i><br><i>Proteus mirabilis</i> <i>Proteus vulgaris</i><br><i>Serratia marcescens</i> |
| <b>Gram-positive anaerobes</b><br><i>Clostridium perfringens</i><br><i>Peptoniphilus asaccharolyticus</i><br><i>Peptostreptococcus</i> species (including <i>P. micros</i> , <i>P. anaerobius</i> , <i>P. magnus</i> )                                                 |
| <b>Gram-negative anaerobes</b><br><i>Bacteroides caccae</i> <i>Bacteroides fragilis</i> group <i>Prevotella bivia</i><br><i>Prevotella disiens</i>                                                                                                                     |
| <b>Species for which acquired resistance may be a problem</b> <b>Gram-positive aerobes</b><br><i>Enterococcus faecium</i> §†<br><b>Gram-negative aerobes</b><br><i>Acinetobacter</i> species<br><i>Burkholderia cepacia</i><br><i>Pseudomonas aeruginosa</i>           |
| <b>Inherently resistant organisms</b><br><b>Gram-negative aerobes</b><br><i>Stenotrophomonas maltophilia</i><br><i>Legionella</i> species<br><b>Other micro-organisms</b>                                                                                              |

|                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Chlamydophila pneumoniae</i><br><i>Chlamydophila psittaci</i> <i>Coxiella</i><br><i>burnetii</i><br><i>Mycoplasma pneumonia</i>                                                                                                                                                                                    |
| \$ Species that show natural intermediate susceptibility<br>£ All methicillin-resistant staphylococci are resistant to meropenem<br>† Resistance rate $\geq$ 50% in one or more EU countries.                                                                                                                         |
| Glanders and melioidosis: Use of meropenem in humans is based on <i>in vitro</i> <i>B.mallei</i> and <i>B. pseudomallei</i> susceptibility data and on limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of glanders and melioidosis. |

## 5.2 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/min at 250 mg falling to 205 ml/min at 2 g. Doses of 500, 1000 and 2000 mg doses infused over 30 minutes give mean C<sub>max</sub> 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 C<sub>max</sub> 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 occur.

A study of 12 patients administered meropenem 1000 mg 8 hourly post-surgically for intra-abdominal infections showed a comparable C<sub>max</sub> and half-life to normal subjects but a greater volume of distribution 2.7 l.

### Distribution

The average plasma protein binding of meropenem was approximately 2 % and was independent 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.

## **Renal insufficiency**

Renal impairment results in higher plasma AUC and longer half-life for meropenem. There were AUC increases of 2.4 fold in patients with moderate impairment (CrCL 33-74 ml/min), 5 fold in severe impairment (CrCL 4-23 ml/min) and 10 fold in haemodialysis patients (CrCL <2 ml/min) when compared to healthy subjects (CrCL >80 ml/min). The AUC of the microbiologically inactive ring opened metabolite was also considerably increased in patients with renal impairment. Dose adjustment is recommended for patients with moderate and severe renal impairment.

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.

## **Adult patients**

Pharmacokinetic studies performed in patients have not shown significant pharmacokinetic differences versus healthy subjects with equivalent renal function. A population model developed from data in 79 patients with intra-abdominal infection or pneumonia, showed a dependence of the central volume on weight and the clearance on creatinine clearance and age.

## **Paediatric population**

The pharmacokinetics in infants and children with infection at doses of 10, 20 and 40 mg/kg showed C<sub>max</sub> values approximating to those in adults following 500, 1000 and

2000 mg doses, respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months  $t_{1/2}$  1.6 hours). The mean meropenem clearance values were 5.8 ml/min/kg (6-12 years), 6.2 ml/min/kg (2- 5 years), 5.3 ml/min/kg (6-23 months) and 4.3 ml/min/kg (2-5 months). Approximately 60 % of the dose is excreted in urine over 12 hours as meropenem with a further 12 % as metabolite. Meropenem concentrations in the CSF of children with meningitis are approximately 20 % of concurrent plasma levels although there is significant inter- individual variability.

The pharmacokinetics of meropenem in neonates requiring anti-infective treatment showed greater clearance in neonates with higher chronological or gestational age with an overall average half-life of 2.9 hours. Monte Carlo simulation based on a population PK model showed that a dose regimen of 20 mg/kg 8 hourly achieved 60 %T>MIC for *P. aeruginosa* in 95 % of pre-term and 91 % of full term neonates.

### **Elderly**

Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

## **6 Pharmaceutical particulars**

### **6.1 List of excipients**

Sodium bicarbonate

### **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

24 months

#### **After reconstitution:**

#### **Intravenous bolus injection administration**

A solution for bolus injection is prepared by dissolving the drug product meropenem in sterile 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 up to 3 hours at controlled room temperature (15-25°C) or up to 8 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.

#### **Intravenous infusion administration**

A solution for infusion is prepared by dissolving the drug product meropenem in either 0.9% sodium chloride solution for infusion or 5% glucose (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 6 hours at controlled room temperature (15-25°C) or upto 12 hours under refrigerated conditions (2-8°C). In this case, the prepared solution if stored under refrigeration (i.e. 2-8°C) should be used within 1 hour after it has left the refrigerator.

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 meropenem in 5% glucose (dextrose) solution should be used immediately, i.e. within 30 minutes following reconstitution.

Do not freeze the reconstituted solution.

#### **6.4 Special precautions for storage**

Store below 25°C. Protect from light.

#### **6.5 Nature and contents of container**

White to off white crystalline powder filled in 20 ml clear glass vial USP Type-III with 20 MM flip off seal and 20 MM GBRS.

#### **6.6 Special precautions for disposal**

##### **Injection**

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

##### **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.

Needle should be inserted only at the center of the rubber stopper, in vertical direction.

### **Infusion**

For intravenous infusion meropenem vial may be directly constituted with 0.9% sodium chloride or 5% glucose (dextrose) solutions for infusion.

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 accordance with local requirements.

## **7.0 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES**

Makcur Laboratories Limited,  
46/4-7, Zak, Tal, Dehgam Dist.  
Gandhinagar – 382330, India

## **8.0 MARKETING AUTHORIZATION NUMBER**

H2010/22640/176

## **9.0 DATE OF FIRST REGISTRATION**

12/08/2026

## **10. DATE OF REVISION OF THE TEXT**

12/08/2026