Meropenem for Injection I.P.

MERONEM®

1. GENERIC NAME

Meropenem for Injection I.P. 500 mg and 1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For Meropenem 500 mg:

Each vial contains:
Meropenem trihydrate equivalent to Anhydrous Meropenem I.P.....500 mg
Anhydrous Sodium Carbonate.....104 mg
Each vial contains 45 mg of Sodium.

For Meropenem 1 g:

Each vial contains:
Meropenem trihydrate equivalent to Anhydrous Meropenem I.P….....1 g
Anhydrous Sodium Carbonate.....208 mg

Each vial contains 90 mg of Sodium.

List of Excipients

Anhydrous Sodium Carbonate.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Powder for solution for injection or infusion.
Meropenem for Injection I.P. 500 mg and 1 g.

® Trademark Proprietor: Pfizer Ireland Pharmaceuticals Unlimited Company
Licensed User: Pfizer Limited

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Meropenem for Injection I.P. is indicated for treatment, in children, of the following infections caused by single or multiple bacteria sensitive to meropenem.

Children:

- Pneumonias and Nosocomial Pneumonias
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections, such as endometritis and pelvic inflammatory disease.
- Skin and Skin structure Infections
- Meningitis
- Septicaemia
- Meropenem has been proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

Adults:

- Pneumonias and Nosocomial Pneumonias
- Urinary Tract Infections
- Intra-abdominal Infections
- Gynaecological Infections
- Skin and Skin tissue Infections
- Meningitis
- Septicaemia
- Empiric treatment, for presumed infections in adult patients with febrile neutropenia.

4.2. Posology and Method of Administration

Posology

The tables below provide general recommendations for dosing.

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, Acinetobacter* spp.), or very severe infections.

Additional considerations for dosing are needed when treating patients with renal insufficiency (see further below).

Adults and adolescents

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	500 mg or 1 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

1 g IV every 8 hours in the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients, septicaemia.

Meropenem is usually given by intravenous infusion over approximately 15 to 30 minutes (see sections 8.1. Incompatibilities, 8.2. Shelf-life and 8.4. Storage and Handling Instructions).

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.

Creatinine Clearance (ml/min)	Dose (based on "unit" dose range of 500 mg or 1 g or, 2 g, see table below)	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 (see section 4.4. Special Warnings and Precautions for Use).

Dose in elderly patients
No dosage 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 has 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 (see section 5.3. Pharmacokinetic Properties).

Children from 3 months to 11 years of age and up to 50 kg body weight
The recommended dose regimens are shown in the table below:

Infection	**Dose to be administered every 8 hours**
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 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 (see sections 8.1. Incompatibilities, 8.2. Shelf-life and 8.4. Storage and Handling Instructions). 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, see section 8.4 Storage and Handling Instructions.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2. List of Excipients.
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam 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 (see sections 4.3. Contraindications and 4.8. Undesirable Effects).

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 (see section 4.8 Undesirable Effects). If signs and symptoms suggestive of these reactions appear, meropenem should be withdrawn immediately and an alternative treatment should be considered.

With other beta-lactam antibiotics there have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8 Undesirable Effects).

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of meropenem. If signs or symptoms of rhabdomyolysis are observed, meropenem should be discontinued and appropriate therapy initiated (see section 4.8 Undesirable Effects).

Drug-induced liver injury (DILI)

Hepatic function should be closely monitored during treatment with meropenem due to the risk of DILI (see section 4.8 Undesirable Effects). If severe DILI occurs, treatment discontinuation should be considered as clinically appropriate. Meropenem should be reintroduced only if assessed as essential for treatment.

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 posology and method of administration).

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 (see section 4.8. Undesirable Effects).

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 (see section 4.8. Undesirable Effects).

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 (See section 4.5. Drug interactions)

Meropenem contains sodium.
Meronem 1 g: This medicinal product contains 90 mg sodium per 1 g vial, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult."

Meronem 500 mg: This medicinal product contains 45 mg sodium per 500 mg vial, equivalent to 2.25% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric Use

Efficacy and tolerability in infants under 3 months old have not been established; therefore, meropenem is not recommended for use below this age. There is no experience in children with altered hepatic or renal function.

Keep all medicines away from children

4.5. Drug Interactions

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 (see section 4.4. Special Warnings and Precaution for Use).

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 normalised 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. Use in Special Populations

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 (see section 6.1. Animal Toxicology or Pharmacology).

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

Breast-feeding

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. 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 headache, paraesthesia and convulsions have been reported for meropenem.

4.8. 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 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 (≥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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

System Organ Class	Frequency	Event
Infections and infestations	Uncommon	oral and vaginal candidiasis
Blood and lymphatic system disorders	Common	thrombocythaemia
	Uncommon	agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia, leukopenia, eosinophilia
Immune system disorders	Uncommon	anaphylaxis (see sections 4.3. Contraindications and 4.4. Special warning and precautions for use) angioedema
Metabolism and nutrition disorders	Uncommon	hypokalaemia
Metabolic (Electrolyte) Disorders	Uncommon	hypokalaemia
Psychiatric disorders	Rare	delirium
Nervous system disorders	Common	headache
	Uncommon	paraesthesia
	Rare	convulsions (see section 4.4. Special Warnings and Precautions for Use)
Gastrointestinal disorders	Common	diarrhoea, abdominal pain, vomiting, nausea
	Uncommon	antibiotic-associated colitis (see section 4.4. Special Warnings and Precautions for Use)
Hepatobiliary disorders	Common	transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased.
	Uncommon	drug-induced liver injury*, blood bilirubin increased
Skin and subcutaneous tissue disorders	Common	rash, pruritus
	Uncommon	toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme (see section 4.4 Special Warnings and Precautions for Use), urticaria
	Not known	drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis (see section 4.4 Special Warnings and Precautions for Use)
Musculoskeletal and connective tissue disorders	Not known	rhabdomyolysis
Renal and urinary disorders	Uncommon	blood creatinine increased, blood urea increased
General disorders and administration site conditions	Common	inflammation, pain
	Uncommon	thrombophlebitis, pain at the injection site

*DILI includes hepatitis and liver failure

Description of selected adverse reactions

Kounis Syndrome
Acute coronary syndrome associated with an allergic reaction (Kounis syndrome) has been reported with other beta-lactam antibiotics (see section 4.4. Special Warnings and Precautions for Use).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

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. Posology and Method of Administration. 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. Undesirable Effects, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. 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).

5.2. Pharmacodynamic Properties

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

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 antibacterial agents when the mechanism involved include impermeability and/or an efflux pump(s).

Breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for meropenem and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

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.

Commonly susceptible species

Gram-positive aerobes

Enterococcus faecalis[$]
Staphylococcus aureus (methicillin-susceptible)[£]
Staphylococcus species (methicillin-susceptible) including *Staphylococcus epidermidis*

Streptococcus agalactiae (Group B)
Streptococcus milleri group (*S. anginosus, S. constellatus,* and *S. intermedius*)
Streptococcus pneumoniae
Streptococcus pyogenes (Group A)

Gram-negative aerobes
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria meningitidis
Proteus mirabilis
Proteus vulgaris
Serratia marcescens

Gram-positive anaerobes
Clostridium perfringens
Peptoniphilus asaccharolyticus
Peptostreptococcus species (including *P. micros, P. anaerobius, P. magnus*)

Gram-negative anaerobes
Bacteroides caccae
Bacteroides fragilis group
Prevotella bivia
Prevotella disiens

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 pneumoniae

[$] Species that show natural intermediate susceptibility
[£] All methicillin-resistant staphylococci are resistant to meropenem
[†] Resistance rate ≥50% in one or more EU countries

Glanders and melioidosis: Use of meropenem in humans is based on *in vitro* *B. mallei* and *B. pseudomallei* 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.

5.3. 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_{max} 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_{max} 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_{max} and half-life to normal subjects but a greater volume of distribution 27 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 (See section 4.2. Posology and method of administration)

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_{max} 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 (See section 4.2. Posology and method of administration)

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

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.

7. DESCRIPTION

A white to light yellow powder.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 8.4 Storage and Handling Instructions.

8.2. Shelf-life

48 months.

After reconstitution:

Intravenous bolus injection administration
A solution for bolus injection is prepared by dissolving the drug product in water for injection to a final concentration of 50 mg/ml. Chemical and physical in-use stability for a prepared solution for bolus injection has been demonstrated for 3 hours at up to 25°C or 12 hours under refrigerated conditions (2-8°C).

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 in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1to 20 mg/ml. Chemical and physical in-use stability for a prepared solution for infusion using 0.9% sodium chloride solution has been demonstrated for 3 hours at up to 25°C or 24 hours under refrigerated conditions (2-8°C).

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 the product in 5% dextrose solution should be used immediately.

The constituted solutions should not be frozen.

8.3. Packaging Information

Clear, type I glass vial with Grey, siliconized, halobutyl rubber stoppers and aluminium crimp seals.

8.4. Storage and Handling Instructions

Store in a dry, well-ventilated place at a temperature not exceeding 30° C.

Do not freeze the reconstituted solution.

For storage conditions after reconstitution of the medicinal product, see section 8.2 Shelf-life.

Injection

Meropenem to be used for bolus intravenous injection should be constituted with sterile Water for Injections

Infusion

For intravenous infusion meropenem vials may be directly constituted with 0.9% sodium chloride or 5% 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.

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

9. PATIENT COUNSELLING INFORMATION

Counsel patients that antibacterial drugs including Meropenem should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When meropenem is prescribed to treat a bacterial infection, tell patients that although it is common to feel better early in the course of therapy, take the medication exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by meropenem or other antibacterial drugs in the future.

Counsel patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible (See section 4.4. Special warnings and precaution for use).

Counsel patients to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with meropenem. If treatment with meropenem is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed (See section 4.4. Special warnings and precaution for use).

Patients receiving meropenem on an outpatient basis must be alerted of adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that meropenem is well tolerated, patients should not operate machinery or motorized vehicles (See section 4.4. Special warnings and precaution for use).

10. DETAILS OF MANUFACTURER

Please refer the outer pack for details.

Imported and Marketed in India By

Pfizer Limited, The Capital – A Wing, 1802, 18th Floor, Plot No C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Please refer the outer pack for import license details

12. DATE OF REVISION

April 2026