Meronem IV®
(Meropenem trihydrate)

1. NAME OF THE MEDICINAL PRODUCT

Meronem IV®, 500 mg, 1 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Meronem IV is presented as a sterile white powder containing meropenem; 500 mg or 1g as the trihydrate blended with anhydrous sodium carbonate for constitution. Meronem IV injection contains 208 mg sodium carbonate for each gram of meropenem (anhydrous potency).

Meronem IV for injection or infusion	**500 mg**	**1 g**
Active ingredients		
Meropenem (as the trihydrate)	570 mg	1.14 g
Equivalent to anhydrous meropenem	500 mg	1 g

3. PHARMACEUTICAL FORM

Powder for constitution for intravenous administration.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults and children

Meronem IV is indicated for treatment of the following infections caused by single or multiple susceptible bacteria and as empiric therapy prior to the identification of the causative organisms:

- Lower respiratory tract infections
- Urinary tract infections including complicated infections
- Intra-abdominal infections
- Gynaecological infections including postpartum infections
- Skin and skin structure infections
- Septicaemia
- Meningitis
- Empiric treatment including initial monotherapy for presumed bacterial infections in host-compromised neutropenic patients.
- Polymicrobial Infections: because of its broad spectrum of bactericidal activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria, meropenem is effective for the polymicrobial infections.
- Intravenous meropenem has been used effectively in patients with cystic fibrosis and chronic lower respiratory tract infections, either as monotherapy or in combination with other antibacterial agents. Eradication of the organism was not always established.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults

The dosage range is 1.5 g to 6 g daily in three divided doses.
Usual dose: 500 mg to 1 g by intravenous administration every 8 hours depending on the type and severity of infection, the known or expected susceptibility of the pathogen(s), and the condition of the patient.

Exceptions: (1) Febrile episodes in neutropenic patients – the dose should be 1 g every 8 hours.

(2) Meningitis/Cystic Fibrosis – the dose should be 2 g every 8 hours.

When treating infections known or suspected to be caused by *Pseudomonas aeruginosa,* a dose of at least 1 g every 8 hours in adults (maximum approved dose is 6 g daily given in 3 divided doses) and a dose of at least 20 mg/kg every 8 hours in children (maximum approved dose is 120 mg/kg daily given in 3 divided doses) are recommended.[22]

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

Meronem IV should be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2 **Incompatibilities** and 6.4. **Special precautions for storage** for constitution details). There is limited safety data available to support the administration of a 2 g bolus dose.[18]

Dosage Schedule for Adults with Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance less than 51 ml/min, as scheduled below.

Creatinine Clearance (ml/min)	Dose (based on "unit" doses of 500 mg to 2 g every 8 hours, see above)	Frequency
26-50	one unit dose	every 12 hours
10-25	one-half unit dose	every 12 hours
<10	one-half unit dose	every 24 hours

Meropenem is cleared by haemodialysis and hemofiltration[1,2,3]; if continued treatment with Meronem IV is necessary, the unit dose based on the infection type and severity is recommended at the completion of the haemodialysis procedure to re-institute effective treatment.

There is no experience with peritoneal dialysis.

Use in Adults with Hepatic Insufficiency.

No dosage adjustment is necessary in patients with hepatic impairment.

Elderly

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

Children

For infants and children over 3 months and up to 12 years of age the IV dose is 10 to 40 mg/kg every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s), and the condition of the patient. In children over 50 kg weight, adult dosage should be used.

Exceptions: (1) Febrile episodes in neutropenic patients – the dose should be 20 mg/kg every 8 hours.

(2) Meningitis/Cystic Fibrosis – the dose should be 40 mg/kg every 8 hours.

Meronem IV should be given as an IV bolus over approximately 5 min or by intravenous infusion over approximately 15 to 30 minutes (see sections 6.2 **Incompatibilities**/6.4. **Special precautions for storage** for constitution details). There is limited safety data available to support the administration of a 40 mg/kg bolus dose.[18]

There is no experience in children with renal impairment.

Constitution and compatibility

Meronem IV to be used for bolus intravenous injection should be constituted with sterile water for injection (10 ml for each 500 mg). This provides an approximate available concentration of 50 mg/ml. Constituted solutions are clear or pale yellow.

For intravenous infusion Meronem IV vials may be directly constituted with a compatible infusion fluid (as listed in section 6.4 **Special precautions for storage**) and then further diluted with the compatible infusion fluid, as needed.

Freshly prepared solutions of Meronem IV should be used whenever possible. However, constituted solutions of Meronem IV maintain satisfactory potency at room temperature (15-25 degrees C) or under refrigeration (4 degrees C) as shown in section 6.4 **Special precautions for storage**.

Meronem IV should not be mixed with or physically added to solutions containing other drugs.

Solutions of Meronem IV should not be frozen.

4.3 CONTRAINDICATIONS

Meronem IV is contraindicated in patients who have demonstrated hypersensitivity to this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients who have a history of hypersensitivity to carbapenems, penicillins or other β-lactam antibiotics may also be hypersensitive to Meronem IV. As with all β-lactam antibiotics rare hypersensitivity reactions (serious and occasionally fatal)[18] have been reported (see section 4.8 **Undesirable effects**).

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 Meronem IV (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.[27]

As with other antibiotics, overgrowth of non-susceptible organisms may occur and repeated evaluation of each patient is necessary. Rarely, pseudomembranous colitis has been reported on Meronem IV as with virtually all antibiotics; therefore, its diagnosis should be considered in patients who develop diarrhoea in association with the use of Meronem IV.

The concomitant use of valproic acid/sodium valproate and Meronem IV is not recommended.[20] Meronem IV may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients (see section 4.5 **Interaction with other medicinal products and other forms of interaction**).

Paediatric use: Efficacy and tolerability in infants under 3 months old have not been established; therefore, Meronem IV is not recommended for use below this age.

Use in patients with renal insufficiency: Refer to dosage recommendations for Meronem IV.

Use in patients with liver disease: Patients with pre-existing liver disorders should have liver function monitored during treatment with Meronem IV.

A positive direct or indirect Coombs test may develop.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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. As the potency and duration of action of Meronem IV dosed without probenecid are adequate, the co-administration of probenecid with Meronem IV is not recommended. The potential effect of Meronem IV on the protein binding of other drugs 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 Meronem IV in patients stabilised on valproic acid is not considered to be manageable and therefore should be avoided (see section 4.4 **Special warnings and precautions for use**)[20].

Meronem IV has been administered concomitantly with many other medications without apparent adverse interaction. However, no specific drug interaction studies other than probenecid were conducted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of Meronem IV in human pregnancy has not been established, although animal studies have not shown an adverse effect on the developing foetus. Meronem IV should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

Lactation

Meropenem has been reported to be excreted in human milk.[24] Meronem IV should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies 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 Meronem IV.

4.8 UNDESIRABLE EFFECTS

Meronem IV is generally well tolerated. Adverse reactions rarely lead to cessation of treatment. Serious adverse reactions are rare.

The following adverse reactions have been identified following clinical studies and post-marketing experience with Meronem IV.

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Infections and infestations	Oral and vaginal candidiasis
Blood and lymphatic system disorders	Agranulocytosis*, haemolytic anaemia*, thrombocytopenia, neutropenia, leucopenia, eosinophilia, thrombocythaemia
Immune system disorders	Manifestations of anaphylaxis*, angioedema*
Psychiatric disorders	Delirium*[28]
Nervous system disorders	Convulsions, paraesthesia, headache
Gastrointestinal disorders	Pseudomembranous colitis*, diarrhoea, vomiting, nausea
Hepatobiliary disorders	Blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis*, Stevens Johnson syndrome*, erythema multiforme*, drug reaction with eosinophilia and systemic symptoms*[26], acute generalised exanthematous pustulosis*[27], rash, pruritus, urticaria
General disorders and administration site conditions	Thrombophlebitis, inflammation, pain

*ADR identified post-marketing.

4.9 OVERDOSE

Intentional overdosing of Meronem IV is unlikely, although overdosing could occur particularly in patients with renal impairment. Limited post-marketing experience indicates that if adverse events occur following over dosage, they are consistent with the adverse event 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 normal individuals rapid renal elimination will occur.

Haemodialysis will remove meropenem and its metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Meropenem is a carbapenem antibiotic for parenteral use, that is stable to human dehydropeptidase-I

(DHP-I). It is structurally similar to imipenem.

Meropenem exerts its bactericidal action by interfering with bacterial cell wall synthesis. The ease with which it penetrates bacterial cells, its high level of stability to most serine β-lactamases and its high affinity for multiple Penicillin Binding Proteins (PBPs) explain the potent bactericidal activity of meropenem against a broad spectrum of aerobic and anaerobic bacteria. The bactericidal concentrations are generally within one doubling dilution of the minimum inhibitory concentrations (MICs).

Meropenem is stable in susceptibility tests and these tests can be performed using the normal routine systems. *In vitro* tests show that meropenem can act synergistically with various antibiotics. It has been demonstrated both *in vitro* and *in vivo* that meropenem has a post-antibiotic effect against Gram-positive and Gram-negative organisms.

Mechanisms of resistance

Bacterial resistance to meropenem may result from one or more factors: (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 β-lactamases that can hydrolyse carbapenems.

Localised clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.

The susceptibility to meropenem of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

The antibacterial spectrum of meropenem includes the following species, based on clinical experience and therapeutic guidelines.

Commonly susceptible species: Gram-positive aerobes

Enterococcus faecalis (note that *E. faecalis* can naturally display intermediate susceptibility), *Staphylococcus aureus* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSA are resistant to meropenem), *Staphylococcus* species including *Staphylococcus epidermidis* (methicillin-susceptible strains only: methicillin-resistant staphylococci including MRSE are resistant to meropenem), *Streptococcus agalactiae* (Group B streptococcus), *Streptococcus milleri* group (*S. anginosus, S. constellatus, and S. intermedius*), *Streptococcus pneumoniae*, *Streptococcus pyogenes* (Group A streptococcus)

Commonly susceptible species: 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

Commonly susceptible species: Gram-positive anaerobes

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

Commonly susceptible species: Gram-negative anaerobes

Bacteroides caccae, Bacteroides fragilis, Prevotella bivia, Prevotella disiens

Species for which acquired resistance may be a problem: Gram-positive aerobes

Enterococcus faecium (*E. faecium* can naturally display intermediate susceptibility even without acquired resistance mechanisms)

Species for which acquired resistance may be a problem: Gram-negative aerobes

Acinetobacter species, *Burkholderia cepacia, Pseudomonas aeruginosa*

Inherently resistant organisms: Gram-negative aerobes

Stenotrophomonas maltophilia, Legionella species

Other inherently resistant organisms

Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Mycoplasma pneumoniae

The published medical microbiology literature describes *in-vitro* meropenem-susceptibilities of many other bacterial species. However the clinical significance of such *in-vitro* findings is uncertain. Advice on the clinical significance of *in-vitro* findings should be obtained from local infectious diseases and clinical microbiology experts and local professional guidelines.

Meropenem is active *in vitro* against many strains resistant to other β-lactam antibiotics. This is explained in part by enhanced stability to β-lactamases. Activity *in vitro* against strains resistant to unrelated classes of antibiotics such as aminoglycosides or quinolones is common.

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.[19]

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 and the mean clearance is 239 ml/min at 500 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.[4,5]

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.[6]

Distribution

The average plasma protein binding of meropenem was approximately 2% and was independent of concentration. 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.[7]

Metabolism

Meropenem is metabolised by hydrolysis of the β-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.[8,9]

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.[10]

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**).[11]

Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.[12]

Hepatic insufficiency

A study in patients with alcoholic cirrhosis has shown 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.[13]

Paediatrics

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 t1/2 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.[14,15]

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.[16]

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**).[17]

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.

Meropenem is generally well tolerated by the CNS. Effects were seen only at very high doses of 2000 mg/kg and above.

The i.v. LD_{50} of meropenem in rodents is greater that 2000 mg/kg. In repeat dose studies of up to 6 months duration only minor effects were seen including a small decrease in red cell parameters and an increase in liver weight in dogs at 500 mg/kg.

There was no evidence of mutagenic potential in the 5 tests conducted and no evidence of reproductive toxicity including teratogenic potential in studies at the highest possible level in rats and monkeys. (The no effect dose level of a small reduction in F1 body weight in rat was 120 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 intramuscular formulation caused reversible injection site necrosis.

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Meronem IV for IV injection and infusion includes the excipient anhydrous sodium carbonate.
Incompatibilities
Meronem IV should not be mixed with or added to other drugs.
Meronem IV is compatible with the following infusion fluids:
0.9% Sodium Chloride solution 5% or 10% Glucose solution
5% Glucose solution with 0.02% Sodium Bicarbonate 5% Glucose solution and 0.9% Sodium Chloride 5% Glucose with 0.225% Sodium Chloride solution 5% Glucose with 0.15% Potassium Chloride solution Mannitol 2.5% or 10% solution.

6.2 INCOMPATIBILITIES

MERONEM IV is compatible with the infusion fluids listed in section 6.4 **Special precautions for storage**:

MERONEM IV should not be mixed with or physically added to solutions containing other drugs.

6.3 SHELF LIFE

Please refer to the expiry date on the outer carton

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Protect from heat, light and moisture.

It is recommended to use freshly prepared solutions of Meronem IV for IV injection and infusion. Reconstituted product, constituted as described above, should be used immediately and must be stored for no longer than 24 hours under refrigeration, only if necessary.
Diluent
Vials constituted with Water for Injections for bolus injection
Solutions (1 - 20 mg/ml) prepared with:
* 0.9% sodium chloride
* 5% glucose
* 5% glucose and 0.225% sodium chloride
* 5% glucose and 0.9% sodium chloride
* 5% glucose and 0.15% potassium chloride
* 2.5% or 10% mannitol intravenous infusion
* 10% glucose
* 5% glucose and 0.02% sodium bicarbonate Intravenous Infusion

6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 glass vials. Vial stoppers are in grey halobutilic rubber with an aluminium cap.

MERONEM IV for injection/ Vial Nominal Capacity
Infusion Packs

500 mg	20
1 g	30

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Refer to "Posology and method of administration" above. Standard aseptic technique should be employed during constitution. Shake constituted solution before use.
All vials are for single use only.

- **Powder for Solution for Injection:**

  A sterile, pyrogen-free **white to light yellow powder** in 20 ml and 30 ml injection vials (nominal capacities). The vial presentations are designed for single dose use. They are sealed with halo butyl rubber stoppers and aluminum crimp seals with flip-off plastic caps.

- **After Reconstitution:**

  The drug product is administered by direct intravenous injection following constitution with an appropriate aqueous diluent. Solutions range from **colorless to pale yellow in appearance.**

The observed variation in color is typical of this class of drugs and has no adverse impact on quality, safety and efficacy of Product.

Meronem IV/LPD/PK-02
According to CDS V 8.0 Dated 31 October 2018; Supersedes CDS V 7.0 dated: 28 October 2015

Marketed By:
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

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