Meropen®

(Meropenem USP)

FOR INTRAVENOUS ADMINISTRATION

PRESENTATION :

Meropen® IV is presented as a sterile white powder containing meropenem USP; 250/500mg or 1g as the trihydrate blended with anhydrous sodium carbonate for constitution. **Meropen**® IV injection contains 208mg sodium carbonate for each gram of meropenem (anhydrous potency).

Vial for IV injection or infusion	Meropen 250mg	Meropen 500mg	Meropen 1g
Active ingredient : Meropenem trihydrate equivalent to anhydrous meropenem	250mg	500mg	1g
Excipient : Anhydrous sodium carbonate	52mg	104mg	208mg

For each gram of meropenem (anhydrous potency) the vial contains 90.2mg of sodium.

THERAPEUTIC INDICATIONS:

Meropen® IV is indicated for treatment, in adults and children, of the following infections caused by single or multiple bacteria sensitive to meropenem.

- 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
- Empiric treatment, for presumed infections in adult patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.

Meropen® has proved efficacious alone or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

There is no experience in paediatric patients with neutropenia or primary or secondary immunodeficiency.

DOSAGE AND ADMINISTRATION :

Adults

The dosage and duration of therapy shall be established depending on type and severity of infection and the condition of the patient.

The recommended daily dosage :

500mg IV every 8 hours in the treatment of pneumonia, UTI, gynaecological infections such as endometritis, skin and skin structure infections.

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

In meningitis the recommended dosage is 2g every 8 hours.

As with other antibiotics, particular caution is recommended in using meropenem as monotherapy in critically ill patients with known or suspected Pseudomonas aeruginosa lower respiratory tract infection.

Regular sensitivity testing is recommeded when treating Pseudomonas aeruginosa infection.

Dosage Schedule for Adults with Impaired Renal Function

Dosage should be reduced in patients with creatinine clearance less than 54ml/min, as scheduled below:

Creatinine Clearance (ml/min)	**Dose** (based on unit doses of 500mg, 1g)	**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; if continued treatment with **Meropen**® is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of **Meropen**® in patients under peritoneal dialysis.

Dosage in Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic insufficiency. *Elderly Patients*

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

Children

For children over 3 months and up to 12 years of age the recommended dose is 10-20 mg/kg every 8 hours depending on type and severity of infection of the pathogen and the condition of the patient.

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

In meningitis the recommended dose is 40mg/kg every 8 hours.

There is no experience in children with renal impairment.

Method of Administration

Meropen® IV can be given as an **intravenous bolus injection** over approximately 3-5 minutes or by **intravenous infusion** over approximately 15 to 30 minutes using the specific available presentations.

Meropen® IV to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 ml per 250mg meropenem). This provides an approximate concentration of 50mg/ml. Constituted solutions are clear, and colorless or pale yellow.

Meropen® IV for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 ml).

CONTRA-INDICATIONS :

Meropen is contraindicated in patients who have, demonstrated hypersensitivity to this product.

WARNINGS AND PRECAUTIONS :

There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins. As with all beta-lactam antibiotics, rare hypersensitivity reactions have been reported. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. **Meropen**® should be used with caution in patients with such a history. If an allergic reaction to meropenem occurs, the drug should be discontinued and appropriate measures taken.

Use of **Meropen**® in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels.

As with other antibiotics, overgrowth of non-susceptible organisms may occur and therefore, continuous monitoring of each patient is necessary.

Use in infections caused by methicillin resistant staphylococci -is not recommended.

Rarely, pseudomembranous colitis has been reported on **Meropen**® as with practically all antibiotics and may vary in severity from slight to life-threatening. Therefore, antibiotics should be prescribed with care for individuals with a history of gastro-intestinal complaints, particularly colitis.

It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhea in association with the use of **Meropen**®. Although studies indicate that a toxin produced by Clostridium difficile is one of the main causes of antibiotic associated colitis, other causes should be considered.

The co-administration of Meropen with potentially nephrotoxic drugs should be considered with caution.

Paediatric use

Efficacy and tolerability in infants under 3 months old have not been established; therefore, 'Meropen' 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.

INTERACTIONS :

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion, with the effect of increasing the elimination half-life and plasma concentration of meropenem. As the potency and duration of action of **Meropen**® dosed without probenecid are adequate, the co-administration of probenecid with M**eropen**® is not recommended.

The potential effect of **Meropen**®, on the protein binding of other drugs or metabolism has not been studied. The protein binding of **Meropen**® is low (approximately 2%) and therefore, no interactions with other compounds based on displacement from plasma proteins would be expected. **Meropen**® has been administered concomitantly with other medications without adverse pharmacological interactions. **Meropen**® may reduce serum valproic acid levels. Subtherapeutic levels may be reached in some patients. However, no specific data regarding potential drug interactions is available (apart from probenecid as mentioned above).

PREGNANCY AND LACTATION :

Pregnancy

The safety of **Meropen**® in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing foetus. The only adverse effect observed in animal reproductive studies was an increased incidence of abortions in monkeys at 13 times the expected exposure in man. **Meropen**® should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus. In every case, it should be used under the direct supervision of the physician.

Lactation

Meropenem is detectable at very low concentrations in animal breast milk. **Meropen**® should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

POSSIBLE ADVERSE REACTIONS :

Serious adverse events are rare. During the clinical trials the following adverse events have been reported. Local intravenous injection site reactions: inflammation, thrombophlebitis, pain at the site of injection. Systemic allergic reactions: rarely, systemic allergic reactions (hypersensitivity) may occur following administration of meropenem. These reactions may include angioedema and manifestations of anaphylaxis.

Skin reactions: rash, pruritus, urticaria: Rarely severe skin reactions, such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been observed. Gastro-intestinal: abdominal pain, nausea, vomiting, diarrhoea. Pseudomembranous colitis has been reported. Blood: Reversible thrombocythaemia, eosinophilia, thrombocytopenia, leucopenia and neutropenia (including very rare cases of agranulocytosis). A positive direct or indirect Coombs test may develop in some subjects; there have been reports of reduction in partial thromboplastin time. Liver function: Increase in serum concentrations of bilirubin, transaminases, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported. Central nervous system: headache, paraesthesiae. Convulsions have been reported although a causal; relationship with **Meropen**® has not been established. Other: Oral and vaginE l candidosis.

OVERDOSAGE:

Accidental over dosage could occur during therapy, particularly in patients with renal impairment. Treatment of over dosage should be symptomatic. In normal individuals rapid renal elimination will occur; in subjects with renal impairment haemodialysis will remove meropenem and its metabolite.

PHARMACOLOGICAL PROPERTIES :

Pharmacodynamic Properties

Meropenem is a carbapenem antibiotic for parenteral use, that is relatively stable to human dehydropeptidase-1 (DHP-1) and therefore, does not require the addition of an inhibitor of DHP-1.

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all series ß-lactamases and its marked affinity for the Penicillin Binding Proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. Minimum bactericidal concentrations (MBC) are commonly the same as the minimum inhibitory concentrations (MIC). For 76% of the bacteria tested, the MBC: MIC ratios were 2 or less.

Meropenem is stable in susceptibility tests and these tests can be performed using normal routine methods. In vitro tests show that meropenem acts synergistically with various antibiotics. It has been demonstrated both in vitro and in vivo that meropenem has a post antibiotic effect.

A single set of meropenem susceptibility criteria are recommended based on pharmacokinetics and correlation of clinical and microbiological outcomes with zone diameter and minimum inhibitory concentrations (MIC) of the infecting organisms.

CATEGORISATION	METHOD OF ASSESSMENT	
	Zone Diameter (mm)	MIC breakpoints (mg/L)
Susceptible	≤14	≤4
Intermediate	12 to 13	8>
Resistant	≥11	≥16

The in vitro antibacterial spectrum of meropenem includes the majority of clinically significant Gram-positive and Gram-negative, aerobic and anaerobic strains of bacteria, as shown below:

Gram-positive aerobes:

Bacillus spp.,Corynebacterium diphtheriae, Enterococcus faecalis, Enterococcus liquifaciens, Enterococcus avium, Listeria monocytogenes, Laactobacillus, spp., Nocardia asteroides, Staphylococcus aureus (penicillinase negative and positive), Staphylococci-coagulase-negative; including, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus capitis, Staphylococcus cohnii, Staphylococcus xylosus, Staphylococcus wameri, Staphylococcus hominis, Staphylococcus simulans, Staphylococcus intermedius, Staphylococcus sciuri, Staphylococcus lugdunensis, Streptococcus penumoniae (penicillin susceptible and resistant), Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus equi, Streptococcus bovis, Streptococcus mites, Streptococcus meteor, Streptococcus milleri, Streptococcus sanguis, Streptococcus viridans, Streptococcus salivarius, Streptococcus morbillorum, Streptococcus Group G, Streptococcus Group F. Rhodococcus equi.

Gram-negative aerobes:

Achromobacter xylosoxidans, Acinetobacter anitratus, Acinetobacter lwoffli, Acinetobacter baumannii, Aeromonas hydrophlia, Aeromonas sorbria, Aeromonas caviae, Alcaligenes faecalis, Bordetelle bronchiseptica, Brucella meliternsis, Campylobacter coli, Campylobacter jejune, Citrobacter freundii, Citrobacter diversus, Citrobacter koseri, Citrobacter amalonaticus, Enterobacter aerogenes, Enterobacter (Pantoea) agglomerans, Enterobacter cloacae, Enterobacter sakazakii, Escherichia coli, Escherichia hermannii, Gardnerella vaginalis, Haemophilus influenzae, (including 13-lactamase positive and ampicillin resistant strains), Haemophilus parainfluenzae, Haemophilus ducreyi, Helicobacter pylori, Neisseria meningitides, Neisseria gonorrhoeae (including B-lactamase positive penicillin resistant and spectinomycin resistant strains), Hafnia alvei, Klebsiella pneumoniae, Klebsiella aerogenes, Klebsiella ozaenae, Klebsiella oxytoca, Moraxella (Branhamella) catarrhalis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Proteus penneri, Providencia rettgeri, Providencia stuartii, Providencia alcalifaciens, Pasteurella multocida, Plesiomonas shigelloides, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas alcaligenes, Burkholderia (Pseudomons) cepacia, Pseudomonas fluorescens, Pseudomonas stutzeri, Pseudomonas pseudomallei, Pseudomonas acidovorans, Salmonella spp; including Salmonella enteritidis/typhi Serratia marcescens, Serratia liquefaciens, Serratia rubidaea, Shigella sonnei, Shigella flexneri, Shigella boyddi, Shigella dysenteriae, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.

Anaerobic bacteria:

Actinomyces odontolyticus Actinomyces meyeri, Bacteroides-PrevotellaPorphyromonas spp., Bacteroides fragilis, Bacteroide vulgatus, Bacteroides variabilis, Bacteroides pneumosintes, Bacteroides coagulans, Bacteroides uniformis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides eggerthii, Bacteroides capsillosis, Prevotella buccalis, Prevotella corporis, Bacteroides gracilis, Prevotella melaninogenica, Prevotella intermedia, Prevotella bivia, Prevotella splanchnicus, Prevotella oralis, Prevotella disiens, Prevotela rumenicola, Bacteroides ureolyticus, Prevotella ores, Prevotella buccae, Prevotella denticola, Bacteroides level, Porphyromonas asaccharolytica, Bifidobacteruium spp., Bilophila wadsworthia, Clostridium perfringens, Clostridium bifermentans Clostridium ramosum. Clostridium sporbgenes, Clostridium cadaveric, Clostridium sordellii, Clostridium butyricum, Clostridium clostridiiformis, Clostriduminnocuum, Clostridum subterminale, Clostridium tertium, Eubacterium lentum, Eubacterium aerofaciens, Fusobacterium mortiferum, Fusobacterium necrophorum, Fusobacterium nucleatum, Fusobacterium varium,, Mobiluncus curtisii, Mobiluncus mulieris, Peptostreptococcus anaerobius, Petostreptococcus micros, Peptostreptococcus saccharolyticus, Peptococcus saccharolyticus, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus, Peptostreptococcus prevotii, Propionibacterium acnes, Propionibacterium avidum, Propionibacterium granulosum.

Stenotrophomonas maltophilia, Enterococcus faecium and methicilin-resistant staphylococci have been found to be resistant to meropenem.

Pharmacokinetic Properties

A 30 minute intravenous infusion of a single dose of 'Meropen' in healthy volunteers results in peak plasma levels of approximately 11 µg/ml for the 250mg dose, 23 µg/ml for the 500mg dose and 49 µg/ml for the 1 g dose.

A 5 minute intravenous bolus injection of **Meropen**® in healthy volunteers results in peak mean plasma levels of approximately 45 µg/ml for the 500mg dose and 112 µg/ml for the 1 g dose.

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

In subjects with normal renal function, meropenem's elimination half-life is approximately 1 hour.

Plasma protein binding of meropenem is approximately 2%.

Approximately 70% of the administered dose is recovered as unchanged meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 pg/ml are maintained for up to 5 hours after the administration of a 500mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500mg administered every 8 hours or 1g administered every 6 hours in volunteers with normal renal function.

The only metabolite of meropenem is microbiologically inactive.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis- achieving concentrations in excess of those required to inhibit most bacteria.

Studies in children have shown that the pharmacokinetics of Meropen® in children are similar to those in adults. The elimination half-life for meropenem was approximately 1.5 to 2.3 hours in children under the age of 2 years and the pharmacokinetics are linear over the dose range of 10 to 40 mg/kg.

Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.

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

Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

PHARMACEUTICAL PARTICULARS :

Incompatibilities

Meropen® should not be mixed with or added to other drugs.
Meropen® is compatible with the following infusion fluids:
0.9% Sodium Chloride solution,
5% or 10% Glucose solution,
0.9% Sodium Chloride and 5% Glucose solution,
5% Glucose with 0.225% Sodium Chloride solution,
5% Glucose with 0.15% Potassium Chloride solution,
Mannitol 2.5% or 10% solution.

Shelf-Life

Please refer to the expiry date on the outer carton

Storage

Meropen® Injections should be stored in a cool (below 30°C) and dry place, away from light and Children.

It is recommended to use freshly prepared solutions of **Meropen**® for I.V. injection and infusion. Reconstituted product, constituted as described above, maintains, satisfactory potency at room temperature (below 30°C) or under refrigeration (4°C) as shown in the following table:-

Diluent	Hours stable at 15-30°C	4°C
Vials constituted with Water for Injection	8	48
for bolus injection		
Solutions (1-20 mg/ml) prepared with:		
*0.9% sodium chloride	8	48
5% glucose	3	14
5% glucose and 0.225% sodium chloride	3	14
5% glucose and 0.9% sodium chloride	3	14
5% glucose and 0.15% potassium chloride	3	14
2.5% or 10% mannitol intravenous infusion	3	14
*10% glucose	2	8
*5% glucose and 0.02% sodium bicarbonate	2	8
Intravenous Infusion		

PACK SIZE :

Please follow the outer carton for pack size

®Trade Mark

Manufactured by
RENATA LIMITED
Rajendrapur, Gazipur, Bangladesh.
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