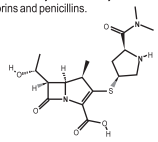
# MEROSOL Injection

( M e r o p e n e m )

میروسول انجیکشن
(میروپینم)

**COMPOSITION:**
**MEROSOL 500mg injection**
Each vial contains:
Meropenem Trihydrate eq. to
Meropenem.....500mg
**(USP Specifications)**
**MEROSOL 1g injectoin**
Each vial contains:
Meropenem Trihydrate eq. to
Meropenem.....1g
**(USP Specifications)**

**DESCRIPTION**
MEROSOL (meropenem) is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. Carbapenems are antibiotics used for the treatment of infections known or suspected to be caused by multidrug-resistant (MDR) bacteria. Their use is primarily in people who are hospitalized. They are members of the beta lactam class of antibiotics, which kill bacteria by binding to penicillin-binding proteins and inhibiting cell wall synthesis. They exhibit a broader spectrum of activity compared to cephalosporins and penicillins.



**MODE OF ACTION**
Meropenem is bactericidal except against Listeria monocytogenes, where it is bacteriostatic. It inhibits bacterial wall synthesis like other β-lactam antibiotics. In contrast to other beta-lactams, it is highly resistant to degradation by β-lactamases or cephalosporinases. In general, resistance arises due to mutations in penicillin-binding proteins, production of metallo-β-lactamases, or resistance to diffusion across the bacterial outer membrane. Unlike imipenem, it is stable to dehydropeptidase-1, so can be given without cilastatin.

**INDICATIONS**
MEROSOL 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-abdominalInfections Gynecological Infections, such endometritis.
• Skin and Skin Structure Infections
• Meningitis
• Septicemia
• Empiric treatment, for presumed infections in adult patients with febrile neutropenia, used as monotherapy or in combination with anti-viral or anti-fungal agents.MEROSOL has proved efficacious alone or in combination with other antimicrobial agents in the treatment of 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. There is no experience in pediatric patients with neutropenia or primary or secondary immunodeficiency.

**DOSAGE & 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 is as follows:-
• In the treatment of pneumonia, UTI, gynecological infectionssuch asendometritis, skin and skin structure infections 500 mg IV every 8 hours.
• In the treatment of nosocomial pneumonias, peritonitis, presumed infections in neutropenic patients.
• Septicemia 1g IV every 8 hours.
• In cystic fibrosis, dose up to 2 g every 8 hours have been used; most patients have beentreated with 2 g every 8 hours.
• In meningitis the recommended dosage is 2 g 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 recommended when treating Pseudomonas aeruginosa infection. 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 500mg, 1g 2g) | 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 hemodialysis; if continued treatment with Merosol is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the hemodialysis procedure to restore therapeutically effective plasma concentrations.
There is no experience with the use of MEROSOL 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 to 20 mg/kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient.
In children over 50 kg weight, adult dosage should be used.
***For children aged 4 to 18 years with cystic fibrosis,*** dose ranging from 25 to 40 mg/kg every 8 hours have been used to treat acute exacerbations of chronic lower respiratory tract Infections. In meningitis the recommended dose is 40mg/kg every 8 hours.
***Renal Impairment:***
There is no experience in children with renal impairment.

**Administration**
MEROSOL IV can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes using the specific available presentations.
MEROSOL IV to be used for bolus intravenous injection should be constituted with sterile Water for Injections (5 ml per 250 mg meropenem). This provides an approximate concentration of 50 mg/ml. Constituted solutions are clear, and colourless or pale yellow.

**MICROBIOLOGY**
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, Lactobacillus spp., Nocardia asteroids, Staphylococcus aureus (penicillinase negative and positive), Staphylococcico agulase negative; including, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus capitis, Staphylococcus cohnii, Staphylococcus xylosus, Staphylococcus warneri, Staphylococcus hominis, Staphylococcus simulans, Staphylococcus intermedius, Staphylococcus sciuri, Staphylococcus lugdunensis, Staphylococcus pneumonia (penicillin susceptible and resistant), Streptococcus agalactiae, Streptococcus pyogenes,Z Streptococcus equi, Streptococcus bovis, Streptococcus mitis, Streptococcus mitior, 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 lwoffii, Acinetobacter baumanii, Aeromonas hydrophila, Aeromonas sorbria, Aeromonas caviae, Alcaligenes faecalis, Bordetella bronchiseptica, Brucella melitensis, Campylobacter coli, Campylobacter jejuni, 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 beta-lactamase positive and ampicillin resistant strains), Haemophilus parainfluenzae, Haemophilus ducreyi, Helicobacter pylori, Neisseria meningitides, Neisseria gonorrhoeae (including beta-lactamase positive, penicillin resistant and spectinomycin resistant strains), Hafnia alvei, Klebsiella pneumonia, Klebsiella aerogenes, Klebsiella ozaenae, Klebsiella oxytoca, Moraxella (Branhamella) catarrhalis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Proteus penneri, Providencia rettgeri, Providencia stuartii, Providencia alcalifaciens, Pasteruella multocida, Plesiomonas shigelloides, Pseudomonas aeruginosa,
Pseudomonas putida, Pseudomonas alcaligenes, Burkholderia (pseudomonas) cepacia, Pseudomonas fluorescens, Pseudomonas stutzeri, Pseudomonas pseudomallei, Pseudomonas acidovorans, Salmonella spp. Including Salmonella enteritidisAyphi, Serratia marcescens, Serratia liquefaciens, Serratia rubidaea, Shigella sonnei, Shigella flexneri, Shigella boydii, Shigella dysenteriae, Vibrio cholarae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.

**Anaerobic bacteria**
Actinomyces odontolyticus, Actinomyces meyeri, Bacterodies-Prevotella-Porhyromonas spp., Bacteroides fragilis, Bacteroides vulgatus, Bacteroides variabilis, Bacteroides pneumosintes, Bacteroides coagulans, Bacteroides uniformis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotao- micron, Bacteroides eggerthii, Bacteroides capsillosis, Prevotella buccalis, Prevotella corporis, Bacteroides gracilis, Prevotella melaninogencia, Prevotella intermedia, Prevotella bivia, Prevotella splanchnicus, Prevotella oralis, Prevotella disiens, Prevotella reumenicola, Bacteroides ureolyticus, Prevotella oris, Prevotella buccae, Prevotella denticola, Bacteroides levii, Porphyromonas asaccharolytica, Bifidobacterium spp., Bilophila wadsworthia, Clostridium perfringens, Clostridium bifermentans, Clostridium ramosum, Clostridium sporogenes, Clostridium cadaveris, Clostridium sordellii, Clostridium butyricum, Clostridium clostridiiformis, Clostridium innocuum, Clostridium subterminale, Clostridium tertium, Eubacterium lentum, Eubacterium aerofaciens, Fusobacte- rium mortiferum, Fusobacterium necrophorum, Fusobacterium necleatum, Fusobacterium varium, Mobiluncus curtisii, Mobiluncus mulieris, Peptostrepto- coccus anaerboius,

Peptostreptococcus micros, Peptostreptococcus saccharo- lyticus, Peptococcus saccharolyticus, Peptostreptococcus asaccharolyticus, Propionibacterium granulosum. Stenotrophomonas maltophilia, Enterococcus faecium and methicillinresistant staphylococci have been found to be resistant to meropenem.

**PHARMACODYNAMICS**

Meropenem is a carbapenem antibiotic for parenteral use, this 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 serine beta-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.

**PHARMACOKINETICS**

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

However, there is no absolute pharmacokinetic proportionality with the administered dose both as regards Cmax and AUC. Furthermore, a reduction in plasma clearance from 287 to 205 ml/min for the range of dosage 250 mg to 2 g has been observed.

A 5 minute intravenous bolus injection of MEROSOL in healthy volunteers results in peak plasma levels of approximately 52 microgram/ml for the 500 mg dose and 112 microgram/ml for the 1 g dose.

Intravenous infusions of 1 g over 2 minutes. 3 Minutes and 5 minutes were compared in a three-way crossover trial.

These durations of infusion resulted in peak plasma levels of 110, 91 and 94 microgram/ml, respectively.

After an IV dose of 500 mg, plasma levels of meropenem decline to values of 1 microgram/ml or less, 6 hours after administration.

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 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 urine excretion is detectable. Urinary concentrations of meropenem in excess of 10 microgram/ml are maintained for up to 5 hours after the administration of a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

The only metabolite of meropenem is microbiology inactive.

Meropenem penetrates will 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 MEROSOL 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.

**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. MEROSOL 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 MEROSOL in patients with hepatic disease should bemade 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 MEROSOL 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 evelop diarrhea in association with the use of MEROSOL. 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.
- Seizures have infrequently been reported during treatment with carbapenems, including meropenem.
- The co-administration of MEROSOL with potentially nephrotoxic drugs should be considered with caution.

**Pregnancy and Lactation**

**Pregnancy:**

The safety of MEROSOL in human pregnancy has not been evaluated MEROSOL should not be used in pregnancy unless the potential benefits 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.MEROSOL should not be used in breast feeding women unless the potential benefits justifies the potential risk to the baby.

**Pediatric Use:**

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

**ADVERSE EFFECTS**

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, urticarial. Rarely severe skin reactions such as erythema multiforme, Stevens-Johnson yndrome and toxic epidermal necrosis have been observed;
- Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea. Pseudomembranous colitis has been reported;
- Blood: Reversible thrombocythemia, 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:**

Increases in serum concentrations of bilirubin, transaminases, alkaline phosphatase and lactic dehydrogenase alone or in combination have been reported;

- Central nervous system: headache, paraesthesieae. Convulsions have been reported but a causal link with MEROSOL has not been established;
- Other: Oral and vaginal candidosis.

**DRUG INTERACTIONS**

***Aminoglycosides***

Potential pharmacologic interaction (synergistic effects against Pseudomonas aeruginosa).

***Probenecid***

Pharmacokinetic interaction (decreased renal tubular secretion of meropenem/ increased systemic exposure and prolonged meropenem half-life). Concomitant use not recommended.

***Valproic Acid***

Pharmacokinetic interaction (valproic acid serum concentrations may be decreased to sub therapeutic concentrations; possible increased risk of seizures). Use concomitantly with caution.

**CONTRAINDICATIONS**

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

**OVER DOSAGE**

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

**INSTRUCTIONS FOR USE AND HANDLING**

Standard aseptic technique should be employed during constitution. Shake constituted solution before use. All vials are for single use only. It is recommended to use freshly prepare solution of MEROSOL for injection and infusion.

**DIRECTION FOR RECONSTITUTION**

**Merosol 500mg injection**

To reconstitute, add 10ml Sterile water for injection in Vial. Shake to ensure complete dissolution.

**Merosol 1g injection**

To reconstitute, add 20ml Sterile water for injection in Vial. Shake to ensure complete dissolution.

**STORAGE & INSTRUCTIONS**

Store between 15-25°C.

Protect from heat, sunlight & moisture. Do not freeze.

Keep away from the reach of children.

Reconstituted solution must be used immediately or may be stable for 3 hours when stored at 25°C and for 12 hours if refrigerated.

**For intravenous use only.**

**To be sold on the prescription of a registered medical practitioner only.**

**HOW SUPPLIED**

**Merosol 500mg injection**

1 vial + 10ml Sterile water for injection.

**Merosol 1g injection**

1 vial + 20ml Sterile water for injection.

## خوراک و ہدایات:

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔ پاؤڈر کو ۱۵۔۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ ڈھوپ، گرمی، نمی اور منجمد ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:

PHARMASOL

PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate, Lahore, Pakistan.