Meropenem

Merop®

500 mg and 1 gram
Powder for I.V. Injection
Antibacterial

FORMULATION
Each vial contains: (For 1 g)
Meropenem Trihydrate, USP equivalent to anhydrous
Meropenem………………………………………………………1 gram
Also contains Sodium as Sodium Carbonate 90.2mg (3.92mEq)

Each vial contains: (For 500 mg)
Meropenem Trihydrate, USP equivalent to anhydrous
Meropenem………………………………………………………500 mg
Also contains Sodium as Sodium Carbonate 45.1mg (1.96mEq)

PHARMACEUTICAL FORM
Powder for constitution for intravenous administration.

DESCRIPTION
Meropenem trihydrate for Injection USP MEROP is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. Meropenem trihydrate for Injection USP MEROP is a white to pale yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3 Meropenem trihydrate for Injection USP MEROP is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very lightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

INDICATIONS
It is used in the treatment of susceptible infections including intra-abdominal infections, meningitis, respiratory tract infections (including cystic fibrosis patients), septicemia, skin infection, urinary tract infections and infections in immunocompromised patients.

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 is as follows:

Therapeutic Indication	Strength	Dosage	Route
Nosocomial & Ventilator Associated Pneumonia	500mg	Every 8 hours	Intravenous
Septicemia	500mg	Every 8 hours	Intravenous
Gynecologic Infections such as Endometritis	500mg	Every 8 hours	Intravenous
Skin and Skin Structure Infections	500mg	Every 8 hours	Intravenous
Urinary Tract Infections	1 gram	Every 8 hours	Intravenous
Presumed infections in neutropenic patients	1 gram	Every 8 hours	Intravenous
Cystic Fibrosis	Up to 2 grams	Every 8 hours	Intravenous
Bacterial Meningitis	2 grams	Every 8 hours	Intravenous

Dosage Schedule for Adults with Impaired Renal Function:
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, 1gram, 2 grams)	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 trihydrate for Injection USP MEROP is cleared by hemodialysis; if continued treatment with Meropenem trihydrate for Injection USP MEROP is necessary, it is recommended that the unit dose (based on the type and severity of infection) be administered at the completion of the hemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of Meropenem trihydrate for Injection USP MEROP 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 20mg/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, doses ranging from 25 to 40mg/kg every 8 hours. There is no experience in children with renal impairment.

PREPARATION OF SOLUTION

For Intravenous Bolus Administration:
Meropenem for Injection USP (500 mg and 1 gram), MEROP is compatible with the following infusion fluids:

Sterile Water for Injection
Sodium Chloride Injection (0.9% w/v)
Dextrose Injection (5% w/v)
Dextrose Injection (10% w/v)
Dextrose and Sodium Chloride Injection (5% w/v & 0.9% w/v)
Ringer Lactate Injection

Use freshly prepared solutions of Meropenem trihydrite for Injection USP MEROP for IV Injection and Infusion.

As shown below, the following diluents maintain satisfactory potency at room temperature (15°C to 25°C) or under refrigerated temperature (4°C)

Reconstituted Solvents & Diluents	Stability Period at 15-25°C	Stability Period at 4°C
Vials constituted with Sterile Water for Injection for I.V. Injection	*9 hours*	*49 hours*
Solution (1-20 mg/mL) prepared with:		
-0.9% sodium chloride	*11 hours*	*49 hours*
-5% dextrose	*4 hours*	*20 hours*
-5% dextrose and 0.3% sodium chloride	*4 hours*	*20 hours*
-5% dextrose and 0.9% sodium chloride	*4 hours*	*20 hours*
-10% dextrose	*3 hours*	*9 hours*
-10% Mannitol	*4 hours*	*21 hours*
-2.5% Mannitol	*5 hours*	*21 hours*

For Infusion: Infusion vials (500mg and 1g) may be directly constituted with a compatible infusion fluid. Alternatively, an injection vial may be constituted, then the resulting solution added to an I.V. container and further diluted with an appropriate infusion fluid.

METHOD OF ADMINISTRATION

Meropenem trihydrate for Injection USP MEROP to be used for bolus intravenous injection should be constituted with sterile water for Injections (10mL per 500mg meropenem). This provides an approximate concentration of 50mg/mL. Constituted solutions is clear, and colorless or pale yellow.

Meropenem trihydrate for Injection USP MEROP for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL).

When constituted as instructed (**see DOSAGE AND ADMINISTRATION; PREPARATION OF SOLUTION**), each 1 gram Meropenem trihydrate for Injection USP MEROP vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq).

CONTRAINDICATIONS

Meropenem trihydrate for Injection USP MEROP 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 trihydrate for Injection USP MEROP careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics.

Meropenem trihydrate for Injection USP MEROP should be used with caution in patients with such a history. If an allergic reaction for Meropenem trihydrate for Injection USP MEROP occurs, the drug should be discontinued and appropriate measures taken.

PEDIATRIC USE

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

DRUG INTERACTIONS

Probenecid competes with Meropenem trihydrate for Injection USP MEROP for active tubular secretion and thus inhibits the renal excretion, with the effect of increasing the elimination half-life and plasma concentration of Meropenem trihydrate Injection USP MEROP. As the potency and duration of action of Meropenem trihydrate Injection USP

MEROP dosed without Probenecid are adequate, the co-administration of Probenecid with Meropenem trihydrate for Injection USP MEROP is not recommended.

Meropenem trihydrate for Injection USP MEROP has been administered concomitantly with other medications without adverse pharmacological interactions. However, no other specific data regarding potential drug interactions is available (apart from probenecid as mentioned above).

PREGNANCY AND LACTATION

PREGNANCY

The safety of Meropenem trihydrate for Injection USP MEROP in human pregnancy has not been evaluated. Animal studies have not shown any adverse effect on the developing fetus. 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. Meropenem trihydrate for Injection USP MEROP should not be used in pregnancy unless the potential benefit justifies the potential risk to the fetus. In every case, it should be used under the direct supervision of the physician.

LACTATION

Meropenem trihydrate for Injection USP MEROP is detectable at very low concentrations in animal breast milk. Meropenem trihydrate for Injection USP MEROP should not be used in breast-feeding women unless the potential benefit justifies the potential risk to the baby.

ADVERSE DRUG EFFECTS

Infections and Infestations: Uncommon: Oral and vaginal candidiasis.

Blood and Lymphatic System Disorders: Common: Thrombocythemia. Uncommon: Eosinophilia, thrombocytopenia, leukopenia, neutropenia. Rare: Agranulocytosis. Very Rare: Hemolytic anemia.

Nervous System Disorders: Common: Headache. Uncommon: Paresthesia. Rare: Convulsions.

Gastrointestinal Disorders: Common: Diarrhea, vomiting, nausea. Very Rare: Pseudomembranous colitis.

Hepatobiliary Disorders: Common: Increased alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, blood lactate dehydrogenase, γ-glutamyltransferase. Uncommon: Increased blood bilirubin.

Skin and Subcutaneous Tissue Disorders: Common: Rash, pruritus. Uncommon: Urticaria. Very Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme.

General Disorders and Administration Site Conditions: Common: Inflammation, pain. Uncommon: Thrombophlebitis.

Immune System Disorders: Very Rare: Angioedema, manifestations of anaphylaxis.

OVERDOSAGE AND TREATMENT

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 trihydrate for Injection USP MEROP and its metabolite.

PHARMACODYNAMICS PROPERTIES

MODE OF ACTION

Meropenem trihydrate for Injection USP MEROP is a carbapenem antibiotic structurally similar to imipenem 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 trihydrate for Injection USP MEROP 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 trihydrate for Injection USP MEROP 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. The invitro antibacterial spectrum of Meropenem trihydrate for Injection USP MEROP includes the majority of clinically significant Gram-positive and Gram-negative, aerobic and anaerobic strains of H bacteria, as shown below:

Gram-positive aerobes:

Bacillus spp., *Corynebacterium diphtheriae, Enterococcus faecalis, Lactobacillus* spp., *Staphylococcus aureus* (penicillinase negative and positive), *Staphylococci-coagulase*-negative; including *Staphylococcus epidermis, Staphylococcus saprophyticus, Staphylococcus intermedius, Streptococcus pneumoniae* (penicillin susceptible and resistant), *Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus bovis, Streptococcus viridans.*

Gram-negative aerobes:

Acinetobacter baumannii, Campylobacter coli, Campylobacter jejuni, Citrobacter freundii, Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae (including beta-lactamase positive and ampicillin resistant strains), *Haemophilus parainfluenzae, Helicobacter pylori, Neisseria gonorrhoeae* (including beta-lactamase positive, penicillin resistant and spectinomycin resistant strains) *Klebsiella pneumoniae, Klebsiella aerogenes, Moraxella catarrhalis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella spp. Vibrio cholerae.*

Anaerobic bacteria:

Bacteroides fragilis, Bacteroides coagulans, Bacteroides uniformis, Clostridium perfringens, Clostridium sporogenes, Clostridium innocuum, Fusobacterium mortiferum, Fusobacterium varium, Peptostreptococcus anaerobius, Peptostreptococcus micros, Peptococcus saccharolyticus, Propionibacterium acnes, Propionibacterium avidum, Enterococcus faecium and methicillin-resistant *staphylococci* have been found to be resistant to meropenem.

PHARMACOKINETICS PROPERTIES

A 30-minute intravenous infusion of a single dose of Meropenem trihydrate for Injection USP MEROP in healthy volunteers results in peak plasma levels of approximately 23 microgram/mL for the 500 mg dose and 49 microgram/mL for the 1g dose.

After an IV dose of 500 mg, plasma levels of Meropenem trihydrate for Injection USP MEROP 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 trihydrate for Injection USP MEROP does not occur. In subjects with normal renal function, Meropenem trihydrate for Injection USP MEROP'S elimination half-life is approximately 1 hour. Plasma protein binding of Meropenem trihydrate for Injection USP MEROP is approximately 2%.

Meropenem trihydrate for Injection USP MEROP 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 Meropenem trihydrate for Injection USP MEROP in children is similar to those in adults. The elimination half-life for Meropenem trihydrate for Injection USP MEROP was approximately 1.5 hours in pediatric patients of age 3 months to 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 trihydrate for Injection USP MEROP 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 trihydrate for Injection USP MEROP, 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 trihydrate for Injection USP MEROP.

SHELF-LIFE: Meropenem trihydrate for Injection USP MEROP has a shelf life of 24 months.

STORAGE: Store at temperatures not exceeding 30°C.

Caution : Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Availability

Meropenem Trihydrate for Injection USP 1g is available in USP Type I Clear Colorless Glass Vial with violet flip-off seal (Box of 1's and 10's)
Meropenem Trihydrate for Injection USP 500 mg is available in USP Type I Clear Colorless Glass Vial with light blue flip-off seal (Box of 1's and 10's)

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Manufactured for: Baxter Pharmaceuticals India Private Limited
Survey No. 415/P, Godown No.- 02 & 03,
B/H. Sarvoday Hotel, Moraiya,
Tal: Sanand (Ahmedabad – Rural) – Pin: 382 213
Manufactured by: Zeiss Pharmaceuticals Pvt. Ltd.
Plot No.72,EPIP-I, Jharmarji
Baddi, Distt. Solan (H.P.),India
Imported by: Claris Lifesciences Philippines Inc.
1108, 11th Floor, Cityland Herrera Tower
98 V.A. Rufino St., cor. Valero St.
Salcedo Village, Makati City, Philippines
Distributed by: UNILAB, INC.
No. 66 United Street, Mandaluyong City
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