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Merocit™ IV Injection

(Meropenem)

میروسٹ انجکشن

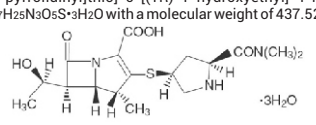
COMPOSITION:
Merocit Injection 500 mg:
Each vial contains:
Meropenem trihydrate equivalent to
anhydrous Meropenem ..... 500 mg.

Product Specs.: USP

Merocit Injection 1 gm:
Each vial contains:
Meropenem trihydrate equivalent to
anhydrous Meropenem ..... 1 gm.

Product Specs.: USP

DESCRIPTION:
Meropenem IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum, carbapenem antibiotic for intravenous administration. It is (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ with a molecular weight of 437.52. Its structural formula is:



Meropenem IV is a white to pale yellow crystalline powder. The solution varies from colorless to yellow depending on the concentration. The pH of freshly constituted solutions is between 7.3 and 8.3. Meropenem is soluble in 5% monobasic potassium phosphate solution, sparingly soluble in water, very slightly soluble in hydrated ethanol, and practically insoluble in acetone or ether.

CLINICAL PHARMACOLOGY:
Mechanism of action: The bactericidal activity of Meropenem results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of Escherichia coli and Pseudomonas aeruginosa; and PBPs 1, 2 and 4 of Staphylococcus aureus. Bactericidal concentrations (defined as a 3 log10 reduction in cell counts within 12 hours to 24 hours) are typically 1-2 times the bacteriostatic concentrations of Meropenem, with the exception of Listeria monocytogenes, against which lethal activity is not observed. Meropenem has significant stability to hydrolysis by β-lactamases, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria. Meropenem should not be used to treat methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE).
Mechanism of resistance: There are several mechanisms of resistance to carbapenems: 1) decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins) causing reduced bacterial uptake, 2) reduced affinity of the target PBPs, 3) increased expression of efflux pump components, and 4) production of antibacterial drug-destroying enzymes (carbapenemases, metallo-β-lactamases). Localized clusters of infections due to carbapenem-resistant bacteria have been reported in some regions.
Cross-Resistance: Cross-resistance is sometimes observed with isolates resistant to other carbapenems.
Interactions with other antibacterial drugs: In vitro tests show Meropenem to act synergistically with aminoglycoside antibacterials against some isolates of Pseudomonas aeruginosa.
Spectrum of activity:
Meropenem has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical Infections:
Gram-positive bacteria:
Enterococcus faecalis (vancomycin-susceptible isolates only)
Staphylococcus aureus (methicillin-susceptible isolates only)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible isolates only)
Streptococcus pyogenes
Viridans group streptococci
Gram-negative bacteria:
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Neisseria meningitidis
Pseudomonas aeruginosa
Proteus mirabilis
Anaerobic bacteria
Bacteroides fragilis
Bacteroides thetaiotaomicron
Pepto streptococcus species
The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following bacteria have exhibited in vitro minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoints for Meropenem. However, the safety and effectiveness of Meropenem in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.
Gram-positive bacteria: Staphylococcus epidermidis (methicillin-susceptible isolates only)
Gram-negative bacteria:
Aeromonas hydrophila
Campylobacter jejuni
Citrobacter koseri (formerly diversus)
Citrobacter freundii
Enterobacter cloacae
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis
Morganella morganii
Pasteurella multocida
Proteus vulgaris
Serratia marcescens
Anaerobic bacteria
Bacteroides distasonis
Bacteroides ovatus
Bacteroides uniformis
Bacteroides ureolyticus
Bacteroides vulgatus
Clostridium difficile
Clostridium perfringens
Eubacterium lentum
Fusobacterium species
Prevotella bivia
Prevotella intermedia
Prevotella melaninogenica
Porphyromonas asaccharolytica
Propionibacterium acnes
Pharmacokinetics:
Absorption: Doses of 500 mg, 1000 mg and 2000 mg of Meropenem infused over 30minutes give mean C max values of approximately 23µg/mL, 49µg/mL and 115µg/mL respectively with corresponding AUC values of 39.3 µg.h/mL, 62.3µg.h/mL and 153µg.h/mL. After infusion over 5 minutes C_{max} values are 52µg/mL and 112µg/mL after 500 mg and 1g doses respectively. When multiple doses are administered 8-hourly to healthy individuals with normal renal function, accumulation of Meropenem does not occur. The mean plasma half-life of Meropenem is approximately 1 hour; the mean volume of distribution is approximately 0.25l/Kg (11-27l) and the mean clearance is 287mL/min at 250mg falling to 205 mL/min at 2 g.
Distribution: The average plasma protein binding of Meropenem is approximately 2% and is 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.
Metabolism: Meropenem is metabolized by hydrolysis of the beta-lactam ring generating a microbiologically inactive metabolite.
Excretion: The elimination half-life of Meropenem is approximately 1 hour. 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. Fecal 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. Urinary concentrations of Meropenem in excess of 10mcg/mL are maintained for up to 5 hours after a 500 mg dose.

NONCLINICAL TOXICOLOGY:
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Carcinogenesis studies have not been performed.
Mutagenesis: Genetic toxicity studies were performed with Meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.
Impairment of fertility: Reproductive studies were performed with Meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 gram every 8 hours). There was no reproductive toxicity seen
Special population:
Renal impairment: 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 hemodialysis patients (CrCL <2 mL/min) when compared to healthy patients (CrCL >80 mL/min).
Hepatic impairment: A pharmacokinetic study with Meropenem IV in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of Meropenem.
Elderly patients: Pharmacokinetic study with Meropenem in elderly patients have shown a reduction in the plasma clearance of Meropenem that correlates with age-associated reduction in creatinine clearance.
Pediatric population: Studies in children have shown that the pharmacokinetics of Meropenem in children is essentially similar to those in adults. The elimination half-life for Meropenem was approximately 1.5 hours in children under the age of 2 years. 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.

THERAPEUTIC INDICATIONS:
Meropenem IV (Meropenem) is indicated for the treatment of the following infections in adults and children over 3 months of age:
- Severe pneumonia including hospital and ventilator-associated pneumonia
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Intra- and post-partum infections
- Complicated skin and soft tissue infections
- Septicemia
- Management of febrile neutropenia
- Acute bacterial meningitis

DOSAGE AND ADMINISTRATION:
The dose of Meropenem IV (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 40mg/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 or Acinetobacter spp.) or very severe infections.

Adults and adolescents:

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	500 mg to 1g
Complicated urinary tract infections	
Complicated intra-abdominal infections	
Intra- and post-partum infections	
Complicated skin and soft tissue infections	
Septicemia	
Management of febrile neutropenic patients	1g
Broncho-pulmonary infections in cystic fibrosis	2g
Acute bacterial meningitis	

Renal impairment: The dose for adults and adolescents should be adjusted with creatinine clearance of 50 mL/min or less, as shown below.

Creatinine clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
25-50	Recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours
<10	One-half recommended dose	Every 24 hours

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Meropenem is cleared by hemodialysis and hemofiltration. The required dose should be administered after completion of the hemodialysis cycle.
Pediatric population:
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 20mg/kg
Complicated urinary tract infections	
Complicated intra-abdominal infections	
Complicated skin and soft tissue infections	
Septicemia	
Management of febrile neutropenic patients	20mg/kg
Broncho-pulmonary infections in cystic fibrosis	40mg/kg
Acute bacterial meningitis	

Children over 50 kg body weight: The adult dose should be administered.

DIRECTIONS FOR USE:
Meropenem IV (Meropenem) is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses of up to 20mg/kg can be given as an intravenous bolus injection over approximately 5 minutes.
Intravenous Injection: Reconstitute Meropenem IV (Meropenem) vial with Sterile Water for Injection as per below table. Shake to dissolve and let stand until clear.

Product	Volume of Diluent added (mL)
MEROPENEM IV (Meropenem) 500mg	10 mL
MEROPENEM IV (Meropenem) 1g	20 mL

The reconstituted solution may be stored for 3 hours at up to 25°C or for 12 hours at 2-8°C.
Intravenous Infusion: Reconstitute Meropenem IV (Meropenem) vial with Sterile Water for Injection as per below table. Shake to dissolve.

Product	Volume of Diluent added (mL)
MEROPENEM IV (Meropenem) 500mg	10 mL
MEROPENEM IV (Meropenem) 1g	20 mL

Further dilute the reconstituted solution with Sodium Chloride Solution for Infusion 0.9% or Dextrose Solution for Infusion 5%. The solution for Infusion (Meropenem concentrations ranging from 1mg/mL to 20mg/mL) prepared with Sodium Chloride Solution for Infusion 0.9% may be stored for 3 hours at up to 25°C or for 24 hours at 2-8°C. Reconstituted solution (Meropenem concentrations ranging from 1mg/mL to 20mg/mL) in Dextrose Solution for Infusion 5% should be used immediately. Alternatively, Meropenem IV (Meropenem) may be directly reconstituted with a compatible infusion solution.

ADVERSE REACTIONS:
Following adverse reactions have been reported during treatment with Meropenem:
Common:
Thrombocythemia, headache, diarrhea, vomiting, nausea, abdominal pain, increased transaminases, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, rash, pruritis, inflammation and pain.
Uncommon:
Oral and vaginal candidiasis, eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, hemolytic anemia, angioedema, anaphylaxis, paraesthesiae, antibiotic-associated colitis, increased blood bilirubin, urticaria, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, increased blood creatinine & urea, thrombophlebitis and pain at the injection site.
Rare: Convulsions.

CONTRAINDICATIONS:
Meropenem is contraindicated in patients:
- With known hypersensitivity to Meropenem or to any excipient of the product.
- Hypersensitive to any other carbapenem antibacterial agent.

Who have demonstrated anaphylactic reactions to any other type of β-lactams antibacterial agent (e.g. Penicillins or cephalosporins).

PRECAUTIONS:
- 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.
- As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions have been reported. Before initiating therapy with Meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactam antibiotics. If a severe allergic reaction occurs, Meropenem should be discontinued and appropriate measures should be taken.
- 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 diarrhea during or subsequent to the administration of Meropenem. 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 have infrequently been reported during treatment with carbapenems, including Meropenem.
- Hepatic function should be closely monitored during treatment with Meropenem due to the risk of hepatic toxicity (hepatic dysfunction with cholestasis and cytolysis).
- Patients with pre-existing liver disorders should have liver function monitored during treatment with Meropenem.
- A positive direct or indirect Coombs test may develop during treatment with Meropenem.
- Prolong use of Meropenem may result in overgrowth of nonsusceptible organisms. If superinfection does occur during therapy, appropriate measures should be taken.
- Prescribing Meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Alert patients receiving Meropenem on an outpatient basis regarding adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment.

Pregnancy:
Pregnancy Category B.There are no adequate and well controlled studies in pregnant women. Meropenem should be used during pregnancy only if clearly needed.
Nursing mother:
Meropenem has been reported to be excreted in human milk. Caution should be exercised when Meropenem is administered to a nursing mother.

DRUG INTERACTIONS:
Probenecid:
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.
Valproic acid:
Decrease in blood levels of valproic acid have been reported when it is co-administered with carbapenem agents resulting in 60-100% decrease in valproic acid levels in about two days. If administration of Meropenem is necessary, then supplemental anti-convulsant therapy should be considered.
Oral Anti-coagulants:
Simultaneous administration of antibiotics with warfarin may augment its anti-coagulant effects. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.

OVERDOSAGE:
Symptoms:
Adverse reactions following overdosage are consistent with the adverse reaction profile of Meropenem and are generally mild in severity and resolve on withdrawal or dose reduction.
Treatment:
Treatment of overdosage should be symptomatic. In individuals with normal renal function, rapid renal elimination will occur. Hemodialysis will remove Meropenem and its metabolite.

INSTRUCTIONS:
- Store in a cool and dry place, below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- Do not freeze.
- Always use freshly reconstituted solution.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Merocit Injection 500 mg : Pack of 500 mg IV injection vial with 10 ml water for injection ampoule.
Merocit Injection 1 gm : Pack of 1 gm IV injection vial with 20 ml water for injection ampoule.

ہدایات:

دوا کو خشک اور ٹھنڈی جگہ، ۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
منجمند ہونے سے بچائیں۔
انجکشن تیار کرنے کے فوراً بعد استعمال کریں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

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