

Meropenem for injection

MEROCRIT

COMPOSITION

MEROCRIT Baby

Each vial Contains

Meropenem

Trihydrate USP equivalent to Anhydrous

Meropenem.....125 mg

Also contains Sodium Carbonate (Sodium 11.275 mg)

MEROCRIT 0.250 gm

Each vial Contains

Meropenem

Trihydrate USP equivalent to Anhydrous

Meropenem..... 250 mg

Also contains Sodium Carbonate (Sodium 22.55 mg)

MEROCRIT 0.5 gm

Each vial Contains

Meropenem

Trihydrate USP equivalent to Anhydrous

Meropenem..... 500 mg

Also contains Sodium Carbonate (Sodium 45.1 mg)

MEROCRIT 1 gm

Each vial Contains

Meropenem

Trihydrate USP equivalent to Anhydrous

Meropenem..... 1gm

Also contains Sodium Carbonate (Sodium 90.2 mg)

DOSAGE FORM/S

Powder for reconstitution and I.V. use only

PHARMACOLOGY

Pharmacodynamics

Meropenem is a broad-spectrum carbapenem antibiotic. 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*. Meropenem has significant stability to hydrolysis by β -lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria.

Meropenem should not be used to treat methicillin-resistant staphylococci (MRSA). *In vitro* tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*. Meropenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (excluding vancomycin-resistant isolates)

Staphylococcus aureus (beta-lactamase and non- beta -lactamase producing, methicillin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus pneumoniae (penicillin-susceptible isolates only)

NOTE: Penicillin-resistant isolates had meropenem MIC₉₀ values of 1 or 2 µg/mL, which is above the 0.12 µg/mL susceptible breakpoint for this species.

Streptococcus pyogenes

Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms

Escherichia coli

Haemophilus influenzae (beta -lactamase and non- beta -lactamase-producing)

Klebsiella pneumoniae

Neisseria meningitidis

Pseudomonas aeruginosa

Proteus mirabilis

Anaerobic microorganisms

Bacteroides fragilis

Bacteroides thetaotaomicron

Peptostreptococcus species

The following *in vitro* data are available, but their clinical significance is unknown.

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for meropenem. However, the safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and facultative Gram-positive microorganisms

Staphylococcus epidermidis (beta -lactamase and non- beta -lactamase-producing, methicillin-susceptible isolates only).

Aerobic and facultative Gram-negative microorganisms

Acinetobacter species

Aeromonas hydrophila
Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Haemophilus influenzae (ampicillin-resistant, non- beta -lactamase producing isolates [BLNAR isolates])
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis (beta -lactamase and non- beta -lactamase-producing isolates)
Morganella morganii
Pasteurella multocida
Proteus vulgaris
Salmonella species
Serratia marcescens
Shigella species
Yersinia enterocolitica

Anaerobic microorganisms

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

At the end of a 30-minute intravenous infusion of a single dose of meropenem I.V. in normal volunteers, mean peak plasma concentrations are approximately 23 µg/mL (range 14–26) for the 500 mg dose and 49 µg/mL (range 39–58) for the 1 g dose. A 5-minute intravenous bolus injection of meropenem I.V. in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/mL (range 18–65) for the 500 mg dose and 112 µg/mL (range 83–140) for the 1 g dose.

Following intravenous doses of 500 mg mean plasma concentrations of meropenem usually decline to approximately 1 µg/mL at 6 hours after administration.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. Plasma protein binding of meropenem is approximately 2%.

In subjects with normal renal function, the elimination half-life of meropenem I.V. is approximately 1 hour. Approximately 70% of the intravenously 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 µg/mL are maintained for up to 5 hours after 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. There is one metabolite that is microbiologically inactive.

Studies performed in paediatric patients using intravenous meropenem 10 to 40 mg/kg infused over 30 minutes have demonstrated that the volume of distribution at steady-state (0.45 L/kg in neonates) and the elimination half-life (3 hours in preterm neonates, 2 hours in full term neonates, 1.4 to 2.3 hours in infants aged 3 to 5 months, 1.1 to 1.5 hours in infants aged 6 to 23 months, and about 1 hour in children aged 2 to 12 years) are increased in infants compared with adults.

Total body clearance (0.12 to 0.19 L/h/kg) and renal clearance (0.05 to 0.07 L/h/kg), and the percentage of drug recovered in the urine, appear to be decreased in neonates versus adults. It is suggested that the volume of distribution is linearly related to weight, and that clearance is nonlinearly related to age after normalization for creatinine clearance.

INDICATIONS

MEROCRIT is indicated for all age group including infants above 3 months of age as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

1. Pneumonias and Nosocomial Pneumonias
2. Urinary Tract Infections
3. Intra-abdominal Infections
4. Gynaecological Infections, such as endometritis and pelvic inflammatory disease
5. Skin and Skin Structure Infections
6. Meningitis
7. Septicemia

8. Empiric treatment, for presumed infection in adult patients with febrile neutropenia, used as monotherapy or in combination with antiviral or antifungal agents.

Meropenem I.V. has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis. It 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.

Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to meropenem.

Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known.

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:-

- 500 mg every 8 hours in treatment of pneumonia, UTI, gynecological infections such as endometritis, skin and skin structure infections.
- 1 g every 8 hours in treatment of nosocomial pneumonia, peritonitis, presumed infections in neutropenic patients and septicaemia.
- In meningitis the recommended dosage is 2g every 8 hours.

Use in Adults with Renal Impairment

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min.

When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance.

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x above value

Recommended MEROCRIT I.V. Dosage Schedule for Adults With Impaired Renal Function		
Creatinine Clearance (mL/min)	Dose (based on unit doses of 500 mg, 1g, 2 g)	Dosing Interval
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 meropenem 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 concentration.

There is no experience with peritoneal dialysis.

Paediatric use

For paediatric patients from 3 months of age and older, the **MEROCRIT** I.V. dose is 10, 20 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection. Paediatric patients weighing over 50 kg should be administered adult **MEROCRIT** I.V. dose.

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

There is no experience in children with renal impairment.

Method of Administration

MEROCRIT I.V. 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 diluents.

Preparation of solution:

Intravenous Bolus Administration

Constitute injection vials (125 mg, 250 mg, 500 mg and 1 g) with sterile water for injection. Shake to dissolve. Constituted solutions are clear, and colorless or pale yellow.

Vial Size	Amount of Diluent Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
125 mg	2.5	2.5	50
250 mg	5	5	50
500 mg	10	10	50
1 g	20	20	50

Intravenous Infusion Administration

MEROCRIT I.V. for intravenous infusion may be constituted with compatible infusion fluids (50 to 200 mL).

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. After reconstitution with 0.9% NaCl solution and sterile water for injection, **MEROCRIT I.V.** is stable at room temperature for 8 hrs and under refrigerator for 18 hrs.

Solutions of intravenous meropenem I.V. should not be frozen.

CONTRAINDICATIONS

MEROCRIT is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. There is some clinical and laboratory evidence of partial cross-allergenicity between other carbapenems and beta-lactam antibiotics, penicillins and cephalosporins. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. As with all beta-lactam antibiotics, rare hypersensitivity reactions have been reported .

There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with **MEROCRIT I.V.**, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to meropenem i.v. occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management, including intubation. Other therapy may also be administered as indicated.

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

Use of Meropenem 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.

Seizures and other adverse CNS experiences have been reported during treatment with meropenem. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of meropenem I.V. re-examined to determine whether it should be decreased or the antibiotic discontinued.

In patients with renal dysfunction, thrombocytopenia has been observed but no clinical bleeding reported. (See **DOSAGE AND ADMINISTRATION - Use in Adults with Renal Impairment.**)

There is inadequate information regarding the use of meropenem I.V. in patients on haemodialysis.

Meropenem may reduce serum valproic acid levels. Sub-therapeutic levels may be reached in some patients.

Rarely pseudomembranous colitis has been reported with nearly all antibacterial 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 diarrhoea subsequent to the administration of antibacterial agents. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Drug interactions

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. This led to statistically significant increase in the elimination half-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of probenecid with meropenem is not recommended.

There is evidence that carbapenem may reduce serum levels of valproic acid and may result in loss of seizure control.

Renal impairment

Please refer under **DOSAGE AND ADMINISTRATION**. There is no experience in paediatric patients with renal impairment.

Hepatic impairment

No dosage adjustment is necessary in patients with impaired hepatic function.

Pregnancy

Pregnancy Category B

There are, no adequate and well- controlled studies in pregnant women. Meropenem should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

Lactation

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

Paediatric use

The safety and effectiveness of meropenem have been established for paediatric patients \geq 3 months of age. Use of meropenem I.V. in paediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population. Use of meropenem I.V. in paediatric patients with intra-abdominal infections is supported by evidence from adequate and wellcontrolled studies with adults with additional data from paediatric pharmacokinetics studies and controlled clinical trials in paediatric patients. Use of meropenem I.V. in paediatric patients with complicated skin and skin structure infections is supported by evidence from an adequate and well-controlled study with adults and additional data from paediatric pharmacokinetics studies.

Geriatric use

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

UNDESIRABLE EFFECTS

Adult patients

Local intravenous injection site reactions:

Inflammation, thrombophlebitis ,pain at the injection site.

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, pruritis, 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.

Central nervous system

Headache, paraesthesiae. Convulsions have been reported although a casual relationship with Meropenem has not been established.

Other:

Oral and vaginal candidosis

Adverse Laboratory Changes

Adverse laboratory changes that were reported irrespective of relationship to meropenem I.V. and occurring in greater than 0.2% of the patients were as follows:

Hepatic

Increased serum concentrations of bilirubin,transaminases,alkaline phosphatase, lactic dehydrogenase alone or in combination have been reported.

Hematologic

Reversible thrombocythaemia, eosinophilia,thrombocytopenia,leucopenia and neutropenia(including very rare cases of agranulocytosis).A positive direct or indirect Coomb's test may develop in some subjects;there have been reports of reduction in partial thromboplastin time.

Renal

Increased creatinine and increased BUN

NOTE: For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure and shock reported irrespective of relationship to meropenem I.V., increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 mL/min).

Urinalysis

Presence of red blood cells

Paediatric patients

The types of clinical adverse events seen in these patients are similar to the adults, with the most common adverse events reported as possibly, probably, or definitely related to meropenem I.V. and their rates of occurrence as follows:

Diarrhea 4.7%, rash (mostly diaper area moniliasis) 3.1%, oral moniliasis 1.9% and glossitis 1.0%

In the meningitis studies the rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents (either cefotaxime or ceftriaxone). In the meropenem I.V. treated group, 12/15 patients with seizures had late onset seizures (defined as occurring on day 3 or later) versus 7/20 in the comparator arm.

OVERDOSAGE

The largest dose of meropenem administered in clinical trials has been 2 g given intravenously every 8 hours. At this dosage, no adverse pharmacological effects or increased safety risks have been observed.

Treatment of overdosage should be symptomatic. Meropenem and its metabolite are readily dialyzable and effectively removed by haemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

INCOMPATIBILITY

MEROCRIT I.V. should not be mixed with or physically added to solutions containing other drugs.

STORAGE AND HANDLING INSTRUCTIONS

Before opening:

Store in dry cool place. Protect from light.

Reconstituted solution:

When reconstituted with 0.9% NaCl solution or sterile water for injection, **MEROCRIT** I.V. is stable at room temperature for 8 hrs and under refrigerator for 18 hrs.

Solutions of intravenous meropenem I.V. should not be frozen.

PACKAGING INFORMATION

MEROCRIT Baby vial of 15mL
MEROCRIT 0.250gm..... vial of 15mL
MEROCRIT 0.5gm.....vial of 15mL
MEROCRIT 1gm.....vial of 15mL

Last Updated: June 2010