

**MEROPENABOL<sup>®</sup>**  
**(meropenem for injection)**  
**Prescribing Information**

MEROPENABOL<sup>®</sup> (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<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>S•3H<sub>2</sub>O with a molecular weight of 437.52.

MEROPENABOL 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.

### **PHARMACODYNAMIC**

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 log<sub>10</sub> reduction in cell counts within 12 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 is a broad-spectrum carbapenem antibiotic. It is active against many Gram-positive and Gram-negative bacteria:

#### ***Aerobic Gram-positive microorganisms***

*Enterococcus faecalis*, *Staphylococcus aureus* (beta-lactamase and non-beta-lactamase producing strains), *Staphylococcus epidermidis* (β-lactamase and non-β-lactamase-producing, methicillin-susceptible isolates only), *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, Viridans group streptococci

#### ***Aerobic Gram-negative microorganisms***

*Aeromonas hydrophila*, *Campylobacter jejuni*, *Escherichia coli*, *Haemophilus influenzae* (beta-lactamase and non-beta-lactamase producing strains), *Klebsiella pneumoniae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter species*, *Citrobacter diversus*, *Citrobacter freundii*, *Enterobacter cloacae*, *Haemophilus influenzae* (incl. ampicillin-resistant 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 fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides distasonis*, *Bacteroides ovatus*, *Bacteroides uniformis*, *Bacteroides ureolyticus*, *Bacteroides vulgatus*, *Clostridium difficile*, *Clostridium perfringens*, *Peptostreptococcus species*, *Eubacterium lentum*, *Fusobacterium species*, *Prevotella bivia*, *Prevotella intermedia*, *Prevotella melaninogenica*, *Porphyromonas asaccharolytic*, *Propionibacterium acnes*.

Meropenem has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive (except methicillin-resistant staphylococci (MRSA)) and Gram-negative bacteria.

*In vitro* tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa*.

## PHARMACOKINETIC

At the end of a 30-minute intravenous infusion of a single dose of MEROPENABOL 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 MEROPENABOL 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.

In subjects with normal renal function, the elimination half-life of MEROPENABOL 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.

Plasma protein binding of meropenem is approximately 2%.

There is one metabolite that is microbiologically inactive.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single intravenous dose of MEROPENABOL, the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 to 1.5 hours) after the start of infusion.

The pharmacokinetics of MEROPENABOL in pediatric patients 2 years of age or older are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 months to 2 years. The pharmacokinetics are linear over the dose range from 10 to 40 mg/kg.

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

Meropenem I.V. is hemodialyzable. A pharmacokinetic study with MEROPENABOL in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

## INDICATIONS

MEROPENABOL is indicated as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

### **Skin and Skin Structure Infections**

Complicated skin and skin structure infections due to *Staphylococcus aureus* ( $\beta$ -lactamase and non- $\beta$ -lactamase producing, methicillin susceptible isolates only), *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans group streptococci, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus species*.

### **Intra-abdominal Infections**

Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus species*.

### **Bacterial Meningitis (Pediatric patients $\geq$ 3 months only)**

Bacterial meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* ( $\beta$ -lactamase and non- $\beta$ -lactamase-producing isolates), and *Neisseria meningitidis*. Also MEROPENABOL has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis.

MEROPENABOL is useful as presumptive therapy in the indicated condition (i.e., intra-abdominal infections) prior to the identification of the causative organisms because of its broad spectrum of bactericidal activity.

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

### **Contraindications**

Hypersensitivity to meropenem, any component of the formulation, or other carbapenems (eg, imipenem); patients who have experienced anaphylactic reactions to other beta-lactams

### **Warnings/Precautions**

#### ***Concerns related to adverse effects:***

- Anaphylaxis/hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams).
- CNS effects: Has been associated with CNS adverse effects, including confusional states and seizures; use caution with CNS disorders (eg, brain lesions, history of seizures, or renal impairment).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

#### ***Disease-related concerns:***

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Increased seizure risk and thrombocytopenia have been reported in patients with renal dysfunction.

#### ***Special populations:***

- Elderly: Lower doses (based upon renal function) are often required in the elderly.

### **Pregnancy Risk Factor**

B

### **Pregnancy Considerations**

Meropenem is classified as pregnancy category B because no evidence of impaired fertility or fetal harm has been found in animals. Adequate and well-controlled studies have not been conducted in pregnant women and it is not known whether meropenem can cause fetal harm.

### **Lactation**

Excretion in breast milk unknown/use caution

### **Breast-Feeding Considerations**

It is not known if meropenem is excreted in breast milk. The manufacturer recommends that caution be exercised when administering meropenem to breast-feeding women. Most penicillins and carbapenems are safe for use in breast-feeding. Nondose-related effects could include modification of bowel flora.

### **DOSAGE**

#### **Adults**

The recommended dose of MEROPENABOL is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections.

MEROPENABOL should be administered by intravenous infusion over approximately 15 to 30 minutes. Doses of 1 g may also be administered as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

**Use in Adults with Renal Impairment**

Dosage should be reduced in patients with creatinine clearance less than 51 mL/min. (see dosing table below).

**Recommended MEROPENABOL Dosage Schedule for Adults With Impaired Renal Function**

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
≥ 51	Recommended dose (500 mg cSSSI and 1g Intra-abdominal)	Every 8 hours
26-50	Recommended dose	Every 12 hours
10-25	One-half recommended dose	Every 12 hours
< 10	One-half recommended dose	Every 24 hours

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)<sup>5</sup> 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

There is inadequate information regarding the use of MEROPENABOL in patients on hemodialysis.

There is no experience with peritoneal dialysis.

Use in Adults With Hepatic Insufficiency:

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

**Use in Elderly Patients**

No dosage adjustment is required for elderly patients with creatinine clearance values above 50 mL/min.

**Use in Pediatric Patients**

For pediatric patients from 3 months of age and older, the MEROPENABOL dose is 10, 20 or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (complicated skin and skin structure, intra-abdominal or meningitis). (See dosing table below.) Pediatric patients weighing over 50 kg should be administered MEROPENABOL at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 g every 8 hours for intra-abdominal infections and 2 g every 8 hours for meningitis. MEROPENABOL should be given as intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

**Recommended MEROPENABOL Dosage Schedule for Pediatrics With Normal Renal Function**

Type of Infection	Dose (mg/kg)	Up to a Maximum Dose	Dosing Interval
Complicated skin and skin structure Intra-abdominal	10	500 mg	Every 8 hours
	20	1 g	Every 8 hours
Meningitis	40	2 g	Every 8 hours

There is no experience in pediatric patients with renal impairment.

## PREPARATION OF SOLUTION

### For Intravenous Bolus Administration

Constitute injection vials (500 mg and 1g) with sterile Water for Injection. (See table below.)  
Shake to dissolve and let stand until clear.

Vial size	Amount of Diluent Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Average Concentration (mg/mL)
500 mg	10	10	50
1 g	20	20	50

### For Infusion

Infusion vials (500 mg and 1g) may be directly constituted with a compatible infusion fluid (See **Compatibility And Stability**) 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. (See **Compatibility And Stability**)

### Compatibility And Stability

Compatibility of MEROPENABOL with other drugs has not been established.

MEROPENABOL should not be mixed with or physically added to solutions containing other drugs.

Freshly prepared solutions of MEROPENABOL should be used whenever possible. However, constituted solutions of MEROPENABOL maintain satisfactory potency at controlled room temperature 15-25°C (59- 77°F) or under refrigeration at 4°C (39°F) as described below. Solutions of intravenous MEROPENABOL should not be frozen.

### Intravenous Bolus Administration

MEROPENABOL injection vials constituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of MEROPENABOL) may be stored for up to 2 hours at controlled room temperature 15-25°C (59-77°F) or for up to 12 hours at 4°C (39°F).

### Intravenous Infusion Administration

**Stability in Infusion Vials:** MEROPENABOL infusion vials constituted with Sodium Chloride Injection 0.9% (MEROPENABOL concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 2 hours at controlled room temperature 15-25°C (59-77°F) or for up to 18 hours at 4°C (39°F). Infusion vials of MEROPENABOL constituted with Dextrose Injection 5% (MEROPENABOL concentrations ranging from 2.5 to 50 mg/mL) are stable for up to 1 hour at controlled room temperature 15-25°C (59-77°F) or for up to 8 hours at 4°C (39°F).

**Stability in Plastic I.V. Bags:** Solutions prepared for infusion (MEROPENABOL concentrations ranging from 1 to 20 mg/mL) may be stored in plastic intravenous bags with diluents as shown below:

	Number of Hours Stable at Controlled Room Temperature 15-25°C (59-77°F)	Number of Hours Stable at 4°C (39°F)
Sodium Chloride Injection 0.9%	4	24
Dextrose Injection 5.0%	1	4
Dextrose Injection 10.0%	1	2
Dextrose and Sodium Chloride Injection 5.0%/0.9%	1	2
Dextrose and Sodium Chloride Injection 5.0%/0.2%	1	4
Potassium Chloride in Dextrose Injection 0.15%/5.0%	1	6
Sodium Bicarbonate in Dextrose Injection 0.02%/5.0%	1	6

	Number of Hours Stable at Controlled Room Temperature 15-25°C (59-77°F)	Number of Hours Stable at 4°C (39°F)
Dextrose Injection 5.0% in Normosol®-M	1	8
Dextrose Injection 5.0% in Ringers Lactate Injection	1	4
Dextrose and Sodium Chloride Injection 2.5%/0.45%	3	12
Mannitol Injection 2.5%	2	16
Ringers Injection	4	24
Ringers Lactate Injection	4	12
Sodium Lactate Injection 1/6 N	2	24
Sodium Bicarbonate Injection 5.0%	1	4

**Stability in Plastic Syringes, Tubing and Intravenous Infusion Sets:** Solutions of MEROPENABOL (MEROPENABOL concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride Injection 0.9% (for up to 4 hours) or in Dextrose Injection 5.0% (for up to 2 hours) at controlled room temperatures 15-25°C (59-77°F) are stable in plastic tubing and volume control devices of common intravenous infusion sets.

Solutions of MEROPENABOL (MEROPENABOL concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride Injection 0.9% (for up to 48 hours) or in Dextrose Injection 5% (for up to 6 hours) are stable at 4°C (39°F) in plastic syringes.

#### **Adverse Reactions**

1% to 10%:

Cardiovascular: Peripheral vascular disorder

Central nervous system: Headache (2% to 8%), pain (?5%)

Dermatologic: Rash (2% to 3%, includes diaper-area moniliasis in pediatrics), pruritus (1%)

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Diarrhea (4% to 7%), nausea/vomiting (1% to 8%), constipation (1% to 7%), oral moniliasis (up to 2% in pediatric patients), glossitis (1%)

Hematologic: Anemia (?6%)

Local: Inflammation at the injection site (2%), phlebitis/thrombophlebitis (1%), injection site reaction (1%)

Respiratory: Apnea (1%), pharyngitis, pneumonia

Miscellaneous: Sepsis (2%), shock (1%)

<1%: Abdominal enlargement, abdominal pain, agitation/delirium, alkaline phosphatase increased, ALT/AST increased, anemia (hypochromic), anorexia, anxiety, asthma, back pain, bilirubin increased, bradycardia, BUN increased, chest pain, chills, cholestatic jaundice/jaundice, confusion, cough, creatinine increased, depression, diaphoresis, dizziness, dyspepsia, dyspnea, dysuria, eosinophilia, epistaxis (0.2%), fever, flatulence, gastrointestinal hemorrhage (0.5%), hallucinations, heart failure, hemoglobin/hematocrit decreased, hemoperitoneum (0.2%), hepatic failure, hyper-/hypotension, hypervolemia, hypokalemia, hypoxia, ileus, insomnia, intestinal obstruction, LDH increased, leukocytosis, melena (0.3%), MI, nervousness, paresthesia, pelvic pain, peripheral edema, platelets decreased/increased, pleural effusion, prothrombin time decreased, pulmonary edema, pulmonary embolism, renal failure, respiratory disorder, seizure, skin ulcer, somnolence, syncope, tachycardia, urinary incontinence, urticaria, vaginal moniliasis, weakness, WBC decreased, whole body pain

Postmarketing and/or case reports: Agranulocytosis, angioedema, erythema multiforme, hemolytic anemia, leukopenia, neutropenia, positive Coombs test, Stevens-Johnson syndrome, toxic epidermal necrolysis

**Drug Interactions**

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected.

**HOW SUPPLIED**

MEROPENABOL is supplied in 20 mL injection vials containing meropenem 500 mg for intravenous administration. The dry powder should be stored at controlled room temperature 20-25°C (68-77°F).

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