MEROPENEM (Systemic)

Category

Antibacterial (systemic).

Indications

General considerations

Meropenem is a carbapenem antibiotic. It has significant stability to hydrolysis by penicillinases and cephalosporinases produced by gram-positive and gram-negative organisms, with the exception of metallo-beta-lactamases. 1

Cross-resistance is sometimes seen with strains resistant to other carbapenems. 1

Meropenem has been shown to act synergistically with aminoglycosides in vitro against some isolates of Pseudomonas aeruginosa. 1

Accepted

Intra-abdominal infections (treatment)¾Meropenem is indicated as a single agent in the treatment of intra-abdominal infections, including complicated appendicitis and peritonitis caused by susceptible organisms, in adults and children 3 months of age and older. 1

Meningitis, bacterial (treatment)¾Meropenem is indicated as a single agent in the treatment of bacterial meningitis caused by susceptible organisms, in children 3 months of age and older. Meropenem has been found to be effective in eliminating concurrent bacteremia associated with bacterial meningitis. 1

[Neutropenia, febrile (treatment)] *¾Meropenem is indicated for empiric treatment of febrile neutropenia 2, 3, 4, 5, 6, 7, 8, 9, 10.

In patients at high risk of severe infection, including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia, antimicrobial therapy alone may not be appropriate 2, 3, 4, 5, 6, 7, 8, 9, 10.

Unaccepted

Meropenem should not be used to treat methicillin-resistant staphylococci. 1

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Bactericidal; meropenem inhibits cell wall synthesis by penetrating the cell wall of most gram-positive and gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. 1 Its strongest affinity is toward PBPs 2, 3, and 4 of Escherichia coli and Pseudomonas aeruginosa , and PBPs 1, 2, and 4 of Staphylococcus aureus. 1 Bactericidal concentrations are typically one to two times the bacteriostatic concentrations; the exception is Listeria monocytogenes , against which lethal activity has not been observed. 1

Precautions to Consider

Cross-sensitivity and/or related problems

Patients allergic to other beta-lactam antibacterials (e.g., penicillins, cephalosporins, imipenem) may be allergic to meropenem also. 1

Carcinogenicity

Carcinogenicity studies have not been performed. 1

Mutagenicity

No evidence of mutagenic potential was found when the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronuclear test were performed with meropenem. 1

Pregnancy/Reproduction

Fertility¾No impairment of fertility was seen when meropenem was studied in rats at doses of up to 1000 mg per kg of body weight (mg/kg) per day, and in cynomolgus monkeys at doses of up to 360 mg/kg per day. These doses are comparable to 1.8 and 3.7 times, respectively, the human exposure at the usual dose of 1 gram every 8 hours, based on area under the plasma concentration-time curve (AUC). 1

Pregnancy¾Adequate and well-controlled studies in humans have not been done. 1

Studies have been performed in rats at doses of up to 1000 mg/kg per day, and cynomolgus monkeys at doses of up to 360 mg/kg per day. These doses are comparable to 1.8 and 3.7 times, respectively, the human exposure at the usual dose of 1 gram every 8 hours, based on AUC. These studies showed no harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg per day (0.4 times the human exposure at the usual dose of 1 gram every 8 hours, based on AUC) and higher in rats. 1

FDA Pregnancy Category B. 1

Breast-feeding

It is not known whether meropenem is distributed into breast milk. 1

Pediatrics

Safety and efficacy have not been established in children less than 3 months of age. However, use of meropenem in children 3 months of age and older with bacterial meningitis is supported by evidence from adequate and well-controlled studies. Use of meropenem in children 3 months of age and older with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults, with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. 1

Geriatrics

No information is available on the relationship of age to the effects of meropenem in geriatric patients. However, elderly patients are more likely to have an age-related decrease in renal function, which may require a reduction of dosage in patients receiving meropenem.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing the following medication, depending on the amount present, may also interact with this medication.
>> Probenecid

(probenecid competes with meropenem for active tubular secretion, inhibiting the renal excretion of meropenem; this results in a 38% increase in the elimination half-life and a 56% increase in the extent of systemic exposure to meropenem; concurrent administration is not recommended 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Partial thromboplastin time and 1

Prothrombin time 1

(may be shortened or prolonged)

Positive direct or indirect antiglobulin (Coombs') tests 1

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) and 1

Alkaline phosphatase and 1

Aspartate aminotransferase (AST [SGOT]) and 1

Bilirubin and 1

Lactate dehydrogenase (LDH) 1

(serum values may be increased)

Blood urea nitrogen (BUN) and 1

Creatinine, serum 1

(concentrations may be transiently increased)

Hematocrit and 1

Hemoglobin concentrations and 1

White blood count 1

(may be decreased)

Platelet count 1

(may be increased or decreased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Allergy to meropenem or other beta-lactam antibacterials (e.g., penicillins, cephalosporins, imipenem)

Risk-benefit should be considered when the following medical problems exist

>> Central nervous system (CNS) disorders (e.g., brain lesions or history of seizures) or 1

>> Meningitis, bacterial 1

(seizures are more likely to occur in patients with CNS lesions, a history of seizure disorders, bacterial meningitis, and/or renal function impairment)

>> Renal function impairment 1

(because meropenem is primarily excreted through the kidneys, it must be administered in a reduced dosage to patients with impaired renal function; dosage adjustment is also recommended in elderly patients; also, thrombocytopenia has been observed in patients with renal function impairment, but no clinical bleeding has been reported)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Alanine aminotransferase (ALT [SGPT]), serum and 1

Alkaline phosphatase, serum and 1

Aspartate aminotransferase (AST [SGOT]), serum and 1

Bilirubin, serum and 1

Lactate dehydrogenase (LDH), serum 1

(periodic monitoring is advisable during prolonged therapy)

Blood urea nitrogen (BUN) concentrations and 1

Creatinine, serum 1

(periodic monitoring is advisable during prolonged therapy)

Hematocrit and 1

Hemoglobin concentrations and 1

Platelet count 1

White blood count 1

(periodic monitoring is advisable during prolonged therapy)

Side/Adverse Effects

Note: The incidence of seizures was reported to be 0.5% in patients treated for infections outside the CNS during clinical trials 1.

All patients who experienced seizures had pre-existing contributing factors, including a prior history of seizures or CNS abnormality and concurrent administration of medications with seizure potential 1.

Adherence to the recommended dose is strongly recommended, especially in patients with known factors that predispose them to seizure activity 1.

Thrombocytopenia has been seen in patients with renal dysfunction; however, no clinical bleeding has been reported. 1

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Inflammation at site of injection 1 redness and swelling at site of injection)
Incidence less frequent

Skin rash and itching 1; thrombophlebitis 1 pain at site of injection)
Incidence rare

Bleeding events 1 black, bloody stools); black, bloody vomit); nosebleed); pseudomembranous colitis 1 abdominal or stomach cramps and pain, severe); diarrhea, watery and severe, which may also be bloody); fever); seizures 1 convulsions)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Gastrointestinal disturbances 1 (constipation; diarrhea; nausea and vomiting)
Incidence less frequent

Headache 1
Those indicating the need for medical attention if they occur after medication is discontinued

Pseudomembranous colitis 1 (abdominal or stomach cramps and pain, severe; diarrhea, watery and severe, which may also be bloody; fever)

Overdose

No cases of overdose have been reported in humans to date. The largest dose of meropenem administered in clinical trials has been 2 grams every 8 hours and no increased safety risks have been seen. 1

Large doses (2200 to 4000 mg per kg of body weight) of meropenem were administered to rats and mice; toxicities included ataxia, dyspnea, convulsions, and mortalities. 1

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Treatment of overdose

There is no specific information available for the treatment of meropenem overdose. In the event of an overdose, the medication should be discontinued and supportive care administered until meropenem

can be eliminated through the kidneys. Meropenem and its metabolite are dialyzable; however, there is no information available on the use of hemodialysis in the event of an overdose. 1

Supportive care¾Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Meropenem (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance)
Before using this medication

>> Conditions affecting use, especially:

Hypersensitivity to meropenem or other beta-lactam antibiotics
Other medications, especially probenecid
Other medical problems, especially bacterial meningitis, central nervous system disorders, or renal function impairment
Proper use of this medication

>> Importance of receiving medication for full course of therapy and on regular schedule

>> Proper dosing
Precautions while using this medication

>> Continuing anticonvulsant therapy in patients with a history of seizures

>> For severe diarrhea, checking with physician before taking any antidiarrheals; for mild diarrhea, taking kaolin- or attapulgite-containing, but not other, antidiarrheals; checking with physician or pharmacist if mild diarrhea continues or worsens

Side/adverse effects

Signs of potential side effects, especially inflammation at site of injection, skin rash and itching, thrombophlebitis, bleeding events, pseudomembranous colitis, and seizures

General Dosing Information

For treatment of adverse effects

Anticonvulsants should be continued in the treatment of patients receiving meropenem who have known seizure disorders. In patients who develop symptoms of CNS toxicity (e.g., focal tremors, myoclonus, or seizures) during treatment with meropenem, anticonvulsant therapy (e.g., phenytoin or benzodiazepines) should be initiated, and the dosage of meropenem should be reduced or the drug should be discontinued. 1

For serious anaphylactic reactions, emergency treatment should include epinephrine, oxygen, intravenous corticosteroids, and airway management. 1

For antibiotic-associated pseudomembranous colitis (AAPMC)¾

Some patients may develop AAPMC, caused by Clostridium difficile toxin, during or following administration of meropenem. Mild cases may respond to discontinuation of the drug alone. 1 Moderate to severe cases may require fluid, electrolyte, and protein replacement. 1 In cases not responding to the above measures or in more severe cases, treatment with an antibacterial medication effective against AAPMC may be necessary. 1

Parenteral Dosage Forms

MEROPENEM FOR INJECTION

Usual adult and adolescent dose

Antibacterial¾

Intravenous, 1 gram, administered by intravenous infusion over fifteen to thirty minutes or by rapid intravenous injection over three to five minutes, every eight hours. 1

Note: Adults with impaired renal function may require a reduction in dose as given below 1 :

Creatinine Clearance (mL/min)/(mL/sec)	Dose
³ 51/0.85	See Usual adult and adolescent dose
26-50/0.43-0.83	1 gram every 12 hours
10-25/0.17-0.42	500 mg every 12 hours
< 10/0.17	500 mg every 24 hours

[Neutropenia, febrile] *¾

Intravenous, 1 gram, administered by intravenous infusion over twenty to thirty minutes, every eight hours. Adults with impaired renal function may require a reduction in dose as given above 2, 3, 4, 5, 6, 7, 8, 9, 10.

Usual pediatric dose

Intra-abdominal infections¾

Children 3 months of age and older and weighing 50 kg of body weight and over: Intravenous, 1 gram, administered by intravenous infusion over fifteen to thirty minutes or by rapid intravenous injection over three to five minutes, every eight hours 1.

Children 3 months of age and older and weighing up to 50 kg of body weight: Intravenous, 20 mg per kg of body weight, administered by intravenous infusion over fifteen to thirty minutes or by rapid intravenous injection over three to five minutes, every eight hours 1.

Infants up to 3 months of age: Safety and efficacy have not been established.
Meningitis¾
Children 3 months of age and older and weighing 50 kg of body weight and over: Intravenous, 2 grams, administered by intravenous infusion over fifteen to thirty minutes or by rapid intravenous injection over three to five minutes, every eight hours 1.

Children 3 months of age and older and weighing up to 50 kg of body weight: Intravenous, 40 mg per kg of body weight, administered by intravenous infusion over fifteen to thirty minutes or by rapid intravenous injection over three to five minutes, every eight hours 1.

Infants up to 3 months of age: Safety and efficacy have not been established.
[Neutropenia, febrile] *¾
Children 3 months of age and older and weighing 50 kg of body weight and over: Intravenous, 1 gram, administered by intravenous infusion over twenty to thirty minutes, every eight hours 2, 3, 4, 5, 6, 7, 8, 9, 10.

Children 3 months of age and older and weighing up to 50 kg of body weight: Intravenous, 20 mg per kg of body weight, administered by intravenous infusion over twenty to thirty minutes, every eight hours 2, 3, 4, 5, 6, 7, 8, 9, 10.

Infants up to 3 months of age: Safety and efficacy have not been established 2, 3, 4, 5, 6, 7, 8, 9, 10.

Usual pediatric prescribing limits

2 grams every eight hours. 1

Strength(s) usually available

U.S.¾500 mg per 20 mL (Rx)[Merrem I.V. (sodium 45.1 mg)]

1 gram per 30 mL (Rx)[Merrem I.V. (sodium 90.2 mg)]

500 mg per 100 mL (Rx)[Merrem I.V. (sodium 45.1 mg)]

1 gram per 100 mL (Rx)[Merrem I.V. (sodium 90.2 mg)]

Packaging and storage:

Store at controlled temperature between 20 and 25 °C (68 and 77 °F). 1

Preparation of dosage form:

For rapid intravenous injection¾Add 10 mL of sterile water for injection to the 500-mg-in-20-mL vial and 20 mL of sterile water for injection to the 1-gram-in-30-mL vial, for a final concentration of approximately 50 mg per mL. Shake to dissolve and let stand until clear. 1

For intravenous infusion¾The infusion bottles (500 mg in 100 mL and 1 gram in 100 mL) may be reconstituted with 0.45% sodium chloride injection, 0.9% sodium chloride injection, or 5% dextrose injection. Alternatively, a 500-mg or 1-gram injection vial may be reconstituted, the resultant solution added to an intravenous container and further diluted with an appropriate infusion fluid. 1

Stability:

For rapid intravenous injection¾Reconstituted meropenem with sterile water for injection maintains its potency at controlled room temperature between 15 and 25 °C (59 and 77 °F) for up to 2 hours or for up to 12 hours under refrigeration at 4 °C (39 °F). 1

For intravenous infusion¾Reconstituted meropenem with 0.9% sodium chloride injection maintains its potency at controlled room temperature between 15 and 25 °C (59 and 77 °F) for up to 2 hours or for up to 18 hours under refrigeration at 4 °C (39 °F). Reconstituted meropenem with 5% dextrose injection maintains its potency at controlled room temperature between 15 and 25 °C (59 and 77 °F) for up to 1 hour or for up to 8 hours under refrigeration at 4 °C (39 °F). 1

Incompatibilities:

Compatibility of meropenem with other medications has not been established. Meropenem should not be mixed with or physically added to solutions containing other medications. 1

Note: Reconstituted meropenem should be visually inspected for particulate matter and discoloration prior to administration. 1