

MERREM[®] IV

meropenem for injection

For Intravenous Use Only

30132-06

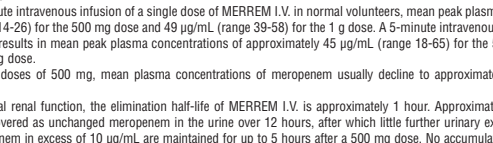
Rev 03/08



To reduce the development of drug-resistant bacteria and maintain the effectiveness of MERREM[®] I.V. (meropenem for injection) and other antibacterial drugs, MERREM I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

MERREM[®] I.V. (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]-1-(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is C₁₇H₂₅N₃O₅S·3H₂O with a molecular weight of 437.52. Its structural formula is:



MERREM I.V. 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.

When constituted as instructed (see **DOSE AND ADMINISTRATION, PREPARATION OF SOLUTION**), each 1 g MERREM I.V. vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500 mg MERREM I.V. vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).

CLINICAL PHARMACOLOGY

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

In subjects with normal renal function, the elimination half-life of MERREM I.V. is approximately 1 hour. Approximately 70% of the intravenously administered dose is recovered as unchanged meropenem in the urine over 12 hours, 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 MERREM I.V., the highest mean concentrations of meropenem were found in tissues and fluids at 1 hour (0.5 to 1.3 hours) after the start of infusion, except where indicated in the tissues and fluids listed in the table below.

Table 1. Meropenem Concentrations in Selected Tissues (Highest Concentrations Reported)

| Tissue | I.V. Dose (g) | Number of Samples | Mean [µg/mL or µg(g)]* | Range [µg/mL or µg(g)] |
|---------------------|---------------|-------------------|------------------------|------------------------|
| Endometrium | 0.5 | 7 | 4.2 | 1.7-10.2 |
| Myometrium | 0.5 | 15 | 3.8 | 0.4-8.1 |
| Ovary | 0.5 | 8 | 2.8 | 0.8-4.8 |
| Cervix | 0.5 | 2 | 7.0 | 5.4-8.5 |
| Fallopian tube | 0.5 | 9 | 1.7 | 0.3-3.4 |
| Skin | 0.5 | 22 | 3.3 | 0.5-12.6 |
| Interstitial fluid† | 0.5 | 9 | 5.5 | 3.2-8.6 |
| Skin | 1.0 | 10 | 5.3 | 1.3-16.7 |
| Interstitial fluid† | 1.0 | 5 | 26.3 | 20.9-37.4 |
| Colon | 1.0 | 2 | 2.6 | 2.5-2.7 |
| Bile | 1.0 | 7 | 14.6 (3 h) | 4.0-25.7 |
| Gall bladder | 1.0 | 1 | - | 3.9 |
| Peritoneal fluid | 1.0 | 9 | 30.2 | 7.4-54.6 |
| Lung | 1.0 | 2 | 4.8 (2 h) | 1.4-8.2 |
| Bronchial mucosa | 1.0 | 7 | 4.5 | 1.3-11.1 |
| Muscle | 1.0 | 2 | 6.1 (2 h) | 5.3-6.9 |
| Fascia | 1.0 | 9 | 8.8 | 1.5-20 |
| Heart valves | 1.0 | 7 | 9.7 | 6.4-12.1 |
| Myocardium | 1.0 | 10 | 15.5 | 5.2-25.5 |
| CSF (inflamed) | 20 mg/kg‡ | 8 | 1.1 (2 h) | 0.2-2.8 |
| CSF (uninflamed) | 40 mg/kg§ | 5 | 3.3 (3 h) | 0.9-6.5 |
| CSF (uninflamed) | 1.0 | 4 | 0.2 (2 h) | 0.1-0.3 |

* at 1 hour unless otherwise noted
 † obtained from blister fluid
 ‡ in pediatric patients of age 5 months to 8 years
 § in pediatric patients of age 1 years to 15 years

The pharmacokinetics of MERREM I.V. 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 MERREM I.V. 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. (See **DOSE AND ADMINISTRATION - Use in Adults with Renal Impairment**.) A pharmacokinetic study with MERREM I.V. in elderly patients with renal insufficiency has shown a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.

Meropenem I.V. is hemodialyzable. However, there is no information on the usefulness of hemodialysis to treat overdosage. (See **OVERDOSAGE**.) A pharmacokinetic study with MERREM I.V. in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Microbiology

Meropenem is a broad-spectrum carbapenem antibiotic. It is active against Gram-positive and Gram-negative bacteria. 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 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 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*.

Mechanism of Action

Meropenem exerts its action by penetrating bacterial cells readily and interfering with the synthesis of vital cell wall components, which leads to cell death.

Resistance

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 penicillin binding proteins (PBP); 3) increased expression of efflux pump components; and 4) production of antibiotic-destroying enzymes (carbapenemases, metallo-β-lactamases).

Cross-Resistance

Cross-resistance is sometimes observed with isolates resistant to other carbapenems.

Lists of Microorganisms

Meropenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms

- Enterococcus faecalis* (excluding vancomycin-resistant isolates)
- Streptococcus aureus* (β-lactamase and non-β-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* (β-lactamase and non-β-lactamase-producing)
- Klebsiella pneumoniae*
- Neisseria meningitidis*
- Pseudomonas aeruginosa*
- Proteus mirabilis*

Anaerobic microorganisms

- Bacteroides fragilis*
- Bacteroides thetaiotaomicron*
- 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 breakpoint 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* (β-lactamase and non-β-lactamase-producing, methicillin-susceptible isolates only).

Aerobic and facultative Gram-negative microorganisms

- Moraxella catarrhalis* (β-lactamase and non-β-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*

SUSCEPTIBILITY TEST METHODS

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method^{1,3} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{2,3} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10-µg of meropenem to test the susceptibility of microorganisms to meropenem. The disk diffusion interpretive criteria are provided in Table 2.

Streptococcus pneumoniae isolates should be tested using 1-µg/oxacillin disk. Isolates with oxacillin zone sizes of ≥ 20 mm are susceptible (MIC ≤ 0.06 µg/mL) to penicillin and can be considered susceptible to meropenem for approved indications, and meropenem need not be tested. A meropenem MIC should be determined on isolates of *S. pneumoniae* with oxacillin zone sizes of ≤ 19 mm. The disk test does not distinguish penicillin intermediate isolates (i.e., MICs = 0.12-1.0 µg/mL) from isolates that are penicillin resistant (i.e., MICs ≥ 2 µg/mL). Viridans group streptococci should be tested for meropenem susceptibility using an MIC method. Reliable disk diffusion tests for meropenem do not yet exist for testing streptococci.

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to meropenem as MICs can be determined by standardized test methods.⁴ The MIC values obtained should be interpreted according to the criteria provided in Table 2.

Table 2. Susceptibility Interpretive Criteria for Meropenem

| Pathogen | Susceptibility Test Result Interpretive Criteria | | |
|---|--|----|---------------------------------------|
| | Minimum Inhibitory Concentrations (µg/mL) | R* | Disk Diffusion (zone diameters in mm) |
| Enterobacteriaceae, <i>Acinetobacter</i> spp. and <i>Pseudomonas aeruginosa</i> | ≤ 4 | 8 | ≥ 16 |
| <i>Haemophilus influenzae</i> | ≤ 0.5 | 8 | ≥ 20 |
| <i>Staphylococcus aureus</i> † | ≤ 4 | -- | ≥ 16 |
| <i>Streptococcus pneumoniae</i> † | ≤ 0.12 | -- | -- |
| <i>Streptococcus agalactiae</i> † and <i>Streptococcus pyogenes</i> † | ≤ 0.5 | -- | -- |
| Anaerobes ‡ | ≤ 4 | 8 | ≥ 16 |

* The current absence of data on resistant isolates precludes defining any category other than "Susceptible." If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

† No disk diffusion (zone diameter) interpretive criteria have been established for testing *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*. Use Dilutions (MICs) techniques results.

‡ MIC values using either Brucella blood or Wilkins Chalgren agar (former reference medium) are considered equivalent, based upon published *in vitro* literature and a multicenter collaborative trial for these antimicrobial agents.

No interpretive criteria have been established for testing enterococci and *Neisseria meningitidis*. A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of *Intermediate* indicates that this result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category includes possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard meropenem powder should provide the following range of values noted in Table 3.

Table 3. Acceptable Quality Control Ranges for Meropenem

| QC Strain | Minimum Inhibitory Concentrations (MICs = µg/mL) | Disk Diffusion (Zone diameters in mm) |
|--|--|---------------------------------------|
| <i>Staphylococcus aureus</i> ATCC 29213 | 0.03-0.12 | |
| <i>Staphylococcus aureus</i> ATCC 25923 | | 29-37 |
| <i>Streptococcus pneumoniae</i> ATCC 49619 | 0.06-0.25 | 28-35 |
| <i>Enterococcus faecalis</i> ATCC 29212 | 2.0-8.0 | |
| <i>Escherichia coli</i> ATCC 25922 | 0.008-0.06 | 28-34 |
| <i>Haemophilus influenzae</i> ATCC 49766 | 0.03-0.12 | |
| <i>Haemophilus influenzae</i> ATCC 49247 | | 20-28 |
| <i>Pseudomonas aeruginosa</i> ATCC 27853 | 0.25-1.0 | 27-33 |
| <i>Bacteroides fragilis</i> * ATCC 25285 | 0.03-0.25 | |
| <i>Bacteroides thetaiotaomicron</i> * ATCC 29711 | 0.125-0.5 | |
| <i>Eubacterium lentum</i> * ATCC 43055 | 0.125-1 | |

* Using the Reference Agar Dilution procedure.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of MERREM I.V. and other antibacterial drugs, MERREM I.V. should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

MERREM I.V. 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* (β-lactamase and non-β-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 ≥ 3 months only)

Bacterial meningitis caused by *Streptococcus pneumoniae*†, *Haemophilus influenzae* (β-lactamase and non-β-lactamase-producing isolates), and *Neisseria meningitidis*.

† The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin nonsusceptible isolates of *Streptococcus pneumoniae* has not been established.

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

For information regarding use in pediatric patients (3 months of age and older) see **PRECAUTIONS-Pediatrics**, **ADVERSE REACTIONS**, and **DOSE AND ADMINISTRATION** sections.

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 MERREM I.V.

MERREM I.V. 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

MERREM I.V. 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 β-lactams.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING MERREM I.V. WITH β-LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF REACTIONS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHOSE EXPERIENCE SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER β-LACTAM. BEFORE INITIATING THERAPY WITH MERREM I.V. CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER β-LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO MERREM 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.

Seizure Potential:

Seizures and other CNS adverse experiences have been reported during treatment with MERREM I.V. (See **PRECAUTIONS AND ADVERSE REACTIONS**.) Carbapenems, including meropenem, may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs. (See **Drug Interactions**.)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including MERREM I.V., and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hyper-toxin producing strains of *C. difficile* cause increased morbidity and mortality, and as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General: Prescribing MERREM I.V. 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.

Seizures and other adverse CNS experiences have been reported during treatment with MERREM I.V. 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.

During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had CNS-existing contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Dosage adjustment is recommended in patients with advanced age and/or reduced renal function. (See **DOSE AND ADMINISTRATION - Use in Adults with Renal Impairment**.)

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Known factors that 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 MERREM 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 **DOSE AND ADMINISTRATION - Use in Adults with Renal Impairment**.)

There is inadequate information regarding the use of MERREM I.V. in patients on hemodialysis.

As with other broad-spectrum antibiotics, prolonged use of meropenem may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient is essential. If superinfections does occur during therapy, appropriate measures should be taken.

Laboratory Tests: While MERREM I.V. possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Drug Interactions: Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. This led to statistically significant increases in the elimination half-life (38%) and in the extent of systemic exposure (56%). Therefore, the coadministration of a clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics and may result in loss of seizure control. Although the mechanism of this interaction is not fully understood, data from *in vitro* and animal studies suggest that carbapenem antibiotics may inhibit valproic acid glucuronide hydrolysis. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antib

MERREM I.V.® (meropenem for injection)

events. Many patients in these trials were severely ill and had multiple background diseases, physiological impairments and were receiving multiple other drug therapies. In the seriously ill patient population, it was not possible to determine the relationship between observed adverse events and therapy with MERREM I.V.

The following adverse reaction frequencies were derived from the clinical trials in the 2904 patients treated with MERREM I.V.

Local Adverse Reactions

Local adverse reactions that were reported irrespective of the relationship to therapy with MERREM I.V. were as follows:

| | |
|------------------------------------|------|
| Inflammation at the injection site | 2.4% |
| Injection site reaction | 0.9% |
| Phlebitis/thrombophlebitis | 0.8% |
| Pain at the injection site | 0.4% |
| Edema at the injection site | 0.2% |

Systemic Adverse Reactions

Systemic adverse clinical reactions that were reported irrespective of the relationship to MERREM I.V. occurring in greater than 1.0% of the patients were diarrhea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritus (1.2%).

Additional adverse systemic clinical reactions that were reported irrespective of relationship to therapy with MERREM I.V. and occurring in less than or equal to 1.0%, but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency:

Bleeding events were seen as follows: gastrointestinal hemorrhage (0.5%), melena (0.3%), epistaxis (0.2%), hemoperitoneum (0.2%), summing to 1.2%.

Body as a Whole: pain, abdominal pain, chest pain, fever, back pain, abdominal enlargement, chills, pelvic pain

Cardiovascular: heart failure, heart arrest, tachycardia, hypertension, myocardial infarction, pulmonary embolism, bradycardia, hypotension, syncope

Digestive System: oral moniliasis, anorexia, cholestatic jaundice/jaundice, flatulence, ileus, hepatic failure, dyspepsia, intestinal obstruction

Hemic/Lymphatic: anemia, hypochromic anemia, hypervolemia

Metabolic/Nutritional: peripheral edema, hypoxia

Nervous System: insomnia, agitation/delirium, confusion, dizziness, seizure (see **PRECAUTIONS**), nervousness, paresthesia, hallucinations, somnolence, anxiety, depression, asthenia

Respiratory: respiratory disorder, dyspnea, pleural effusion, asthma, cough increased, lung edema

Skin and Appendages: urticaria, sweating, skin ulcer

Urogenital System: dysuria, kidney failure, vaginal moniliasis, urinary incontinence

Adverse Laboratory Changes

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

Hepatic: increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH and bilirubin

Hematologic: increased platelets, increased eosinophils, decreased platelets, decreased hemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time and shortened partial thromboplastin time, leukocytosis, hypokalemia

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 MERREM I.V., increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 mL/min).

Urinanalysis: presence of red blood cells

Complicated Skin and Skin Structure Infection

In a study of complicated skin and skin structure infection, the type of clinical adverse reactions were similar to those listed above. The patients with the most common adverse events with an incidence of >5% were: headache (7.8%), constipation (7.0%), diarrhea (7.0%), shock (1.2%), and pain (5.1%). Adverse events with an incidence of >1%, and not listed above, include: pharyngitis, accidental injury, gastrointestinal disorder, hypoglycemia, peripheral vascular disorder, and pneumonia.

Pediatric Patients

Clinical Adverse Reactions

MERREM I.V. was studied in 515 pediatric patients (≥ 3 months to < 13 years of age) with serious bacterial infections (excluding meningitis). See next section at dosages of 10 to 20 mg/kg every 8 hours. 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 MERREM I.V. and their rates of occurrence as follows:

| | |
|---------------------|------|
| Diarrhea | 3.5% |
| Rash | 1.6% |
| Nausea and Vomiting | 0.8% |

MERREM I.V. was studied in 321 pediatric patients (≥ 3 months to < 17 years of age) with meningitis at a dosage of 40 mg/kg every 8 hours. 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 MERREM I.V. and their rates of occurrence as follows:

| | |
|--------------------------------------|------|
| Diarrhea | 4.7% |
| Rash (mostly diaper area moniliasis) | 3.1% |
| Oral Moniliasis | 1.9% |
| 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 MERREM 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.

Adverse Laboratory Changes:

Laboratory abnormalities seen in the pediatric-aged patients in both the pediatric and the meningitis studies are similar to those reported in adult patients. There is no experience in pediatric patients with renal impairment.

Post-marketing Experience:

Worldwide post-marketing adverse events not otherwise listed in the product label and reported as possibly, probably, or definitely drug related are listed within each body system in order of decreasing severity. Hematologic - agranulocytosis, neutropenia, and leukopenia; a positive direct or indirect Coombs test, and hemolytic anemia. Skin - toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiforme.

OVERDOSAGE

In mice and rats, large intravenous doses of meropenem (2200-4000 mg/kg) have been associated with ataxia, dyspnea, convulsions, and mortalities. Intentional overdosing of MERREM I.V. is unlikely, although accidental overdosing might occur if large doses are given to patients with reduced renal function. 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.

Limited post-marketing experience indicates that if adverse events occur following overdosage, they are consistent with the adverse event profile described in the Adverse Reactions section and are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered. In individuals with normal renal function, rapid renal elimination takes place. Meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

CLINICAL STUDIES

Skin and Skin Structure

Adult patients with complicated skin and skin structure infections including complicated cellulitis, complex abscesses, perirectal abscesses, and skin infections requiring intravenous antimicrobials, hospitalization, and surgical intervention were enrolled in a randomized, multi-center, international, double-blind trial. The study evaluated meropenem at doses of 500 mg administered intravenously every 8 hours and imipenem-cilastatin at doses of 500 mg administered intravenously every 8 hours. The study compared the clinical response between treatment groups in the clinically evaluable population at the follow-up visit (test-of-cure). The trial was conducted in the United States, South Africa, Canada, and Brazil. At enrollment, approximately 37% of the patients had underlying diabetes, 12% had underlying peripheral vascular disease and 67% had a surgical intervention. The study included 510 patients randomized to meropenem and 527 patients randomized to imipenem-cilastatin. Two hundred and sixty-one (261) patients randomized to meropenem and 287 patients randomized to imipenem-cilastatin were clinically evaluable. The success rates in the clinically evaluable patients at the follow-up visit were 86% (225/261) in the meropenem arm and 83% (238/287) in imipenem-cilastatin arm.

The following table provides the results for the overall as well as subgroup comparisons in clinically evaluable population.

| Population | Success Rate* | |
|----------------------|-------------------------|---------------------------------|
| | MERREM I.V. n/N† (%) | Imipenem-cilastatin n/N† (%) |
| Total | 225/261 (86) | 238/287 (83) |
| Diabetes mellitus | 83/97 (86) | 76/105 (72) |
| No diabetes mellitus | 142/164 (87) | 162/182 (89) |
| <65 years of age | 190/218 (87) | 205/241 (85) |
| ≥65 years of age | 35/43 (81) | 33/46 (72) |
| Men | 130/148 (88) | 137/172 (80) |
| Women | 95/113 (84) | 101/115 (88) |

* Percent of satisfactory clinical response at follow-up evaluation.

† n=number of patients with satisfactory response.

‡ n=number of patients in the clinically evaluable population or respective subgroup within treatment groups.

The following clinical efficacy rates were obtained, per organism. The values represent the number of patients clinically cured/number of clinically evaluable patients at the post-treatment follow-up visit, with the percent cure in parentheses (Fully Evaluable analysis set).

| MICROORGANISMS* | MERREM I.V. n/N† (%)§ | Imipenem-cilastatin n/N† (%)§ |
|--|--------------------------|----------------------------------|
| Gram-positive aerobes | | |
| <i>Staphylococcus aureus</i> , | 82/88 (93) | 84/100 (84) |
| <i>Staphylococcus epidermidis</i> | | |
| <i>Streptococcus pyogenes</i> (Group A) | 26/29 (90) | 28/32 (88) |
| <i>Streptococcus agalactiae</i> (Group B) | 12/17 (71) | 16/19 (84) |
| <i>Enterococcus faecalis</i> | 9/12 (75) | 14/20 (70) |
| <i>Streptococcus viridans</i> Group, nos | 11/12 (92) | 5/6 (83) |
| Gram-negative aerobes | | |
| <i>Escherichia coli</i> | 12/15 (80) | 15/21 (71) |
| <i>Pseudomonas aeruginosa</i> | 11/15 (73) | 13/15 (87) |
| <i>Proteus mirabilis</i> | 11/13 (85) | 6/7 (86) |
| Anaerobes | | |
| <i>Bacteroides fragilis</i> | 10/11 (91) | 9/10 (90) |
| <i>Peptostreptococcus</i> species | 10/13 (77) | 14/16 (88) |

* Patients may have more than one pretreatment pathogen.

† n=number of patients with satisfactory response.

‡ n=number of patients in the clinically evaluable population or subgroup within treatment groups.

§ %= Percent of satisfactory clinical response at follow-up evaluation.

The proportion of patients who discontinued study treatment due to an adverse event was similar for both treatment groups (meropenem, 2.5% and imipenem-cilastatin, 2.7%).

Intra-abdominal:

One controlled clinical study of complicated intra-abdominal infection was performed in the United States where meropenem was compared with clindamycin/tobramycin. Three controlled clinical studies of complicated intra-abdominal infections were performed in Europe; meropenem was compared with imipenem (two trials) and cefotaxime/metronidazole (one trial). Using strict evaluability criteria and microbiologic eradication and clinical cures at follow-up which occurred 7 or more days after completion of therapy, the following presumptive microbiologic eradication/clinical cure rates and statistical findings were obtained:

| Treatment Arm | No. evaluable/ N, enrolled (%) | Microbiologic Eradication Rate | Clinical Cure Rate | Outcome |
|------------------------------|-----------------------------------|-----------------------------------|-----------------------|---|
| meropenem | 146/516 (28%) | 98/146 (67%) | 101/146 (69%) | |
| imipenem | 65/220 (30%) | 40/65 (62%) | 42/65 (65%) | Meropenem equivalent to control |
| cefotaxime/ metronidazole | 26/85 (30%) | 22/26 (85%) | 22/26 (85%) | Meropenem not equivalent to control |
| clindamycin/ tobramycin | 50/212 (24%) | 38/50 (76%) | 38/50 (76%) | Meropenem equivalent to control |

The finding that meropenem was not statistically equivalent to cefotaxime/metronidazole may have been due to uneven assignment of more seriously ill patients to the meropenem arm. Currently there is no additional information available to further interpret this observation.

Bacterial Meningitis:

Four hundred forty-six patients (397 pediatric patients ≥ 3 months to < 17 years of age) were enrolled in 4 separate clinical trials and randomized to treatment with meropenem (n=225) at a dose of 40 mg/kg q 8 hours or a comparator drug, i.e., cefotaxime (n=187) or ceftriaxone (n=34), at the approved dosing regimens. A comparable number of patients were found to be clinically evaluable (ranging from 61-68%) and with a similar distribution of pathogens isolated on initial CSF culture.

Patients were defined as clinically not cured if any one of the following three criteria were met:

- At the 5-7 week post-completion of therapy visit, the patient had any one of the following: moderate to severe motor, behavior or development deficits, hearing loss of >60 decibels in one or both ears, or blindness.
- During therapy the patient's clinical status necessitated the addition of other antibiotics.
- Either during or post-therapy, the patient developed a large subdural effusion needing surgical drainage, or a cerebral abscess, or a bacteriologic relapse.

Using the definition, the following efficacy rates were obtained, per organism. The values represent the number of patients clinically cured/number of clinically evaluable patients, with the percent cure in parentheses.

| MICROORGANISM | MERREM I.V. n/N† (%) | COMPARATOR n/N† (%) |
|-----------------------------|-------------------------|------------------------|
| <i>S. pneumoniae</i> | 17/24 (71) | 19/30 (63) |
| <i>H. influenzae</i> (+)* | 8/10 (80) | 6/6 (100) |
| <i>H. influenzae</i> (-NT)† | 44/59 (75) | 44/60 (73) |
| <i>M. meningitidis</i> | 30/35 (86) | 35/39 (90) |
| TOTAL (including others) | 102/131 (78) | 108/140 (77) |

* (+) β-lactamase-producing

† (-NT) non-β-lactamase-producing or not tested

Sequelae were the most common reason patients were assessed as clinically not cured.

Five patients were found to be bacteriologically not cured, 3 in the comparator group (1 relapse and 2 patients with cerebral abscesses) and 2 in the meropenem group (1 relapse and 1 with continued growth of *Pseudomonas aeruginosa*).

The adverse events seen were comparable between the two treatment groups both in type and frequency. The meropenem group did have a statistically higher number of patients with transient elevation of liver enzymes. (See **ADVERSE REACTIONS**.) Rates of seizure activity during therapy were comparable between patients with no CNS abnormalities who received meropenem and those who received comparator agents. In the MERREM 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.

With respect to hearing loss, 263 of the 271 evaluable patients had at least one hearing test performed post-therapy. The following table shows the degree of hearing loss between the meropenem-treated patients and the comparator-treated patients.

| Degree of Hearing Loss (in one or both ears) | Meropenem n = 128 | Comparator n = 135 |
|---|----------------------|-----------------------|
| No loss | 61% | 56% |
| 20-40 decibels | 20% | 24% |
| >40-60 decibels | 8% | 7% |
| >60 decibels | 9% | 10% |

ADULTS AND ADMINISTRATION

Adults: The recommended dose of MERREM I.V. is 500 mg given every 8 hours for skin and skin structure infections and 1 g given every 8 hours for intra-abdominal infections. MERREM I.V. 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.)

| Creatinine Clearance (mL/min) | Recommended MERREM I.V. Dosage Schedule for Adults With Impaired Renal Function | |
|----------------------------------|--|-----------------|
| | Dose (dependent on type of infection) | Dosing Interval |
| ≥51 | Recommended dose (500 mg cSSSI and 1 g 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)⁵ may be used to estimate creatinine clearance.

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

$$\text{Females: } 0.85 \times \text{above value}$$

There is inadequate information regarding the use of MERREM I.V. 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 MERREM I.V. 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 MERREM I.V. 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. MERREM I.V. 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.

| Type of Infection | Recommended MERREM I.V. Dosage Schedule for Pediatrics With Normal Renal Function | | |
|-------------------------------------|---|----------------------|-----------------|
| | Dose/(mg/kg) | Up to a Maximum Dose | Dosing Interval |
| Complicated skin and skin structure | 10 | 500 mg | Every 8 hours |
| Intra-abdominal | 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 1 g) with sterile Water for Injection. (See table below.) Shake to dissolve and let stand until clear.

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

For Infusion

For infusion (500 mg and 1 g) 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**.)

WARNING: Do not use flexible container in series connections.

COMPATIBILITY AND STABILITY

Compatibility of MERREM I.V. with other drugs has not been established. MERREM I.V. should not be mixed with or physically added to solutions containing other drugs.

Freshly prepared solutions of MERREM I.V. should be used whenever possible. However, constituted solutions of MERREM I.V. 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 MERREM I.V. should not be frozen.

Intravenous Bolus Administration

MERREM I.V. injection vials constituted with sterile Water for Injection for bolus administration (up to 50 mg/mL of MERREM I.V.) 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: MERREM I.V. infusion vials constituted with Sodium Chloride Injection 0.9% (MERREM I.V. 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 MERREM I.V. constituted with Dextrose Injection 5% (MERREM I.V. 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 (MERREM I.V. 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 |
| Potassium Chloride in Dextrose Injection 0.15%/5.0% | 1 | 4 |
| Sodium Bicarbonate in Dextrose Injection 0.02%/5.0% | 1 | 6 |
| Dextrose Injection 5.0% in Normosol®-M† | 1 | 6 |
| 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 Baxter Minibag Plus: Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus bags with Sodium Chloride Injection 0.9% may be stored for up to 4 hours at controlled room temperatures 15-25°C (59-77°F) or for up to 24 hours at 4°C (39°F). Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus bags with Dextrose Injection 5.0% may be stored up to 1 hour at controlled room temperatures 15-25°C (59-77°F) or for up to 6 hours at 4°C (39°F).

Stability in Plastic Syringes, Tubing and Intravenous Infusion Sets: Solutions of MERREM I.V. (MERREM I.V. concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride Injection 0.9% (for up to 2 hours) or in 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 MERREM I.V. (MERREM I.V. 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% (for up to 6 hours) are stable at 4°C (39°F) in plastic syringes.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

MERREM I.V. is supplied in 20 mL and 30 mL injection vials containing sufficient meropenem to deliver 500 mg or 1 g for intravenous administration, respectively. The dry powder should be stored at controlled room temperature 20-25°C (68-77°F) [see USP].