

# Meropenem For Injection, USP (I.V.)

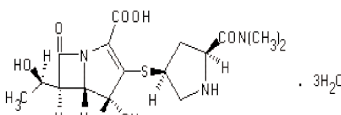
Rx Only

FOR INTRAVENOUS USE ONLY

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Meropenem for Injection I.V. and other antibacterial drugs, Meropenem for Injection I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## DESCRIPTION

Meropenem for Injection I.V. 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 molecular formula is  $C_{17}H_{25}N_3O_5S \cdot 3H_2O$  with a molecular weight of 437.52. Its structural formula is:



Meropenem for Injection 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 500 mg Meropenem for Injection I.V. vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq). Each 1 g Meropenem for Injection I.V. vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq).

## CLINICAL PHARMACOLOGY

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

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

In subjects with normal renal function, the elimination half-life of Meropenem for Injection 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 mcg/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 29%.

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

The pharmacokinetics of Meropenem for Injection 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 Meropenem for Injection 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 Meropenem for Injection 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 Meropenem for Injection 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 log<sub>10</sub> reduction in cell counts within 12 to 24 hours) are typically 1 to 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  $\beta$ -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- $\beta$ -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)

*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 MIC<sub>90</sub> values of 1 or 2 mcg/mL, which is above the 0.12 mcg/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 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 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 distans*

*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<sup>1,3</sup> (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<sup>2,3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 10 mcg 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 mcg/mL oxacillin disk. Isolates with oxacillin zone sizes of  $\geq 20$  mm are susceptible (MIC  $\leq 0.06$  mcg/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  $\leq 19$  mm. The disk test does not distinguish penicillin intermediate isolates (i.e., MICs = 0.12 to 1 mcg/mL) from isolates that are penicillin resistant (i.e., MICs  $\geq 2$  mcg/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<sup>4</sup>. 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 (mcg/mL)		Disk Diffusion (zone diameters in mm)			
	S	R*	S	I	R*	
Enterobacteriaceae, Acinetobacter spp. and <i>Pseudomonas aeruginosa</i>	$\leq 4$	8	$\geq 16$	$\geq 16$	14 to 15 $\leq 13$	
<i>Haemophilus influenzae</i>	$\leq 0.5$	--	--	$\geq 20$	--	
<i>Staphylococcus aureus</i> <sup>†</sup>	$\leq 4$	8	$\geq 16$	$\geq 16$	14 to 15 $\leq 13$	
<i>Streptococcus pneumoniae</i> <sup>‡</sup>	$\leq 0.12$	--	--	--	--	
<i>Streptococcus agalactiae</i> <sup>‡</sup> and <i>Streptococcus pyogenes</i> <sup>‡</sup>	$\leq 0.5$	--	--	--	--	
Anaerobes <sup>§</sup>	$\leq 4$	8	$\geq 16$	--	--	

\* 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.

† Staphylococci that are resistant to methicillin/oxacillin must be considered resistant to meropenem.

‡ No Disk diffusion (zone diameter) interpretive criteria have been established for testing *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and *Streptococcus pyogenes*. Use Dilution (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 the 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 implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dose 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 = mcg/mL)	Disk Diffusion (Zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 29213	0.03 to 0.12	
<i>Staphylococcus aureus</i> ATCC 25923		29 to 37
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06 to 0.25	28 to 35
<i>Enterococcus faecalis</i> ATCC 29212	2 to 8	
<i>Escherichia coli</i> ATCC 25922	0.008 to 0.06	28 to 34
<i>Haemophilus influenzae</i> ATCC 49766	0.03 to 0.12	
<i>Haemophilus influenzae</i> ATCC 49247		20 to 28
<i>Pseudomonas aeruginosa</i> ATCC 27853	0.25 to 1	27 to 33
<i>Bacteroides fragilis</i> * ATCC 25285	0.03 to 0.25	
<i>Bacteroides thetaiotaomicron</i> * ATCC 29741	0.125 to 0.5	
<i>Eubacterium lentum</i> * ATCC 43055	0.125 to 1	

\* Using the Reference Agar Dilution procedure.

## INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Meropenem for Injection I.V. and other antibacterial drugs, Meropenem for Injection 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.

Meropenem for Injection 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* ( $\beta$ -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*<sup>†</sup>, *Haemophilus influenzae* ( $\beta$ -lactamase and non- $\beta$ -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.

Meropenem for Injection 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 DOSAGE 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 Meropenem for Injection I.V.

Meropenem for Injection 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

Meropenem for Injection 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  $\beta$ -lactams.

## WARNINGS

**SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS** HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH  $\beta$ -LACTAMS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGEN

A pharmacokinetic study with Meropenem for Injection 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. (See **DOSE AND ADMINISTRATION; Use in Adults with Renal Impairment**).

Meropenem for Injection I.V. is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

**Information For Patients:** Patients should be counseled that antibacterial drugs including Meropenem for Injection I.V. should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When Meropenem for Injection I.V. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Meropenem for Injection I.V. or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

#### ADVERSE REACTIONS

**Adult Patients:** During clinical investigations, 2904 immunocompetent adult patients were treated for non-CNS infections with Meropenem for Injection I.V. (500 mg or 1000 mg q 8 hours). Deaths in 5 patients were assessed as possibly related to meropenem; 36 (1.2%) patients had meropenem discontinued because of adverse 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 Meropenem for Injection I.V.

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

**Local Adverse Reactions:** Local adverse reactions that were reported irrespective of the relationship to therapy with Meropenem for Injection 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 Meropenem for Injection I.V. occurring in greater than 1% 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 Meropenem for Injection I.V. and occurring in less than or equal to 1% 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%), hemopterionemum (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 embolus, 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 Meropenem for Injection 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 Meropenem for Injection I.V. increased in patients with moderately severe renal impairment (creatinine clearance >10 to 26 mL/min).

**Urinalysis:** 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%), nausea (7.8%), constipation (7%), diarrhea (7%), anemia (5.5%), 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

Meropenem for Injection 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 Meropenem for Injection I.V. and their rates of occurrence as follows:

Diarrhea	3.5%
Rash	1.6%
Nausea and Vomiting	0.8%

Meropenem for Injection 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 Meropenem for Injection 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%

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 for Injection 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.

To report SUSPECTED ADVERSE EVENTS, contact FDA at 1-800-FDA-1088 or [www.fda.gov](http://www.fda.gov).

#### OVERDOSAGE

In mice and rats, large intravenous doses of meropenem (2200 to 4000 mg/kg) have been associated with ataxia, dyspnea, convulsions, and mortalities.

Intentional overdosing of Meropenem for Injection 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	Meropenem for Injection I.V. n <sup>1</sup> /N <sup>†</sup> (%)	Imipenem-cilastatin n <sup>1</sup> /N <sup>†</sup> (%)
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.

<sup>1</sup>n=number of patients with satisfactory response.

<sup>†</sup>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*	Meropenem for Injection I.V. n <sup>1</sup> /N <sup>†</sup> (%)§	Imipenem-cilastatin n <sup>1</sup> /N <sup>†</sup> (%)§
<b>Gram-positive aerobes</b>		
<i>Staphylococcus aureus</i> , methicillin susceptible	82/88 (93)	84/100 (84)
<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)
<b>Gram-negative aerobes</b>		
<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)
<b>Anaerobes</b>		
<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.

<sup>1</sup>n=number of patients with satisfactory response.

<sup>†</sup>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/No. enrolled (%)	Microbiologic Eradication Rate	Clinical Cure Rate	Outcome
meropenem	146/516 (28%)	98/146 (67%)	101/146 (69%)	Meropenem equivalent to control
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 to 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 to 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.

MICROORGANISMS	Meropenem for Injection I.V.	COMPARATOR
<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) <sup>†</sup>	44/59 (75)	44/60 (73)
<i>N. meningitidis</i>	30/35 (86)	35/39 (90)
Total (including others)	102/131 (78)	108/140 (77)

\* (+) β-lactamase-producing

<sup>†</sup> (-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 Meropenem for Injection 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 to 40 decibels	20%	24%
>40 to 60 decibels	8%	7%
>60 decibels	9%	10%

#### DOSE AND ADMINISTRATION

**Adults:** The recommended dose of Meropenem for Injection 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. Meropenem for Injection 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 to 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 Meropenem for Injection I.V. 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 to 50	Recommended dose	Every 12 hours
10 to 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 Meropenem for Injection 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 Meropenem for Injection 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 Meropenem for Injection 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. Meropenem for Injection 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 to 5 minutes.

#### Recommended Meropenem for Injection I.V. 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	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 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**.)

**WARNING: Do not use flexible container in series connections.**

#### COMPATIBILITY AND STABILITY

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

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

##### Intravenous Bolus Administration

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

##### Intravenous Infusion Administration

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

**Stability in Plastic I.V. Bags:** Solutions prepared for infusion (Meropenem 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 to 25°C (59 to 77°F)	Number of Hours Stable at 4°C (39°F)
Sodium Chloride Injection 0.9%	4	24
Dextrose Injection 5%	1	4
Dextrose Injection 10%	1	2
Dextrose and Sodium Chloride Injection 5%/0.9%	1	2
Dextrose and Sodium Chloride Injection 5%/0.2%	1	4
Potassium Chloride in Dextrose Injection 0.15%/5%	1	6
Sodium Bicarbonate in Dextrose Injection 0.02%/5%	1	6
Dextrose Injection 5% in Normosol <sup>®</sup> -M <sup>†</sup>	1	8
Dextrose Injection 5% 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%	1	4

**Stability in Baxter Minibag Plus<sup>®</sup> (manufactured by Baxter, Inc.):** Solutions of Meropenem (Meropenem concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus<sup>®</sup> (manufactured by Baxter, Inc.) bags with Sodium Chloride Injection 0.9% may be stored for up to 4 hours at controlled room temperatures 15 to 25°C (59 to 77°F) or for up to 24 hours at 4°C (39°F). Solutions of Meropenem (Meropenem concentrations ranging from 2.5 to 20 mg/mL) in Baxter Minibag Plus<sup>®</sup> (manufactured by Baxter