MERREM® IV
meropenem for injection

For Intravenous Use Only

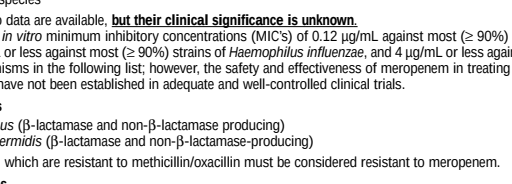
64213-01 Rev 01/04

F.P.O.

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]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate. Its empirical formula is $C_{17}H_{25}N_3O_5S \cdot 3H_2O$ 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 **DOSAGE 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).

MERREM I.V. in the ADD-Vantage† vial is intended for intravenous use only after dilution with the appropriate volume of diluent solution in the Abbott ADD-Vantage® diluent container. (See **DOSAGE AND ADMINISTRATION; PREPARATION OF SOLUTION.**) MERREM I.V. in the ADD-Vantage vial is available in two strengths. Each 1 g ADD-Vantage vial of MERREM I.V. will deliver 90.2 mg of sodium as sodium carbonate (3.92 mEq), and each 500 mg ADD-Vantage vial will deliver 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, after which little further urinary excretion is detectable. Urinary concentrations of meropenem in excess of 10 µg/mL are maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed with regimens using 500 mg administered every 8 hours or 1 g administered every 6 hours in volunteers with normal renal function.

Plasma protein binding of meropenem is approximately 2%.

There is one metabolite which 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 1.5 hours) after the start of infusion, except where indicated in the tissues and fluids listed in the table below.

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
Skin	1.0	10	5.3	1.3-16.7
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
Interstitial fluid	1.0	5	26.3	20.9-37.4
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
	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

* in pediatric patients of age 5 months to 8 years
** in pediatric patients of age 1 month to 15 years
*** at 1 hour unless otherwise noted

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 **DOSAGE 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

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 $\log_{10}$ 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, with the exception of metallo-β-lactamases. Meropenem should not be used to treat methicillin-resistant staphylococci. Cross resistance is sometimes observed with strains resistant to other carbapenems.

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

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

Gram-Positive Aerobes

Streptococcus pneumoniae (excluding penicillin-resistant strains)
Viridans group streptococci

NOTE: Penicillin-resistant strains had meropenem MIC_{90} values of 1 or 2 µg/mL, which is above the 0.12 µg/mL susceptible breakpoint for this species.

Gram-Negative Aerobes

Escherichia coli
Haemophilus influenzae (β-lactamase and non-β-lactamase-producing)
Klebsiella pneumoniae
Neisseria meningitidis
Pseudomonas aeruginosa

Anaerobes

Bacteroides fragilis
Bacteroides thetaiotaomicron
Peptostreptococcus species

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

Meropenem exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.12 µg/mL against most (≥ 90%) strains of *Streptococcus pneumoniae*, 0.5 µg/mL or less against most (≥ 90%) strains of *Haemophilus influenzae*, and 4 µg/mL or less against most (≥ 90%) strains of the other microorganisms in the following list; however, the safety and effectiveness of meropenem in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-Positive Aerobes

Staphylococcus aureus (β-lactamase and non-β-lactamase producing)
Staphylococcus epidermidis (β-lactamase and non-β-lactamase-producing)

NOTE: Staphylococci which are resistant to methicillin/oxacillin must be considered resistant to meropenem.

Gram-Negative Aerobes

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

Anaerobes

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 Tests

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of meropenem powder. The MIC values should be interpreted according to the following criteria for indicated aerobic organisms other than *Haemophilus* species and streptococci:

MIC (µg/mL)	Interpretation
≤ 4	(S) Susceptible
8	(I) Intermediate
≥ 16	(R) Resistant

Haemophilus Test Media (HTM) and the following interpretive criteria should be used when testing *Haemophilus* species:

MIC (µg/mL)	Interpretation
≤ 0.5	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

The following criteria should be used when testing streptococci including *Streptococcus pneumoniae*:

When testing *S. pneumoniae:*

MIC (µg/mL)	Interpretation
≤ 0.12	(S) Susceptible

When testing viridans group streptococci:

MIC (µg/mL)	Interpretation
≤ 0.5	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of 'Susceptible' indicates that the pathogen is likely to be inhibited 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 high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of 'Resistant' indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard meropenem powder should provide the following MIC values:

Microorganism	ATCC	MIC (µg/mL)
Enterococcus faecalis	29212	2.0-8.0
Escherichia coli	25922	0.008-0.06
Haemophilus influenzae	49766	0.03-0.12
Pseudomonas aeruginosa	27853	0.25-1.0
Streptococcus pneumoniae	49619	0.06-0.25

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] 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.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 10-µg disk should be interpreted according to the following criteria for indicated aerobic organisms other than *Haemophilus* species and streptococci:

Zone Diameter (mm)	Interpretation
≥ 16	(S) Susceptible
14-15	(I) Intermediate
≤ 13	(R) Resistant

Haemophilus Test Media and the following criteria should be used when testing *Haemophilus* species:

Zone Diameter (mm)	Interpretation
≥ 20	(S) Susceptible

The current absence of resistant strains precludes defining any categories other than "Susceptible". Strains yielding results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

Streptococcus pneumoniae isolates should be tested using 1-µg/mL 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 strains (i.e., MIC's = 0.12-1.0 µg/mL) from strains that are penicillin resistant (i.e. MIC's ≥ 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.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for meropenem.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 10-µg meropenem disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	ATCC	Zone Diameter (mm)
Escherichia coli	25922	28-34
Haemophilus influenzae	49247	20-28
Pseudomonas aeruginosa	27853	27-33

Anaerobic Techniques:

For anaerobic bacteria, susceptibility to meropenem as MIC's can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 4	(S) Susceptible
8	(I) Intermediate
≥ 16	(R) Resistant

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized meropenem powder should provide the following MIC values:

Microorganism	ATCC	MIC (µg/mL)
Bacteroides fragilis	25285	0.06-0.25
Bacteroides thetaiotaomicron	29741	0.125-0.5

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 strains of the designated microorganisms:

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 strains), and *Neisseria meningitidis*.

‡ The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin nonsusceptible strains 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 **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 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 THERAPY 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 INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED 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.**

Seizures and other CNS adverse experiences have been reported during treatment with MERREM I.V. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including meropenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

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

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 CNS adverse 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 the initial clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS, with the overall seizure rate being 0.7% (based on 20 patients with this adverse event). All meropenem-treated patients with seizures had pre-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 **DOSAGE 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. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of 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 **DOSAGE 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 nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection 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 probenecid with meropenem is not recommended.

There is evidence that meropenem may reduce serum levels of valproic acid to subtherapeutic levels (therapeutic range considered to be 50 to 100 µg/mL total valproate).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Carcinogenesis studies have not been performed.

Mutagenesis: Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

Impairment of fertility: Reproductive studies were performed with meropenem in rats at doses up to 1000 mg/kg/day, and cynomolgus monkeys at doses up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). There was no reproductive toxicity seen.

Pregnancy Category B: Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day, and cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of AUC comparisons, approximately 1.8 times and 3.7 times, respectively, to the human exposure at the usual dose of 1 g every 8 hours). These studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 g every 8 hours) and above in rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pediatric Use: The safety and effectiveness of MERREM I.V. have been established for pediatric patients ≥ 3 months of age. Use of MERREM I.V. in pediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population. Use of MERREM I.V. in pediatric patients with intra-abdominal infections is supported by evidence from adequate and well-controlled studies with adults with additional data from pediatric pharmacokinetics studies and controlled clinical trials in pediatric patients. (See **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION,** and **CLINICAL STUDIES** sections.)

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MERREM I.V. is administered to a nursing woman.

Geriatric Use: Of the total number of subjects in clinical studies of MERREM I.V., approximately 1100 (30%) were 65 years of age and older, while 400 (11%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; spontaneous reports and other reported clinical experience have not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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. (See **DOSAGE AND ADMINISTRATION; Use in Adults with Renal Impairment**.)

MERREM 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 MERREM I.V. should only be used to treat bacterial infections. They do not treat viral infections (eg, the common cold). When MERREM 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 MERREM I.V. or other antibacterial drugs in the future.

(CONTINUED ON REVERSE SIDE)

ADVERSE REACTIONS

Adult Patients:

During clinical investigations, 2904 immunocompetent adult patients were treated for infections outside the CNS with MERREM 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 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 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 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).

Urinalysis: presence of urine red blood cells

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 previously 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. Skin - toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiform.

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.

No specific information is available for the treatment of MERREM I.V. overdosage. In the event of an overdose, MERREM I.V. should be discontinued and general supportive treatment given until 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

Intra-abdominal:

One controlled clinical study of complicated intra-abdominal infection was performed in the United States where meropenem was compared to clindamycin/tobramycin. Three controlled clinical studies of complicated intra-abdominal infections were performed in Europe; meropenem was compared to 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. enrolled (%)	No. evaluable/ Eradication Rate	Microbiologic Rate	Clinical Cure 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:

1. 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.
2. During therapy the patient's clinical status necessitated the addition of other antibiotics.
3. 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.	COMPARATOR
S. pneumoniae	17/24 (71)	19/30 (63)
H. influenzae (+)	8/10 (80)	6/6 (100)
H. influenzae (-/NT)	44/59 (75)	44/60 (73)
N. meningitidis	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%

DOSAGE AND ADMINISTRATION

Adults: One gram (1 g) by intravenous administration every 8 hours. MERREM I.V. should be given by intravenous infusion, over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes.

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

Recommended MERREM I.V. Dosage Schedule for Adults With Impaired Renal Function

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
26-50	recommended dose (1000 mg)	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)[4] 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 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 20 or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (intra-abdominal or meningitis). (See dosing table below.) Pediatric patients weighing over 50 kg should be administered MERREM I.V. at a dose of 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.

Recommended MERREM I.V. Dosage Schedule for Pediatrics With Normal Renal Function

Type of Infection	Dose(mg/kg)	Dosing Interval
Intra-abdominal	20	every 8 hours
Meningitis	40	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 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 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**.)

NOTE: ADD-VANTAGE VIALS ARE NOT TO BE USED IN THIS MANNER.

For ADD-Vantage Vials

ADD-Vantage vials of MERREM I.V. are to be constituted only with Sodium Chloride Injection 0.45%, Sodium Chloride Injection 0.9% or Dextrose Injection 5% in the 50, 100, and 250 mL Abbott ADD-Vantage® flexible diluent containers. MERREM I.V. supplied in single-use ADD-Vantage vials should be prepared as directed.

DIRECTIONS FOR USE OF MERREM I.V. (meropenem for injection) IN ADD-VANTAGE VIALS:

To Open Diluent Container: Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Figure 1

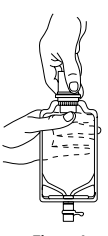


Figure 4

To Assemble ADD-Vantage Vial and Flexible Diluent Container: (Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:

a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see Figure 1), then pull straight up to remove the cap. (See Figure 2.)

NOTE: Once the breakaway cap has been removed, do not access vial with syringe.

b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See Figure 3.)

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (See Figure 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.

NOTE: ONCE VIAL IS SEATED, DO NOT ATTEMPT TO REMOVE.

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Figure 2

Figure 3

To Prepare Admixture:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See Figure 5.)
3. Pull the inner cap from the drug vial. (See Figure 6.) Verify that the rubber stopper has been pulled out and invert the system several times, allowing the drug and diluent to mix.
4. Mix contents thoroughly and use within the specified time.

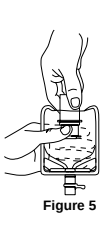


Figure 5

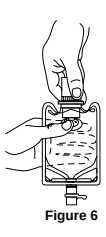


Figure 6

Preparation For Administration: (Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.

NOTE: See full directions on administration set carton.

6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

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 (55-77°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
Dextrose and Sodium Chloride Injection 5.0%/0.2%	1	4
Potassium Chloride in Dextrose Injection 0.15%/5.0%	1	6
Sodium Bicarbonate in Dextrose Injection 0.02%/5.0%	1	6
Dextrose Injection 5.0% in Normosol®-M	1	8
Dextrose Injection 5.0% in Ringers Lactate Injection	1	4
Dextrose and Sodium Chloride Injection 2.5%/0.45%	3	12
Mannitol Injection 2.5%	2	16
Ringers Injection	4	24
Ringers Lactate Injection	4	12
Sodium Lactate Injection 1/6 N	2	24
Sodium Bicarbonate Injection 5.0%	1	4

Stability in 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 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 48 hours) or in Dextrose Injection 5% (for up to 6 hours) are stable at 4°C (39°F) in plastic syringes.

ADD-Vantage Vials: ADD-Vantage vials diluted in Sodium Chloride Injection 0.45% (MERREM I.V. concentrations ranging from 5 to 20 mg/mL) may be stored for up to 6 hours at controlled room temperature 15-25°C (59-77°F) or for 24 hours at 4°C (39°F). ADD-Vantage vials diluted in Sodium Chloride Injection 0.9% (MERREM I.V. concentrations ranging from 1-20 mg/mL) may be stored for up to 4 hours at controlled room temperature 15-25°C (59-77°F) or for 24 hours at 4°C (39°F). ADD-Vantage vials diluted with Dextrose Injection 5.0% (MERREM I.V. concentrations ranging from 1-20 mg/mL) may be stored for up to 1 hour at controlled room temperature 15-25°C (59-77°F) or for 8 hours at 4°C (39°F).

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. MERREM I.V. is supplied in 100 mL infusion vials containing sufficient meropenem to deliver 500 mg or 1 g for intravenous administration. The dry powder should be stored at controlled room temperature 20-25°C (68-77°F) [see USP].

MERREM I.V. is also supplied as ADD-Vantage Vials containing sufficient meropenem to deliver 500 mg or 1 g for intravenous administration.

500 mg Injection Vial	(NDC 0310-0325-20)
1 g Injection Vial	(NDC 0310-0321-30)
500 mg ADD-Vantage	(NDC 0310-0325-15)
1 g ADD-Vantage	(NDC 0310-0321-15)

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically — Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA; December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests — Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA; December 1993.
3. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Third Edition. Approved Standard NCCLS Document M11-A3, Vol. 13, No. 26, NCCLS, Villanova, PA; December 1993.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16:31-41.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: ACS Dobfar SpA
Viale Addetta, 4/12
20067 Tribiano, Milano, Italy

Made in Italy

64213-01
Rev 01/04

AstraZeneca

F.P.O.