

PRODUCT MONOGRAPH

MERREM[®]

(meropenem for injection)

500 mg and 1 g vials

For intravenous use

Antibiotic

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
www.astrazeneca.ca

Date of Revision:
February 27, 2007

Control Number: 110164

MERREM[®] is a trade-mark of the AstraZeneca group of companies.

PRODUCT MONOGRAPH

NAME OF DRUG

MERREM[®]

(meropenem for injection)

500 mg and 1 g vials

For intravenous use

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

MERREM (meropenem) is a broad spectrum, β -lactamase-resistant, carbapenem antibiotic for parenteral administration.

The bactericidal activity of meropenem results from the inhibition of bacterial cell wall synthesis. Meropenem readily penetrates through the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin binding protein (PBP) targets. Its greatest affinity is for PBP 2 of *Escherichia coli*, PBP 2 and 3 of *Pseudomonas aeruginosa* and 1, 2 and 4 of *Staphylococcus aureus*.

Meropenem is stable in the presence of all serine β -lactamases (both penicillinases and cephalosporinases) produced by Gram-positive and Gram-negative bacteria.

Pharmacokinetics

At the end of a 30-minute intravenous infusion of a single dose of meropenem in healthy, male volunteers, mean peak plasma concentrations are approximately 23 $\mu\text{g/mL}$ for the 500 mg dose, 49 $\mu\text{g/mL}$ for the 1 g dose and 115 $\mu\text{g/mL}$ for the 2 g dose.

Intravenous bolus injections of a 1 g dose of meropenem over 2 minutes, 3 minutes and 5 minutes were compared in a three-way crossover trial in healthy male volunteers. This resulted in peak plasma levels of 110, 91 and 94 $\mu\text{g/mL}$, respectively.

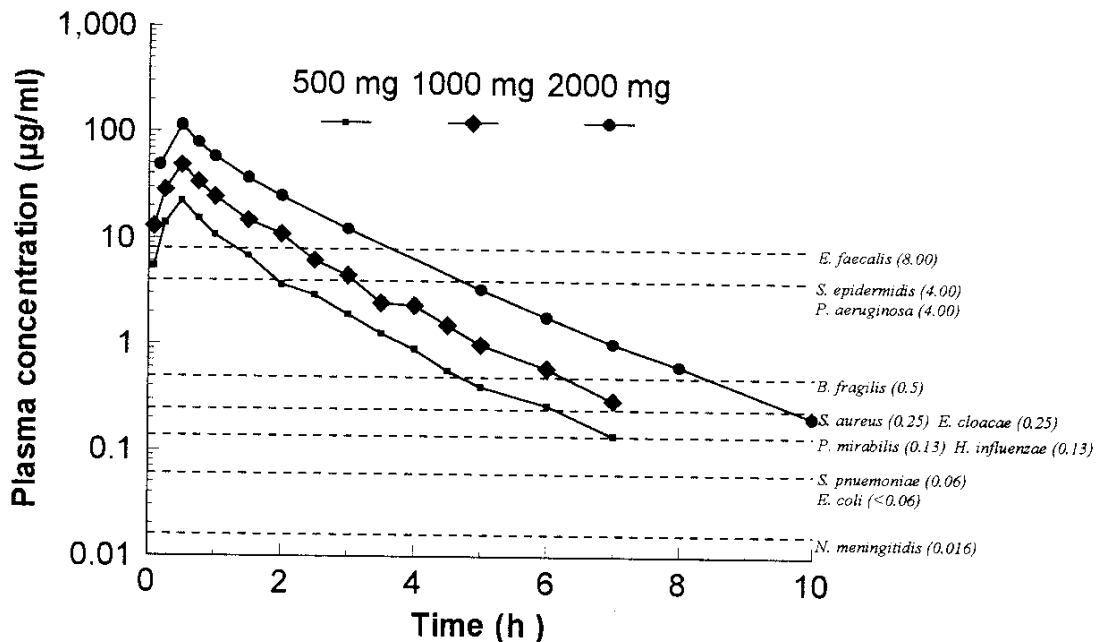
A 5 minute intravenous bolus injection of meropenem in healthy, male volunteers results in mean peak plasma levels of approximately 52 $\mu\text{g/mL}$ for the 500 mg dose and 112 $\mu\text{g/mL}$ for the 1 g dose.

At doses of 500 mg, mean plasma levels of meropenem decline to 1 µg/mL or less, 6 hours after administration.

In subjects with normal renal function, the elimination half-life of meropenem is approximately one hour. Approximately 70% of the administered dose is recovered unchanged 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 at least 5 hours at the 500 mg dose. No clinically important 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. In healthy subjects, the AUC for this metabolite was approximately 10% of the AUC for meropenem.

Figure 1 Mean Plasma Concentration-Time Profiles After Single Intravenous Infusions of MERREM Over 30 Minutes Compared to MIC₉₀ of Target Pathogens



Note: See HUMAN PHARMACOLOGY Table 10 for meropenem concentrations in select tissues and body fluids. See MICROBIOLOGY for susceptibility break points.

Meropenem penetrates well into most body fluids and tissues. However, it does not penetrate readily into cerebrospinal fluid or aqueous humor in the absence of inflammation at the sites. In children and adults with bacterial meningitis, meropenem concentrations in the

cerebrospinal fluid, after intravenous administration of recommended doses, are in excess of those required to inhibit susceptible bacteria.

The pharmacokinetics of MERREM in children over age 2 are essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in children of age 3 months to 2 years. The pharmacokinetics for children are linear for doses of 10, 20 and 40 mg/kg and the peak plasma concentrations and AUC values are similar to those seen in healthy adult volunteers after 500 mg, 1 g and 2 g doses, respectively. (See HUMAN PHARMACOLOGY - Pharmacokinetics for details of pharmacokinetics in adults and children.)

Pharmacokinetic studies of MERREM 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). A pharmacokinetic study with MERREM in elderly patients with renal insufficiency has shown that a reduction in plasma clearance of meropenem correlates with age-associated reduction in creatinine clearance.

A pharmacokinetic study of MERREM in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

INDICATIONS AND CLINICAL USE

MERREM (meropenem) is indicated for treatment of the following infections when caused by susceptible strains of the designated micro-organisms:

Lower Respiratory Tract

Community-acquired pneumonia caused by *Staphylococcus aureus* (β -lactamase-producing and non- β -lactamase-producing), *Streptococcus pneumoniae*, *Escherichia coli* and *Haemophilus influenzae* (β -lactamase-producing and non- β -lactamase-producing).

Nosocomial pneumonia caused by *Staphylococcus aureus* (non- β -lactamase-producing), *Escherichia coli*, *Haemophilus influenzae* (non- β -lactamase-producing), *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. As with other antibiotics, caution may be required in critically ill patients with known or suspected *Pseudomonas aeruginosa* lower respiratory tract infections.

Urinary Tract

Complicated urinary tract infections caused by *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia marcescens*.

Intra-abdominal

Complicated intra-abdominal infections caused by *Streptococcus milleri*, *Streptococcus mitior*, *Streptococcus sanguis*, *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Pseudomonas aeruginosa*,

Bacteroides distasonis, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, *Clostridium* species, *Eubacterium lentum*, *Fusobacterium* species and *Peptostreptococcus* species.

Clinical trials of MERREM in patients with complicated intra-abdominal infections have demonstrated that the efficacy against *Enterococcus faecalis* is 71%.

Gynecologic

Gynecologic infections caused by *Enterococcus faecalis*, *Staphylococcus aureus* (β -lactamase-producing and non- β -lactamase producing), *Staphylococcus epidermidis* (non- β -lactamase-producing), *Escherichia coli*, *Fusobacterium* species, *Prevotella bivia*, *Prevotella disiens*, *Prevotella intermedia* and *Peptostreptococcus* species.

Pelvic inflammatory disease caused by *Staphylococcus epidermidis* (non- β -lactamase-producing), *Streptococcus agalactiae*, *Escherichia coli*, *Neisseria gonorrhoeae* (non- β -lactamase-producing) and *Prevotella bivia*.

NOTE: MERREM has no activity against *Chlamydia trachomatis*. Additional antimicrobial coverage is required if this pathogen is expected.

Uncomplicated Skin and Skin Structure

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (β -lactamase-producing and non- β -lactamase-producing), *Streptococcus agalactiae*, *Streptococcus pyogenes* and *Escherichia coli*.

Complicated Skin and Skin Structure

Complicated skin and skin structure infections, except infected burns, due to *Staphylococcus aureus* (methicillin-susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus faecalis* (excluding vancomycin-resistant isolates), Viridans group streptococci, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Peptostreptococcus* species, *Prevotella* species, and *Bacteroides fragilis*.

Bacterial Meningitis

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

NOTE: There is limited adult efficacy data for MERREM in the treatment of bacterial meningitis. Support for the adult meningitis indication is largely provided by pediatric data.

Bacterial Septicemia

Bacterial septicemia caused by *Escherichia coli*.

Therapy with MERREM may be initiated on the basis of clinical judgement before results of sensitivity testing are available. Continuation of therapy should be re-evaluated on the basis of bacteriological findings and on the patient's clinical condition. Regular sensitivity testing is recommended when treating *Pseudomonas aeruginosa* infections.

CONTRAINDICATIONS

MERREM (meropenem) is contraindicated in patients with known hypersensitivity to any component of this product or in patients who have demonstrated anaphylactic reactions to β -lactam antibiotics.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH β -LACTAM ANTIBIOTICS. 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 REACTIONS WHEN TREATED WITH ANOTHER β -LACTAM ANTIBIOTIC. BEFORE INITIATING THERAPY WITH MERREM (MEROPENEM), CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER β -LACTAM ANTIBIOTICS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO MERREM OCCURS, DISCONTINUE THE DRUG IMMEDIATELY. **ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, ANTIHISTAMINES AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, MAY BE REQUIRED.**

Pseudomembranous colitis has been reported with many antibiotics, including MERREM, therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. This type of colitis may range in severity from mild to life threatening. (see Adverse Reactions: Post-Marketing Experience)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *Clostridia*. Studies indicated that a toxin produced by *Clostridium difficile* is one 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 effective against *C. difficile*.

MERREM should not be used to treat infections caused by methicillin resistant *staphylococci*.

PRECAUTIONS

General

As with other broad-spectrum antibiotics, prolonged use of MERREM (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.

MERREM, like all β -lactam antibiotics, has the potential to cause seizures. Diminished renal function and central nervous system lesions may increase the risk of seizures. When MERREM is indicated in patients with these risk factors, caution is advised.

Convulsions have been observed in a temporal association with use of MERREM, although a causal relationship has not been established.

Use of MERREM may lead to the development of a positive direct or indirect Coombs test.

MERREM may reduce serum valproic acid levels. Subtherapeutic levels of valproic acid may be reached in some patients. Subtherapeutic levels of valproic acid are known to increase patients' pre-disposition to seizure (see Drug Interactions).

Pediatrics

The safety and effectiveness of MERREM in the pediatric population 3 months of age and older have been established. MERREM is not recommended for use in infants under the age of 3 months.

The use of MERREM in pediatric patients with bacterial meningitis is supported by evidence from adequate and well controlled studies in the pediatric population. Use of MERREM in pediatric patients for all other indications, as listed in the INDICATIONS section, is supported by evidence from adequate and well controlled studies in adults with additional data from pediatric pharmacokinetic studies and controlled clinical trials in pediatric patients (see DOSAGE AND ADMINISTRATION, children).

NOTE: Inadequate data are available to support the pediatric indications for nosocomial pneumonia, septicemia and complicated skin and skin structure infections.

Pregnancy

There are 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. Reproduction studies have been performed in rats and Cynomolgous monkeys at doses up to 1000 mg/kg/day (approximately 16 times the usual human 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 240 mg/kg/day and above in rats.

Nursing Mothers

MERREM is detected in animal breast milk, however, it is not known whether MERREM is excreted in human milk. MERREM should not be given to breast-feeding women unless the potential benefit justifies the potential risk to the baby.

Liver Disease

Patients with pre-existing liver disorders should have their liver function monitored during treatment with MERREM.

Renal Impairment

Dosage adjustment is recommended for patients with renal insufficiency (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing the elimination half-life and plasma concentration of MERREM. The coadministration of probenecid with MERREM is neither required nor recommended.

Other than probenecid, no specific drug interaction studies were conducted.

MERREM may reduce serum valproic acid levels. Subtherapeutic levels of valproic acid may be reached in some patients. Subtherapeutic levels of valproic acid are known to increase patients' pre-disposition to seizure (see PRECAUTIONS, General).

ADVERSE REACTIONS

MERREM (meropenem) is generally well tolerated. Many patients receiving MERREM are severely ill, have multiple background diseases, physiological impairments and receive multiple other drug therapies. In such seriously ill patients, it is difficult to establish the relationship between adverse events and MERREM.

Clinical Trials

The following adverse reaction frequencies were derived from all clinical trials in 3187 patients treated with MERREM administered intravenously.

Local Adverse Reactions

Local adverse clinical reactions that were reported by the investigator as possibly, probably or definitely related to therapy with MERREM were: inflammation at the injection site 1.6%, phlebitis/thrombophlebitis 0.5%, injection site reaction 0.4%, pain at the injection site 0.1% and edema at the injection site 0.1%.

Systemic Adverse Reactions

Systemic adverse clinical reactions that were reported by the investigator as possibly, probably or definitely related to MERREM and occurring in greater than 0.2% of the patients were: diarrhea (2.5%), nausea/vomiting (1.2%), rash (1.1%), pruritus (0.6%), headache (0.5%), urticaria (0.3%), vaginal moniliasis (0.7%), vaginitis (0.3%), oral moniliasis (0.3%) and fever (0.2%).

Additional adverse systemic clinical reactions reported by the investigator as possibly, probably or definitely related to MERREM and occurring in less than 0.2% of the patients are listed below within each body system in order of decreasing frequency.

<u>Body as a whole:</u>	abdominal pain, moniliasis, chills, infection, pain
<u>Nervous system:</u>	agitation, convulsions, dizziness, hallucinations, paresthesias, neuropathy
<u>Skin and appendages:</u>	sweating
<u>Special senses:</u>	taste perversion
<u>Digestive system:</u>	constipation
<u>Metabolic/nutritional:</u>	peripheral edema
<u>Renal:</u>	renal impairment
<u>Hematological:</u>	thrombocytopenia

Adverse Laboratory Changes

Adverse laboratory changes that were reported by the investigator as possibly, probably or definitely related to MERREM occurring in greater than 0.2% of the patients were as follows:

<u>Hepatic:</u>	increased SGPT (ALT), SGOT (AST), alkaline phosphatase, LDH and bilirubin
<u>Hematologic:</u>	increased platelets, increased eosinophils, abnormal prothrombin time, abnormal partial thromboplastin time, decreased platelets, decreased WBC, leukopenia and neutropenia (including rare cases of agranulocytosis)
<u>Renal:</u>	increased creatinine and increased BUN

Pediatric Patients

Drug-related diarrhea (5.0%) and increases in platelets (7.0%) appear to occur more frequently in pediatric patients than in adults treated with MERREM.

Post-Marketing Experience

Very rare cases of the following have been reported: Pseudomembranous colitis, hypokalemia, hypomagnesemia, severe skin reactions such as erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, thrombocytopenia; and severe hypersensitivity reactions of angioedema and anaphylaxis.

Very rare reports of cholestasis, hepatitis, thrombocytopenia with bleeding and hemolytic anemia have been received. A causal relationship could not be excluded in spite of concomitant medications and/or illnesses.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Intentional overdosing of MERREM (meropenem) is unlikely, although accidental overdosing might occur particularly in patients with reduced renal function. The largest dose of meropenem administered in clinical trials has been 2 g given intravenously every 8 hours to adult patients with normal renal function and 40 mg/kg every 8 hours to children with normal renal function. At these dosages, no adverse pharmacological effects were observed.

Limited post-marketing experience indicates that if adverse events occur following overdosage, they are generally consistent with the adverse event profile described under ADVERSE REACTIONS.

In the event of an overdose, MERREM should be discontinued and general supportive treatment given until renal elimination takes place. MERREM and its metabolite are readily dialyzable and effectively removed by hemodialysis; however, no information is available on the use of hemodialysis to treat overdosage.

The intravenous LD₅₀ of meropenem in mice and rats is more than 2500 mg/kg and is approximately 2000 mg/kg in dogs.

DOSAGE AND ADMINISTRATION

Adults

The usual dose is 500 mg to 1 g by intravenous infusion every 8 hours, depending on type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient (see table below). Doses up to 2 g every 8 hours have been used. MERREM (meropenem) should be given by intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 5 minutes.

The recommended dose to be given for adults is as follows:

Type of Infection	Dose	Dosage Interval
Complicated urinary tract	500 mg	every 8 hours
Uncomplicated skin and skin structure	500 mg	every 8 hours
Complicated skin and skin structure	500 mg	every 8 hours
Gynecologic and Pelvic Inflammatory Disease	500 mg	every 8 hours
Lower respiratory		
Community-acquired pneumonia	500 mg	every 8 hours
Nosocomial pneumonia	1 g	every 8 hours
Complicated intra-abdominal	1 g	every 8 hours
Meningitis	2 g	every 8 hours
Septicemia	1 g	every 8 hours

Impaired Renal Function

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

Creatinine clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
26-50	recommended dose (500 mg to 2000 mg)	every 12 hours
10-25	one-half recommended dose	every 12 hours
<10	one-half recommended dose	every 24 hours

Meropenem is removed by hemodialysis; if continued treatment with MERREM is necessary, the dose, based on the infection type and severity, should be administered at the completion of the hemodialysis procedure to reinstitute effective treatment.

There are no data on appropriate doses in patients requiring peritoneal dialysis.

Adults with Hepatic Insufficiency

No dosage adjustment is necessary in patients with hepatic dysfunction as long as renal function is normal.

Elderly

Dosage adjustment is recommended for the elderly with an estimated or measured creatinine clearance value below 50 mL/min (see section on Impaired Renal Function).

Children

For infants and children over 3 months of age and weighing up to 50 kg, the recommended dose of MERREM is 10 to 40 mg/kg every 8 hours, depending on type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient (see table below). Children weighing over 50 kg require the adult dosage. MERREM should be given as an intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 5 minutes.

Type of Infection	Dose (mg/kg)	Dosing Interval
Complicated urinary tract	10	every 8 hours
Uncomplicated skin and skin structure	10 - 20	every 8 hours
Community acquired pneumonia	10 - 20	every 8 hours
Complicated intra-abdominal	20	every 8 hours
Meningitis	40	every 8 hours

There are no data on appropriate doses for children with renal impairment.

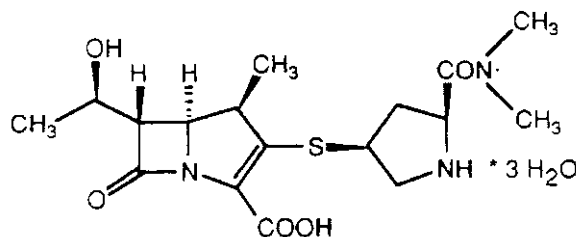
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name meropenem

Chemical Name (-)-(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

Structural Formula



Molecular Formula C₁₇H₃₁N₃O₈S

Molecular Weight 437.51

Description Meropenem is a white to light yellow, crystalline powder which is soluble in 5% sodium bicarbonate solution, sparingly soluble in water, very slightly soluble in absolute ethanol and practically insoluble in ether.

The pH of a 1% w/v solution in water ranges from 4.0 to 6.0. The pKa values are 2.9 and 7.4. The melting point is difficult to determine because decomposition and colour changes occur before melting. The n-octanol:water partition coefficient is small ($<1 \times 10^{-3}$).

Composition

For vials, each 1 g MERREM vial will deliver 1 g of meropenem anhydrous as meropenem trihydrate and 90.2 mg of sodium as sodium carbonate and each 500 mg vial will deliver 500 mg meropenem anhydrous as meropenem trihydrate and 45.1 mg of sodium as sodium carbonate.

Stability And Storage Recommendations

Store between 15 - 30°C.

Parenteral Products

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

Freshly prepared solutions of MERREM should be used whenever possible. Solutions of MERREM should not be frozen.

All vials are for single use only. Standard aseptic technique should be employed during constitution and administration.

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

Intravenous Bolus Administration

Reconstitute injection vials (500 mg/20 mL and 1 g/30 mL) 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/20mL	10	10	50
1 g/30mL	20	20	50

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

Infusion

Injection vials may be reconstituted, then the resulting solution added to an i.v. container and further diluted with an appropriate infusion fluid (see below).

Stability in Plastic i.v. Bags

Solutions prepared for infusion (MERREM concentrations ranging from 1 to 20 mg/mL) may be stored in plastic i.v. bags with diluents as shown in the table below. Diluted Intravenous Infusion solutions should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration, whenever solution and container permit. Discard unused portion.

Diluent	Number of Hours Stable at Controlled Room Temperature 15 - 25°C	Number of Hours Stable at 4°C
Sodium Chloride 0.9% Injection	4	24
Dextrose 5.0% Injection	1	4
Dextrose 10% Injection	1	2
Dextrose 5.0% and Sodium Chloride 0.9% Injection	1	2
Dextrose 5.0% and Sodium Chloride 0.2% Injection	1	4
Potassium Chloride 0.15% in Dextrose 5.0% Injection	1	6
Sodium Bicarbonate 0.02% in Dextrose 5.0% Injection	1	6
Dextrose 5.0% Injection in Normosol [®] - M	1	8
Dextrose 5.0% Injection in Ringers Lactate Injection	1	4
Dextrose 2.5% and Sodium Chloride 0.45% Injection	3	12
Mannitol Injection 2.5%	2	16
Ringers Injection	4	24
Ringers Lactate Injection	4	12
Sodium Lactate Injection 1/6N	2	24
Sodium Bicarbonate 5.0% Injection	1	4

Stability in Plastic Syringes, Tubing and i.v. Infusion Sets

Solutions of MERREM (MERREM concentrations ranging from 1 to 20 mg/mL) in Water for Injection or Sodium Chloride 0.9% Injection (for up to 4 hours) or in Dextrose 5.0% Injection

(for up to 2 hours) at controlled room temperatures 15 - 25°C are stable in plastic syringes, plastic tubing, drip chambers, and volume control devices of common i.v. infusion sets.

AVAILABILITY OF DOSAGE FORMS

MERREM (meropenem) is supplied in 20 mL and 30 mL injection vial sizes containing sufficient meropenem to deliver 500 mg and 1 g of meropenem anhydrous respectively for intravenous administration.

MICROBIOLOGY

The *in vitro* activity of meropenem against clinical isolates of Gram-positive and Gram-negative aerobic and anaerobic bacteria are shown in Table 1. Susceptibility was determined using NCCLS-recommended methods for MICs and agar disk diffusion using inoculum sizes of 10⁴ to 10⁵ colony forming units per spot.

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<u>Gram-positive Aerobes</u>					
<i>Staphylococcus aureus</i>	(2607)	0.083	0.008-32	≤ 0.06	0.25
<i>Staphylococcus aureus (MR)</i>	(475)	3.7	≤ 0.016-64	4.00	32.00
<i>Staphylococcus epidermidis</i>	(1029)	0.298	0.008-64	0.13	4.00
<i>Staphylococcus epidermidis (MR)</i>	(315)	2.566	0.03-64	4.00	16.00
<i>Staphylococcus saprophyticus</i>	(173)	0.219	0.06-32	0.25	0.50
<i>Staphylococcus haemolyticus</i>	(100)	1.482	≤ 0.016-64	2.00	> 16.00
<i>Staphylococcus capitis</i>	(28)	0.080	0.016-0.5	≤ 0.06	0.25
<i>Staphylococcus cohnii</i>	(33)	0.254	0.03-4	0.50	1.00
<i>Staphylococcus warneri</i>	(90)	0.197	0.008-16	0.13	2.00
<i>Staphylococcus hominis</i>	(79)	0.267	0.03-32	0.25	2.00
<i>Staphylococcus simulans</i>	(58)	0.241	0.008-16	0.13	4.00
<i>Staphylococcus intermedius</i>	(21)	0.033	≤ 0.016-0.25	0.03	0.06
<i>Staphylococcus sciuri</i>	(11)	0.500	0.03-16	0.50	4.00
<i>Staphylococcus lugdunensis</i>	(19)	0.417	0.25-0.5	0.50	0.50
<i>Staphylococcus saccharolyticus</i>	(15)	0.014	≤ 0.008 – 0.25	0.008	0.25
<i>Streptococcus pyogenes</i>	(302)	0.009	≤ 0.008-0.13	≤ 0.008	≤ 0.06

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<i>Streptococcus agalactiae</i>	(376)	0.033	≤ 0.008-4	0.03	0.06
<i>Streptococcus equi</i>	(64)	0.009	≤ 0.008-0.13	0.008	0.03
<i>Streptococcus (Group G)</i>	(63)	0.009	≤ 0.008- ≤ 0.06	0.008	0.03
<i>Streptococcus pneumoniae</i>	(452)	0.012	0.008-2	0.016	0.06
<i>Streptococcus pneumoniae (PR)</i>	(97)	0.293	0.03-2	0.50	1.00
<i>Streptococcus bovis</i>	(21)	0.056	0.016-4	0.03	0.25
<i>Streptococcus mitis</i>	(33)	0.079	0.008-4	0.06	1.00
<i>Streptococcus mitior</i>	(11)	0.020	0.008-0.13	0.016	0.03
<i>Streptococcus milleri</i>	(27)	0.028	0.008-0.13	0.03	0.06
<i>Streptococcus sanguis</i>	(65)	0.060	0.008-4	0.06	1.00
<i>Streptococcus viridans</i>	(90)	0.064	≤ 0.008-4	0.06	2.00
<i>Streptococcus (Group F)</i>	(19)	0.306	≤ 0.016-83	4.00	8.00
<i>Enterococcus liquifaciens</i>	(65)	5.335	4.0-1.6	4.00	8.00
<i>Enterococcus avium</i>	(32)	0.282	0.008-64	0.13	4.00
<i>Enterococcus hirae</i>	(10)	2.308	0.016-16	8.00	16.00
<i>Enterococcus faecium</i>	(175)	9.108	0.008 - >128	>8.00	64.00
<i>Enterococcus faecalis</i>	(1277)	3.651	0.008 - >128	4.00	8.00
<i>Corynebacterium diphtheriae</i>	(24)	0.272	0.008-8	0.50	0.50
<i>Corynebacterium jeikeium</i>	(36)	4.321	≤ 0.008 - >128	2.00	128.00
<i>Listeria monocytogenes</i>	(154)	0.167	0.06-4	0.13	0.25
<i>Lactobacillus spp.</i>	(18)	1.31	0.06-8	2.00	8.00
<i>Bacillus spp.</i>	(52)	0.117	0.03-2	0.06	0.50
<i>Nocardia asteroides</i>	(15)	1.097	0.13-8	1.00	8.00
<u><i>Nutritionally Fastidious Isolates</i></u>					
<i>Legionella pneumophila</i>	(24)	0.012	≤ 0.008-0.13	0.008	0.06
<i>Haemophilus influenzae</i>	(1163)	0.050	≤ 0.008-1	0.06	0.13
<i>Haemophilus parainfluenzae</i>	(11)	0.058	0.016-0.25	0.03	0.25
<i>Haemophilus ducreyi</i>	(111)	0.074	0.016-0.13	0.06	0.13

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<i>Neisseria gonorrhoeae</i> (PS)	(237)	0.010	≤ 0.008-0.13	0.008	0.015
<i>Neisseria gonorrhoeae</i> (PR)	(119)	0.010	≤ 0.008-0.13	0.008	0.03
<i>Neisseria meningitidis</i>	(98)	≤ 0.008	≤ 0.008-0.03	0.008	0.016
<i>Moraxella spp.</i>	(12)	0.071	0.008-8	0.016	2.00
<i>Moraxella catarrhalis</i>	(212)	≤ 0.008	≤ 0.008-0.25	≤ 0.008	0.008
<i>Bordetella spp.</i>	(11)	0.151	0.03-2	0.06	2.00
<i>Gardnerella vaginalis</i>	(35)	0.028	0.008-0.13	0.03	0.06
<i>Campylobacter jejuni</i>	(65)	0.010	≤ 0.008-0.06	0.008	0.03
<i>Helicobacter pylori</i>	(11)	0.079	0.06-0.13	0.06	0.13
<u><i>Selected Gram-negative Organisms</i></u>					
<i>Escherichia coli</i>	(3683)	0.023	≤ 0.008-4	0.03	<0.06
<i>Citrobacter diversus</i>	(235)	0.03	≤ 0.008->8	0.03	≤ 0.06
<i>Citrobacter freundii</i>	(656)	0.038	≤ 0.008-32	0.06	0.13
<i>Citrobacter amalonaticus</i>	(16)	0.037	0.016-0.06	0.06	0.06
<i>Salmonella spp.</i>	(308)	<0.008	≤ 0.008-0.13	0.03	0.06
<i>Salmonella typhi</i>	(79)	0.019	≤ 0.008 - ≤ 0.06	0.016	<0.06
<i>Shigella sonnei</i>	(46)	0.03	0.016-0.06	0.03	0.06
<i>Shigella flexneri</i>	(28)	0.026	0.016 - ≤ 0.06	0.03	0.03
<i>Klebsiella pneumoniae</i>	(1241)	0.034	≤ 0.008-4	0.06	0.06
<i>Klebsiella aerogenes</i>	(35)	0.016	≤ 0.008-0.06	0.016	0.03
<i>Klebsiella ozaenae</i>	(16)	0.059	0.016-0.25	0.06	0.25
<i>Klebsiella oxytoca</i>	(518)	0.035	≤ 0.008-4	≤ 0.06	0.06
<i>Enterobacter cloacae</i>	(1201)	0.053	≤ 0.008-16	≤ 0.06	0.25
<i>Enterobacter aerogenes</i>	(427)	0.045	≤ 0.008-8	≤ 0.06	0.13
<i>Enterobacter agglomerans</i>	(97)	0.042	≤ 0.008-1	0.06	0.13
<i>Enterobacter sakazakii</i>	(26)	0.052	0.016-2	0.06	0.13
<i>Serratia marcescens</i>	(764)	0.059	≤ 0.008-32	≤ 0.06	0.25
<i>Serratia liquefaciens</i>	(68)	0.053	≤ 0.008-2	0.06	0.13

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<i>Hafnia alvei</i>	(97)	0.028	≤ 0.008-0.5	0.03	0.06
<i>Proteus mirabilis</i>	(1398)	0.06	≤ 0.008-4	0.06	0.13
<i>Proteus vulgaris</i>	(377)	0.069	≤ 0.008-4	≤ 0.06	0.25
<i>Proteus penneri</i>	(17)	0.066	0.016-0.5	0.06	0.50
<i>Morganella morganii</i>	(567)	0.086	0.0.016->8	0.06	0.25
<i>Providencia rettgeri</i>	(203)	0.078	0.016-2	0.06	0.25
<i>Providencia alcalifaciens</i>	(27)	0.040	≤ 0.008-0.5	0.06	0.13
<i>Providencia stuartii</i>	(361)	0.090	≤ 0.008-8	0.06	0.50
<i>Yersinia enterocolitica</i>	(105)	0.030	0.016-0.06	0.03	0.06
<i>Aeromonas hydrophila</i>	(109)	0.078	0.008->128	≤ 0.06	0.50
<i>Aeromonas sobria</i>	(19)	0.156	≤ 0.06-1	0.13	1.00
<i>Aeromonas caviae</i>	(61)	0.021	≤ 0.016-0.25	0.03	<0.06
<i>Plesiomonas shigelloides</i>	(24)	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
<i>Vibrio Cholerae</i>	(20)	0.233	≤ 0.06-0.5	0.25	0.25
<i>Vibrio parahaemolyticus</i>	(27)	0.018	≤ 0.008- 0.06	≤ 0.06	≤ 0.06
<i>Vibrio vulvniificus</i>	(20)	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
<i>Pasteurella multocida</i>	(19)	0.032	0.008-0.13	0.03	0.13
<u>'Non-fermenting' Gram-negative Aerobes</u>					
<i>Alcaligenes faecalis</i>	(15)	0.086	0.03-0.25	0.13	0.25
<i>Acinetobacter calcoaceticus</i>	(117)	0.996	0.03-64	1.00	2.00
<i>Acinetobacter calcoaceticus var anitratus</i>	(461)	0.602	0.03->128	0.50	2.00
<i>Acinetobacter calcoaceticus var lwoffii</i>	(48)	0.165	0.016-4	0.13	0.50
<i>Acinetobacter baumannii</i>	(60)	0.755	0.016-4	1.00	2.00
<i>Stenotrophomonas maltophilia</i>	(408)	43.0	≤ 0.008-128	64.00	>128.00
<i>Pseudomonas aeruginosa</i>	(3018)	0.668	0.008->128	0.50	4.00
<i>Pseudomonas putida</i>	(46)	2.00	0.13-8	2.00	8.00

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<i>Pseudomonas cepacia</i>	(166)	1.368	0.008->64	2.00	8.00
<i>Pseudomonas fluorescens</i>	(70)	1.579	0.008-32	2.00	8.00
<i>Pseudomonas stutzeri</i>	(24)	0.362	0.06-16	0.25	4.00
<i>Pseudomonas acidoverans</i>	(22)	0.159	0.03-0.25	0.25	0.25
<i>Achromobacter xylosoxidans</i>	(30)	0.741	0.06->128	0.50	4.00
<i>Flavobacterium Group II B</i>	(11)	14.1	2.0-64	16.00	64.00
<i>Flavobacterium meningosepticum</i>	(14)	19.5	8.0-32	16.00	>16.00
<u>Anaerobic Organisms</u>					
<i>Bacteroides fragilis</i>	(1067)	0.151	≤ 0.008->128	0.13	0.50
<i>Bacteroides vulgatus</i>	(109)	0.191	0.03-4	0.13	0.50
<i>Bacteroides uniformis</i>	(57)	0.154	≤ 0.03-16	0.13	0.50
<i>Bacteroides distasonis</i>	(131)	0.232	0.03-16	0.25	1.00
<i>Bacteroides thetaiotaomicron</i>	(244)	0.174	0.008-8	0.13	0.50
<i>Bacteroides ovatus</i>	(79)	0.261	≤ 0.06-16	0.25	0.50
<i>Bacteroides asaccharolyticus</i>	(33)	0.031	≤ 0.008-0.13	0.03	0.06
<i>Bacteroides splanchnicus</i>	(12)	0.020	≤ 0.016-0.25	0.03	0.03
<i>Bacteroides ureolyticus</i>	(39)	0.021	≤ 0.008-0.25	0.016	0.13
<i>Bacteroides levii</i>	(10)	0.012	≤ 0.008-0.13	≤ 0.016	0.03
<i>Prevotella melaninogenica</i>	(44)	0.084	0.008-1	0.06	0.50
	(13)	0.019	≤ 0.008-0.25	0.016	0.06
<i>Prevotella intermedia</i>	(61)	0.067	0.016-8	0.06	0.25
<i>Prevotella bivia</i>	(159)	0.089	0.008-4	0.06	0.50
<i>Prevotella oralis</i>	(65)	0.060	≤ 0.08-0.5	0.06	0.25
<i>Prevotella disiens</i>	(36)	0.086	≤ 0.008->32	0.06	0.25
<i>Prevotella oris</i> (previously listed as <i>B. rumenicol</i> and <i>B. oris</i>)	(21)	0.032	0.016-0.06	0.03	0.06
	(13)	0.075	0.016-0.5	0.06	0.50
<i>Prevotella buccae</i>	(36)	0.065	0.008-1	0.06	0.13
<i>Prevotella denticola</i>	(10)	0.023	≤ 0.008-0.06	0.03	0.03

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Table 1 **The *In Vitro* Activity* of Meropenem Against Clinical Isolates of Various Gram-Positive and Gram-Negative Aerobic and Anaerobic Species**

Organism	No. Strains	Geom. Mean MIC₅₀	Range	MIC₅₀	MIC₉₀
<i>Fusobacterium mortiferum</i>	(27)	0.188	0.008-8	0.13	2.00
<i>Fusobacterium necrophorum</i>	(24)	0.010	≤ 0.008->128	≤ 0.016	0.03
<i>Fusobacterium nucleatum</i>	(71)	0.019	≤ 0.008-1	0.016	0.13
<i>Fusobacterium varium</i>	(31)	0.233	0.016->128	0.13	1.00
<i>Veillonella parvula</i>	(30)	0.020	≤ 0.008-2	0.016	0.13
<i>Eubacterium lentum</i>	(17)	0.046	0.016-0.25	0.03	0.13
<i>Propioni-bacterium acnes</i>	(37)	0.053	≤ 0.008-0.25	0.06	0.25
<i>Bifido-bacterium spp.</i>	(19)	0.116	≤ 0.008-2	0.06	1.00
<i>Anaerobic streptococcus</i>	(10)	0.047	≤ 0.06-0.13	≤ 0.06	0.13
<i>Peptostreptococcus anaerobius</i>	(79)	0.224	≤ 0.008-4	0.25	2.00
<i>Peptostreptococcus asaccharolyticus</i>	(42)	≤ 0.008	≤ 0.008-0.13	≤ 0.008	0.03
<i>Peptostreptococcus magnus</i>	(52)	0.039	≤ 0.008-0.5	0.03	0.13
<i>Peptostreptococcus micros</i>	(36)	0.023	≤ 0.008-0.25	0.03	0.25
<i>Peptostreptococcus prevotii</i>	(39)	0.038	≤ 0.008-0.5	0.03	0.50
<i>Peptostreptococcus saccharolyticus</i>	(46)	0.013	≤ 0.008-1	≤ 0.016	0.13
<i>Anaerobic cocci</i>	(49)	0.029	≤ 0.008-0.13	0.03	0.06
<i>Clostridium perfringens</i>	(336)	0.008	≤ 0.008-1	0.008	≤ 0.06
<i>Clostridium bif fermentans</i>	(17)	0.056	0.008-0.25	0.06	0.13
<i>Clostridium ramosum</i>	(18)	0.480	0.016-1	0.50	1.00
<i>Clostridium sporogenes</i>	(28)	0.068	0.03-1	0.06	0.25
<i>Clostridium difficile</i>	(212)	0.68	0.008-4	1.00	2.00
<i>Clostridium sordellii</i>	(21)	0.023	≤ 0.008-0.25	0.03	0.06
<i>Clostridium butyricum</i>	(20)	0.278	0.03-1	0.25	0.50
<i>Clostridium clostridiiformis</i>	(25)	0.199	0.016-4	0.25	1.00
<i>Clostridium innocuum</i>	(16)	0.523	0.06-4	0.50	2.00
<i>Clostridium subterminale</i>	(11)	0.565	0.03->128	0.25	4.00
<i>Actinomyces adontolyticus</i>	(20)	0.105	0.03-2	0.06	0.25
<i>Mobiluncus spp.</i>	(20)	0.017	≤ 0.008-0.06	0.008	0.06

*mg/L; MR, MS, PR, PS: Methicillin-or penicillin-resistant or susceptible, respectively

Few strains of *E. faecium*, *S. maltophilia*, or *F. meningosepticum* are inhibited by meropenem at $\leq 8 \mu\text{g/mL}$.

Table 2 **MBC:MIC Ratios for Meropenem**

Organism	(n)	Percent of strains (Number of Strains) with MBC:MIC ratio of			
		2	4	8	>16
<u>Gram-positive organism</u>					
<i>Staphylococcus aureus</i> (MR)	(5)	60(3)	20(1)	20(1)	
<i>Staphylococcus aureus</i> (MS)	(6)	67(4)	33(2)		
<i>Enterococcus faecalis</i>	(5)	60(3)	40(2)		
<u>Nutritionally fastidious aerobes</u>					
<i>Haemophilus influenzae</i>	(9)	89(8)	11(1)		
<i>Moraxella catarrhalis</i>	(10)	80(8)	20(2)		
<u>Enterbacteriaceae</u>					
<i>Escherichia coli</i>	(16)	88(14)	6(1)	6(1)	
<i>Citrobacter freundii</i>	(7)	100(7)			
<i>Klebsiella pneumoniae</i>	(6)	100(6)			
<i>Enterobacter cloacae</i>	(19)	95(18)	5(1)		
<i>Serratia marcescens</i>	(49)	92(45)	2(1)	6(3)	
<i>Proteus mirabilis</i>	(33)	91(30)	9(3)		
<i>Proteus vulgaris</i>	(12)	100(12)			
<i>Morganella morganii</i>	(11)	73(8)	27(3)		
<i>Providencia rettgeri</i>	(3)	33(1)	67(2)		
<i>Providencia stuartii</i>	(35)	71(25)	20(7)	9(3)	
<u>Non-fermenting Gram-negative aerobes</u>					
<i>Acinetobacter antiratus</i>	(6)	100(6)			
<i>Pseudomonas aeruginos</i>	(55)	85(47)	13(7)	2(1)	
<u>Aerobes</u>					
<i>Bacteroides fragilis</i>	(31)	84(26)	16(5)		
<i>Clostridium perfringes</i>	(11)	100(11)			
<i>Clostridium difficile</i>	(8)	38(3)			62(5)

MR: methicillin-resistant
MS: methicillin-susceptible

MICs and MBCs are little affected by changes in inoculum concentration from 10^4 to 10^8 cfu/mL or when conducted in broth adjusted in pH over the range of 5-7 or in test medium

supplemented with 50% human serum. At pH 8, only *P. aeruginosa* showed increased MICs and MBCs.

Meropenem post-antibiotic effects ≥ 0.5 h were obtained with 87% of all strains tested including Enterobacteriaceae strains, Gram-positive aerobes, *B. fragilis* and *in vivo* in neutropenic mice infected with *P. aeruginosa*.

In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of *Pseudomonas aeruginosa* and some of the Enterobacteriaceae. Meropenem and vancomycin act synergistically against some enterococci and coagulase-positive and coagulase-negative staphylococcal strains, including those resistant to methicillin. These *in vitro* tests show meropenem does not act antagonistically with aminoglycosides or vancomycin against Gram-negative and Gram-positive aerobes, respectively.

Assessment of Resistance

Meropenem is active against many bacteria which are resistant to other antibiotics. Meropenem was active against bacteria with known mechanisms of resistance, e.g. *S. aureus*, *S. epidermidis*, *N. gonorrhoeae* or *M. catarrhalis* which produce β -lactamase; *H. influenzae* which are resistant to ampicillin or produce β -lactamases and *S. pneumoniae* which are resistant to penicillin. Meropenem has excellent activity against strains of *Staphylococci*, *Enterobacteriaceae* and *P. aeruginosa* expressing plasmid or chromosomally-encoded β -lactamases. It is unaffected when tested against strains of Enterobacteriaceae harbouring transferable (plasmid-mediated) β -lactamases which hydrolyze ceftazidime, cefotaxime and other third generation cephalosporins.

Serial passage in meropenem did not select resistant *S. aureus*. While 10 serial passages in meropenem elevated the MIC of one strain each of *K. pneumoniae*, *E. cloacae* or *S. marcescens*, 2 further studies failed, using point mutation, to select Enterobacteriaceae with elevated MICs.

Laboratory mutants of *P. aeruginosa* are selected at normal frequency (10^{-6} - 10^{-10}) by imipenem or meropenem. Elevation of the MIC occurs due to diminished, or no expression of a 45-48Kd outer membrane protein (omp). This is a known mechanism of carbapenem resistance. Strains of *P. aeruginosa* selected during therapy with imipenem show the same omp changes; susceptibility to meropenem was greater (MIC 0.5-4 $\mu\text{g/mL}$) than to imipenem (8-16 $\mu\text{g/mL}$).

Susceptibility Testing

Standard susceptibility tests using diffusion techniques and 10 μg meropenem disks should be interpreted according to Table 3. A single set of meropenem susceptibility criteria are recommended based on pharmacokinetics and correlation of clinical and microbiological outcomes with zone diameter and minimum inhibitory concentrations (MIC) of the infecting organisms. A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of meropenem in blood. A report of "Intermediate or Moderately Susceptible" indicates that the result should be considered equivocal, and if the

micro-organisms are 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 the maximum acceptable dose of the drug can be used. This category also provides a buffer that prevents small uncontrolled technical factors from causing major discrepancies in interpretations. A report of “Resistant” indicates that usually achievable concentrations of meropenem in blood are unlikely to be inhibitory and that other therapy should be selected.

The MIC values obtained for meropenem using standardized dilution methods should be interpreted according Table 3.

Table 3 Interpretation of Susceptibility Criteria for Meropenem

Interpretation	Zone Diameter (mm)	MIC (µg/mL)
Susceptible (S)	≥ 14	≤ 4
Intermediate (I) or Moderately Susceptible (MS)	12 - 13	8
Resistant (R)	≤ 11	≥ 16

Susceptibility results using laboratory control organisms are shown in the table below.

Table 4 Susceptibility of Laboratory Control Organisms to Meropenem

Micro-organism	ATCC	Zone Diameter (mm)	MIC (µg/mL)
<i>Pseudomonas aeruginosa</i> *	27853	27 - 33	0.25 - 1
<i>Enterococcus faecalis</i>	29212	NR	2 - 8
<i>Staphylococcus aureus</i>	29213	NR	0.03 - 0.125
<i>Haemophilus influenzae</i> *	49247	20 - 28	0.06 - 0.25
<i>Escherichia coli</i>	25922	28 - 34	0.0008 - 0.03
<i>Bacteroides fragilis</i> **	25285	NR	0.6 - 0.25
<i>Bacteroides thetaiotaomicron</i> **	29741	NR	0.125 - 0.5
<i>Eubacterium lentum</i> **	43055	NR	0.125 - 0.5

NR Not Reported

* Media lot variation may occasionally increase MICs twofold

** Anaerobic bacteria, agar dilution method used for MIC

PHARMACOLOGY

Animal Pharmacology

Meropenem failed to cause any changes of biological significance in the following series of general pharmacology tests.

Autonomic Pharmacology *In Vitro*

In vitro data suggest that meropenem does not possess potent histaminergic, acetylcholinergic, alpha-adrenergic or beta-adrenergic activity when tested at 1×10^{-3} M. A weak increase in resting tone was observed in the rat fundic strip indicating a possibility of 5-hydroxytryptaminergic activity.

Sympathetic Function *In Vivo*

Single intravenous administrations of meropenem (300 mg/kg) to anaesthetized cats produced weak effects of short duration on the nictitating membrane. This suggested weak sympatholytic activity which would account for the transient fall in blood pressure observed.

Gastrointestinal Pharmacology

No effect upon gastrointestinal motility was seen in mice following a single intravenous administration of meropenem (300 mg/kg).

Intravenous administration (one dose of 100 mg/kg) to male beagle dogs (with Heidenhain pouches) had no effect on stimulated gastric acid secretion and is therefore unlikely to cause acid hypersecretion.

Cardiovascular Function

In conscious male beagle dogs, a single intravenous dose of meropenem (300 mg/kg) did not produce significant changes in blood pressure, heart rate, ECG (P-R interval), cardiac output, central venous pressure or total peripheral resistance. Cardiac force decreased slightly but this was thought not to have any biological significance. No behavioural side effects were noted in this study.

Intravenous dosing at 300 mg/kg on two consecutive days to spontaneously hypertensive rats did not produce significant changes in blood pressure or heart rate on day 1. On day 2, a fall in mean arterial blood pressure, which was of borderline significance, was seen 2 hours after dosing. The effect was not seen at further time points and was thought to be biologically insignificant.

Renal Pharmacology

In fasted male rats, orally loaded with physiological saline, a single intravenous dose of meropenem (300 mg/kg) did not cause diuretic or natriuretic activity or biologically significant changes in urinary chloride or potassium levels. Hence, there was no evidence of effect upon the renal function of the rat.

However, chronic administration of meropenem was associated with increased kidney size.

Central Nervous System Pharmacology

Meropenem (given as a single intravenous dose of 300 mg/kg) did not elicit biologically significant changes in central nervous system function in rats or mice. The drug did not modify neuromuscular co-ordination or affect gross behaviour or body temperature. In mice

there was no significant change in sodium barbital-induced sleeping time or in the current required to elicit tonic extensor seizures.

Spontaneous EEG and arousal response in rabbits was unaltered following an intravenous dose of meropenem (1000 mg/kg). Imipenem (300 mg/kg) evoked a response in 4/7 rabbits and cefazolin, dosed at 300 or 1000 mg/kg, evoked responses in 1/7 and 6/7 rabbits, respectively.

Intravenous administration of a single dose of meropenem (50 to 400 mg/kg) to mice failed to elicit any biologically significant potentiation of metrazole-induced convulsions. Conversely, imipenem alone (200 mg/kg) or in combination with cilastatin (400 mg/kg + 400 mg/kg), did produce a significant potentiation of seizures ($p < 0.05$).

Metabolic Homeostasis

A single intravenous administration of meropenem (100 or 300 mg/kg) to rabbits did not cause biologically significant changes in glucose metabolism or lipid metabolism where triglycerides, phospholipids or cholesterol were involved. A decrease in free fatty acid metabolism was recorded in animals given 300 mg/kg; the change was not statistically significant.

Hemostasis

In male rats, dosed intravenously (once) with meropenem (300 mg/kg), there was no significant effect on platelet aggregation.

Meropenem (3×10^{-3} M) did not have any influence on rabbit platelet aggregation in the presence of added adenosine diphosphate (ADP) or collagen.

There was no change in prothrombin time in beagle dogs dosed daily with meropenem (21 and 70 mg/kg, intravenously for 14 days). Changes were observed in values for partial-thromboplastin-time-with-kaolin on days 5 and 14 in animals dosed at 70 mg/kg. These changes were small and similar to variations seen pre-dosing.

A single intravenous administration of meropenem (up to 300 mg/kg) to rabbits had no influence on recalcification time, prothrombin time, activated partial thromboplastin time or thrombin time.

Meropenem (3×10^{-3} M or 3×10^{-4} M) did not cause haemolysis of rat blood.

Respiratory Function

Single doses of meropenem (up to 300 mg/kg, intravenously), had no significant effect on airway resistance, dynamic compliance or histamine induced bronchoconstriction in guinea pigs.

Immune Function

Meropenem (300 mg/kg, given intravenously on each of eight days) showed no immunosuppressive properties in mice sensitized with oxazalone.

Human Pharmacology

Pharmacokinetics

The pharmacokinetics of meropenem are typical of those parenteral β -lactam antibiotics that have low protein binding and predominantly renal excretion.

Meropenem shows biexponential pharmacokinetics after intravenous administration in healthy adult volunteers with normal renal function. There is a rapid distribution phase followed by a terminal elimination phase with a half-life ($t_{1/2}$) of approximately 1 hour. The Pharmacokinetic parameters following three doses of meropenem are shown in Table 5 (see also Figure 1 in ACTIONS AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

Table 5 Pharmacokinetic Parameters of Meropenem in Healthy Volunteers Following a Single Intravenous Infusion Over 30 Minutes

Dose (mg)	C_{max} (µg/mL)	AUC_∞ (µg.h/mL)	t_{1/2} (h)	Volume of Distribution Steady State V_{ss} (L)	Plasma Clearance Cl_p (mL/min)	Renal Clearance (mL/min/kg)	Urinary Recovery (% dose)
500	22.5 (21)	27.1 (15)	0.97 (13)	20.2 (16)	314 (15)	3.05 (20)	73.0 (12)
1,000	48.6 (16)	60.8 (16)	0.96 (14)	18.9 (10)	280 (16)	2.52 (15)	69.0 (6)
2,000	115 (20)	153 (15)	1.18 (8)	15.8 (20)	205 (18)	1.73 (12)	65.4 (18)

mean (coefficient of variation)

The area under the serum concentration time curve (AUC) of meropenem increases approximately 11-fold over the dose range of 250 mg to 2 g. There are no marked changes in the pharmacokinetic parameters. However, there is a reduction in renal clearance with higher doses probably due to the saturation of tubular clearance. These changes in kinetic parameters are not important in otherwise healthy adults.

There were no important changes in the pharmacokinetics of meropenem when administered as a 5 minute infusion, compared with a 30 minute infusion. Peak plasma concentrations of meropenem were doubled after the bolus infusion, but from 1 hour after dosing, plasma concentrations for both rates of administration were similar.

After multiple dose administration in healthy subjects, there was no accumulation of meropenem and no change in the pharmacokinetics of meropenem as a consequence of repeated administration (Table 6).

Table 6 Pharmacokinetic Parameters of Meropenem in Healthy Volunteers Following Multiple Dose (1000 mg) Intravenous Infusions*

Day	C_{max} (µg/mL)	AUC_∞ (µg.h/mL)	t_½ (h)	Plasma Clearance (Cl_p) (mL/min)	Urinary Recovery (% dose)
1	42.4 (13)	71.6 (15)	0.96 (9)	227 (14)	59.4 (6)
4	34.1 (57)	60.4 (25)	0.48 (23)	293 (29)	62.6 (21)
7	40.5 (14)	61.3 (17)	1.11 (32)	279 (17)	53.2 (19)

mean (coefficient of variation)

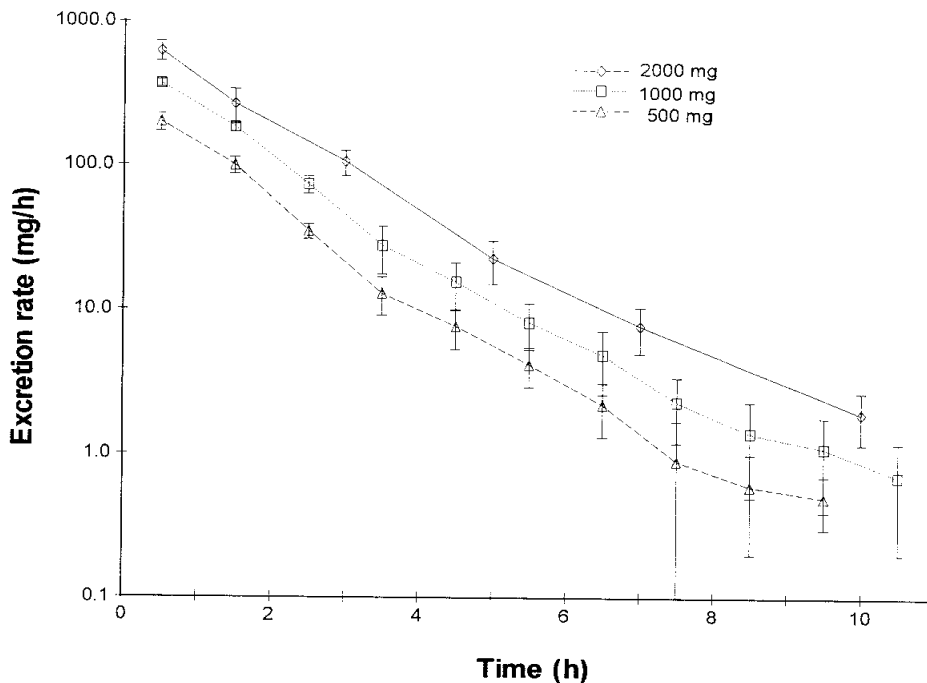
*25 infusions over 60 min at intervals of 6 h for 7 days

Metabolism and Excretion

Meropenem is cleared predominantly by renal excretion, with a combination of glomerular filtration and active tubular secretion.

In vitro studies demonstrate that meropenem is stable to human renal dehydropeptidase. This finding is supported by the urinary excretion of meropenem which is typically 60% to 70% of the administered dose. Thus, there is no requirement to coadminister an inhibitor of dehydropeptidase-1 with meropenem (Fig. 2).

Figure 2 Meropenem Urinary Excretion Profiles (mean \pm SD) After Intravenous Infusion



Meropenem plasma protein binding is low, approximately 2%. Therefore the renal filtration rate should approximate the glomerular filtration rate (GFR). However, renal clearance values are generally in excess of the measured or calculated value for GFR: the difference is due to active tubular secretion of meropenem.

The hydrolysis of the β -lactam bond can occur either chemically in solution or biologically under the influence of enzymes. The reduction in the non-renal clearance of meropenem that occurs as renal function declines suggests that the kidney may be a site of metabolism. The trend to reduction in the non-renal clearance of meropenem seen when meropenem was coadministered with probenecid implies that the proximal renal tubule may be involved in the metabolism of meropenem.

The only identified metabolite of meropenem is ICI 213,689 which is produced by hydrolysis of the β -lactam bond and is bacteriologically inactive. In healthy subjects, the apparent elimination half-life of ICI 213,689 was longer than that of meropenem at approximately 2.3 hours (range 1.8 to 2.8 hours). The AUC for ICI 213,689 was approximately 10% of the AUC for meropenem, showing that exposure to the circulating metabolite is small in subjects with normal renal function.

The administration of probenecid with meropenem did not alter the urinary half-life of ICI 213,689. Exposure to ICI 213,689 does not appear to change on repeated meropenem administration and there are no major changes in the excretion of ICI 213,689 after repeated meropenem administration in persons with normal renal function.

The metabolism and excretion of meropenem were studied by means of administration of [¹⁴C]-labelled meropenem. Radioactivity was very rapidly excreted with 95.4% of the dose recovered in the urine at 8 hours after dosing. This rapid excretion is consistent with the observed lack of accumulation on multiple dosing. Overall, 99.0% of the dose was recovered in the urine, with an additional 2.1% recovered in the feces.

Multiple dosing with meropenem in normal volunteers caused increases, decreases or no change in the fecal flora, depending on the organism. Changes were small and were reversed after cessation of meropenem administration. Meropenem is present in bile at concentrations of up to 25 µg/mL. This biliary excretion of a small proportion of the dose as active antibiotic could account for both the minor disturbance of fecal flora and the fecal recovery of radioactivity.

Factors Affecting Pharmacokinetics

Age (Infants and Children)

The pharmacokinetics of meropenem in infants and children are similar to those of adults, except that the half-life is approximately double to 1.75 hours in the youngest age group (3 to 5 months). The prolongation of half-life and increased volume of distribution of meropenem in the younger subjects is consistent with the reduced renal function and increased extracellular fluid volume in infants of this age. An 8-hours dosing interval is considered acceptable even in the 3 to 5 month age group (Table 7).

In general, meropenem dosing on a mg/kg basis is appropriate in infants and children. Doses of 10, 20, and 40 mg/kg in infants and children produce peak plasma concentrations and AUC values similar to those seen in healthy adult volunteers after 500 mg, 1 g, and 2 g doses, respectively.

Table 7 Pharmacokinetic Parameters of Meropenem in Children

Age	Dose (mg/kg)	C_{max} (µg/mL)	AUC_∞ (µg.h/mL)	t_½ (h)	Volume of Distribution (V_{ss})* (L/kg)	Plasma Clearance (Cl_p)* (mL/min/kg)	Urinary Recovery (% dose)
3-5 Months	10	26.3 (18)	38.8 (30)	1.4 (31)	0.401 (10)	4.6 (35)	64.9 (15)
	20	53.4 (33)	90.0 (29)	1.7 (30)	0.449 (12)	4.0 (30)	37.5 no CV %
	40	125 (48)	228 (80)	2.3 (59)	0.480 (24)	4.3 (8)	21.6 no CV %
6-23 Months	10	28.8 (33)	34.9 (56)	1.1 (49)	0.358 (33)	5.7 (37)	62.8 (31)
	20	64.0 (25)	75.0 (24)	1.3 (37)	0.356 (29)	4.3 (34)	47.4 (29)

Table 7 Pharmacokinetic Parameters of Meropenem in Children

Age	Dose (mg/kg)	C _{max} (µg/mL)	AUC _∞ (µg.h/mL)	t _{1/2} (h)	Volume of Distribution (V _{ss})* (L/kg)	Plasma Clearance (Cl _p)* (mL/min/kg)	Urinary Recovery (% dose)
2-5 Years	40	84.9 (21)	122 (27)	1.5 (35)	0.524 (18)	5.8 (26)	39.6 (62)
	10	29.2 (28)	33.1 (24)	1.1 (35)	0.353 (23)	5.3 (29)	54.5 (24)
	20	51.6 (18)	60.6 (22)	1.0 (4)	0.375 (16)	5.8 (24)	55.3 (16)
6-12 Years	40	79.0 (18)	91.9 (27)	1.1 (47)	0.501 (31)	7.7 (28)	52.6 (32)
	10	32.1 (40)	35.3 (50)	0.9 (30)	0.314 (23)	5.7 (39)	67.2 (7)
	20	58.6 (29)	64.4 (38)	0.8 (43)	0.315 (22)	6.3 (42)	60.4 (10)
	40	79.7 (7)	93.0 (19)	1.0 (24)	0.414 (16)	6.4 (8)	50.3 (12)

mean (coefficient of variation)

* V_{ss}, Cl_p normalized for body weight

Age (Elderly)

In the elderly, there are changes in the pharmacokinetics of meropenem and ICI 213,689 that reflect the age-associated reduction in renal function (Table 8). Dosage reduction, dependent upon renal function, may be necessary.

Table 8 Comparison of Pharmacokinetic Parameters Between Healthy Elderly and Healthy Younger Patients (500 mg infused over 30 min)

Patients (age, years)	Creatinine Clearance (mL/min)	GFR* (mL/min)	C _{max} (µg/mL)	AUC _∞ (µg.h/mL)	t _{1/2} (h)	Volume of Distribution at Steady State (L)	Urinary Recovery (% dose)	Renal Clearance Cl _r (mL/min/kg)
Young (10)	120 (7)	99 (15)	35.6 (17)	39.5 (12)	0.81 (20)	13.8	68.2 (12)	2.18 (20-35) (20)
Elderly (65-80)	68 (17)	72 (17)	37.0 (17)	58.3 (17)	1.29 (14)	14.5 (17)	67.3 (7)	1.51 (11)

mean (coefficient of variation)

* glomerular filtration rate

Impaired Renal Function

Meropenem is excreted predominantly by the kidney and changes in renal function alter meropenem pharmacokinetics.

The reduction in meropenem clearance correlates well with creatinine clearance and is consistent across studies. Even in renally impaired subjects, there is no alteration in the pharmacokinetics of meropenem due to multiple dosing, when it is dosed appropriately. The metabolite accumulates with repeated doses: the clinical importance of this observation is unknown. The physiological reduction in renal function due to age and renal impairment due to disease produce a similar effect on the clearance of meropenem (Table 9).

Table 9 Pharmacokinetic Parameters for Meropenem in Patients With Renal Insufficiency

Creatinine Clearance (mL/min)	Dose (g)	Dosing Interval (h)	C_{max} (µg/mL)	AUC_∞ (µg.h/mL)	t_½ (h)	Renal Clearance Clr (mL/min/kg)	Urinary Recovery (% dose)
<u>Day 1</u>							
51-70	1	8	60.9 (25)	115 (21)	1.59 (26)	1.05 (29)	58.1 (18)
26-50	1	12	75.9 (22)	207 (27)	2.12 (29)	0.53 (62)	55.1 (36)
10-25	0.5	12	32.0 (34)	143 (17)	4.61 (33)	0.20 (33)	32.1 (52)
0	0.5	24	41.0 (28)	320 (30)	6.56 (16)		
<u>Day 4</u>							
51-70	1	8	60.0 (31)	115 (23)	1.45 (23)	0.69 (81)	nd
26-50	1	12	90.6 (32)	229 (31)	2.33 (27)	0.37 (36)	nd
10-25	0.5	12	40.6 (25)	188 (34)	4.87 (30)	0.19 (41)	nd
0	0.5	24	50.7 (38)	306 (26)	7.04 (54)		

mean (coefficient of variation); nd not determined

Tissue Concentrations

Meropenem penetrates into body tissues in sufficient concentrations to treat most commonly occurring pathogens at the principal sites of infection.

Table 10 Meropenem Concentrations in Selected Tissues or Body Fluids (Highest Concentrations Reported)

Tissue	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 - 20.0
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

* at 1 hour unless otherwise noted mean (coefficient of variation)

** in children of age 5 months to 8 years

*** in children of age 1 month to 15 years

TOXICOLOGY

Acute Toxicity

Species	Sex	LD ₅₀ (mg/kg IV)	95% Confidence Interval
Mouse	M	2650	2190 – 3210
Mouse	F	2950	2460 - 3540
Rat	M	2850	2550 – 3190
Rat	F	3200	2670 - 3840
Rabbit	F	>400	
Dog	M/F	approx. 2000	

Short-term Toxicity

Groups of six male and six female Alpk:APfSD (Wistar derived) rats were administered meropenem in a dose of 250 mg/kg/day intravenously for 28 days and no important effects were observed on body weight gain, food consumption, hematology, blood chemistry and compound-related pathology. Groups of 12 male and female Alpk:APfSD rats were administered meropenem at doses of 120, 240 and 1000 mg/kg/day intravenously for three months. At 1000 mg/kg/day, reduced body weight, minimal reversible degenerative changes in the kidney and an increase in relative adrenal weight were observed. Groups of 3 male and 3 female Beagle dogs were administered meropenem at doses of 120, 240 and 500 mg/kg/day intravenously for three months. Slight reduction in red cell indices, associated with a small increase in red cell osmotic fragility in the absence of effects on deformability occurred at 500 mg/kg/day. This was not associated with morphological changes. Increases in plasma alkaline phosphatase, triglycerides and relative kidney weight occurred at 240 and 500 mg/kg/day.

Long-term Toxicity

Groups of 24 male and 24 female Alpk:APfSD rats were administered meropenem at doses of 60, 240 and 1000 mg/kg/day for 6 months. Decreases in ovary weight and increases in adrenal, caecum and spleen weight and ALT occurred at all doses. Clinical observations and decreases in AST occurred at 1000 mg/kg/day. These changes were associated with either changes in the immune activity or microbial status of the animals due to the antibiotic activity of meropenem and the tissue damage and inflammation resulting from the repeated intravenous route of administration over the six month period. Groups of either three or four Beagle dogs were administered meropenem at a dose of 1, 20, 60, 240 or 500 mg/kg/day for 6 months. Increases in liver weight and serum alkaline phosphatase occurred at doses over 20 mg/kg/day; however, no pathological changes or functional abnormalities were observed.

Reproductive Toxicity

Fertility Studies

Four groups of 22 male and 22 female Alpk:APfSD rats were administered meropenem at doses of 0, 240, 500 or 1000 mg/kg/day intravenously. Males were exposed for 11 weeks prior to and throughout the pairing period. Females were exposed for two weeks prior to pairing through to day eight of pregnancy. There was no effect on mating, pregnancy or fetal viability.

Pregnant animals, dosed on two consecutive days at 300 mg/kg, showed normal weight gain with no evidence of abnormal vaginal cytology or bleeding. The fertility of the rats was unaffected. One dead foetus was found in a total of 55 suggesting that the drug had no abortifacient effect. Four days of dosing to males failed to produce significant changes in seminal vesicle weights at necropsy on day five.

Teratology Studies

Four groups of 36 mated female Alpk:APfSD rats were dosed on days 6 - 17 of pregnancy with 0, 240, 500 or 750 mg/kg/day of meropenem, intravenously. Twenty-four were killed on day 20 of pregnancy and the remaining littered and reared their young to day 21 postpartum. There was no evidence of embryotoxicity or teratogenicity and no effects on the functional ability of F1 generation animals.

The teratogenic potential of meropenem in the rabbit could not be studied because of severe diarrhea therefore the Cynomolgous monkey was used as an alternative species. Four groups of 12-16 female monkeys received meropenem at doses of 0, 120, 240 or 360 mg/kg/day, intravenously, from day 20 to 50 post coitum. One skeletal malformation in one foetus at 360 mg/kg, involving proximal fusion of the first and second rib on the left side, was considered to be incidental. There was no evidence of maternal toxicity, embryo toxicity or teratogenicity. Meropenem was shown to cross the placenta.

Perinatal and Postnatal Studies

Four groups of 22 mated, female rats were dosed from days 17 of pregnancy through to day 21 of lactation with 0, 240, 500 and 1000 mg/kg/day of meropenem, intravenously. All females were allowed to litter and rear their young until day 21 postpartum.

Twenty-two male and female offspring per group were selected on day 35 postpartum and retained for F1 cross. All F1 female uterine contents were examined on day 20 of pregnancy. There was a reduction in food consumption during pregnancy in the F0 females from all dose groups and an increase in body weight gain during lactation in the F0 females given 500 and 1000 mg/kg/day only. There was a reduction in body weights during maturation in the F1 females that were offspring of the group given 1000 mg/kg/day. There were no effects on successful pregnancy, parturition or lactation of the F0 dams or the survival behaviour or reproductive performance of the F1 generation.

Mutagenicity Studies

No evidence of mutagenic potential was found in any of the five tests conducted: reverse mutation and induced mutation frequency tests in *S. typhimurium* and *E. coli*, gene mutation in cultured mammalian cells, *in vitro* cytogenetics and the micronucleus test in mice. All *in vitro* studies were conducted with and without a metabolic activation system (S-9). All doses were the highest possible based on preliminary studies except for the micronucleus test which was conducted up to a dose which was lethal in acute toxicity studies (up to 2500 mg/kg intravenously).

Immunogenic and Allergic Potential

Immunogenic and allergenic potential is a characteristic of β -lactam antibiotics. Tests of immunogenic potential have demonstrated that meropenem does not induce IgE anaphylaxis-inducing antibodies although IgG antibody production was forced by concomitant administration of Freund's complete adjuvant. There is consistency in the production of IgG antibodies under these conditions in studies in rabbits and guinea pigs. A lack of response in the passive cutaneous anaphylaxis test in guinea pigs may be due to the different induction regime employed. The induction of IgG by meropenem and cross-reactivity (in studies with synthetic protein conjugates), is similar to that found with other antibiotics. Meropenem has a weak allergenic potential and showed no contact sensitization.

As decomposition products of some antibiotics have an immunogenic potential, "aged" formulations of meropenem reconstituted in water (24h in solution at 25°C) were examined. As with fresh meropenem, IgG antibody production was demonstrated in the PHA (Phytohemagglutinin) test and there were no reactions in the active systemic anaphylaxis or passive cutaneous tests.

Nephrotoxic Potential

No tubular necrosis was caused by meropenem in acute rabbit studies or in six month studies with rats and dogs or after co-administration with furosemide/glycerol to rats. There was mild/moderate fat accumulation and mild tubular necrosis in the *Cynomolgus* monkey at 500 mg/kg but there was no histological change at 180 mg/kg of meropenem.

BIBLIOGRAPHY

General

Chanal C, Sirot D, Chanal M, Cluzel M, Sirot J, Cluzel R. Comparative in-vitro activity of meropenem against clinical isolates including Enterobacteriaceae with expanded-spectrum β -lactamases. *J Antimicrob Chemother* 1989;24(Suppl A):133-141.

Chimata M, Nagase M, Suzuki Y, Shimomura M, Kakuta S. Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. *Antimicrob Agents Chemother* 1993;37:229-233.

Clarke AM, Zemcov SJV. In-vitro activity of meropenem against clinical isolates obtained in Canada. *J Antimicrob Chemother* 1989;23(Suppl A):47-56.

Condon RE, Walker AP, Sirinek KR, White PW, Fabian TC, Nichols RL, Wilson SE. Meropenem versus tobramycin plus clindamycin for treatment of intraabdominal infections: results of a prospective, randomized, double-blind clinical trial. *Clin Inf Dis* 1995;21:544-550.

Cox, CE, Holloway WJ, Geckler RW. A multicenter comparative study of meropenem and imipenem/cilastatin in the treatment of complicated urinary tract infections in hospitalized patients. *Clin Inf Dis* 1995;21:86-92.

Edwards JR. Meropenem: a microbiological overview. *J Antimicrob Chemother* 1995;36(Suppl A):1-17.

Edwards JR, Turner PJ, Wannop C, Withnell ES, Grindey AJ, Nairn K. In-vitro antimicrobial activity of SM-7338, a carbapenem antibiotic with stability to dehydropeptidase I. *Antimicrob Agents Chemother* 1989;33:215-222.

Edwards JR, Williams S, Nairn K. Therapeutic activity of meropenem in experimental infections. *J Antimicrob Chemother* 1989;24(Suppl A):279-285.

Ferrara A, Grassi G, Grassi FA, Piccioni PD, Gialdroni Grassi G. Bactericidal activity of meropenem and interactions with other antibiotics. *J Antimicrob Chemother* 1989;24(Suppl A):239-250.

Garcia-Rodriguez JA, Garcia Sanchez JE, Trujillano I, Sanchez de San Lorenzo A. Meropenem in-vitro activity and kinetics of activity against organisms of the *Bacteroides fragilis* group. *J Antimicrob Chemother* 1991;27:599-606.

Geroulanos SJ. Meropenem versus imipenem/cilastatin in intra-abdominal infections requiring surgery. *J Antimicrob Chemother* 1995;36(Suppl A):191-205.

Granai F, Smart HL, Triger DR. A study of the penetration of meropenem into bile using endoscopic retrograde cholangiography. *J Antimicrob Chemother* 1992;29:711-718.

Hamacher J, Vogel F, Lichey J, Kohl FV, Diwok K, Wendel H, Lode H. Treatment of acute bacterial exacerbations of chronic obstructive pulmonary disease in hospitalised patients - a comparison of meropenem and imipenem/cilastatin. *J Antimicrob Chemother* 1995;36(Suppl A):121-133.

Huizinga WKJ, Warren BL, Baker LW, Valleur P, Pezet, Hoogkamp-korstanjep JAA, Karran SJ. Antibiotic monotherapy with meropenem in the surgical management of intra-abdominal infections. *J Antimicrob Chemother* 1995;36(Suppl A):179-189.

Jones RN, Aldridge KE, Allen SD, Barry AL, Fuchs PC, Gerlach EH, Pfaller MA. Multicenter in-vitro evaluation of SM-7338, a new carbapenem. *Antimicrob Agents Chemother* 1989;33:562-565.

Jorgensen JH, Maher LA, Howell AW. Activity of a new carbapenem antibiotic, meropenem, against *Haemophilus influenzae* strains with β -lactamase and non-enzyme-mediated resistance to ampicillin. *Antimicrob Agents Chemother* 1991;35:600-602.

Jorgensen JH, Maher LA, Howell AW. Comparative activity of meropenem and other contemporary antibiotics against antibiotic resistant or infrequently encountered Gram negative bacilli. *Antimicrob Agents Chemother* 1991;35:2410-2414.

Kanellakopoulou K, Giamarellou H, Papadothomakos P, Tsipras H, Chloroyiannis J, Theakou R, Sfikakis P. Meropenem versus imipenem/cilastatin in the treatment of intraabdominal infections requiring surgery. *Eur J Clin Microbiol Infect Dis* 1993;12:449-453.

Kayser FH, Morenzoni G, Strassle A, Hadorn K. Activity of meropenem against Gram-positive bacteria. *J Antimicrob Chemother* 1989;24(Suppl A):101-112.

Labia R, Morand A, Tiwari K, Sirot D, Chanal C. Interactions of meropenem with β -lactamases, including new enzymes with extended-spectrum activity against third-generation cephalosporins. *J Antimicrob Chemother*;1989;24(Suppl A):219-223.

Moellering RC, Eliopoulos GM, Sentochnik DE. The carbapenems: new broad spectrum beta-lactam antibiotics. *J Antimicrob Chemother* 1989;24(Suppl A):1-7.

Mouton YJ, Beuscart. Empirical monotherapy with meropenem in serious bacterial infections. *J Antimicrob Chemother* 1995;36(Suppl A):145-156.

Mouton JW, Michel MF. Pharmacokinetics of meropenem in serum and suction blister fluid during continuous and intermittent infusion. *J Antimicrob Chemother* 1991;28:911-918.

Nadler H, Pitkin DH, Sheikh W. The postantibiotic effect of meropenem and imipenem on selected bacteria. *J Antimicrob Chemother* 1989;24(Suppl A):225-231.

Nichols RL, Smith JW, Geckler RW, Wilson SE. Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. *Southern Med J* 1995;88:397-404.

Norrby SR, Newell PA, Faulkner KL, Lesky W. Safety profile of meropenem: international clinical experience based on the first 3125 patients treated with meropenem. *J Antimicrob Chemother* 1995;36 (Suppl A):207-223.

Odenholt-Tornqvist, I. Studies on the postantibiotic sub-MIC effect of meropenem. *J Antimicrob Chemother* 1993;31:881-892.

Powell M, Seetulsingh P, Williams JD. In-vitro susceptibility of *Haemophilus influenzae* to meropenem compared with imipenem, five other β -lactams, chloramphenicol and ciprofloxacin. *J Antimicrob Chemother* 1989;24(Suppl A):175-181.

Romanelli G, Cravarezza P, Ragni G, Franchino L. Meropenem IV in lower respiratory tract infections: a multicenter study. *Farmacia & Terapia* 1995;12:1-9.

Sanders CC, Sanders Jr WE, Thompson KS, Iaconis JP. Meropenem: activity against resistant Gram-negative bacteria and interactions with β -lactamases. *J Antimicrob Chemother* 1989;24(Suppl A):187-196.

Schmutzhard E, Williams KJ, Vukmirovits G, Chmelik V, Pfausler B, Featherstone A. A randomised comparison of meropenem with cefotaxime or ceftriaxone for the treatment of bacterial meningitis in adults. *J Antimicrob Chemother* 1995;36(Suppl A):85-97.

Sentochnik DE, Eliopoulos GM, Ferraro MJ, Moellering Jr RC. Comparative in-vitro activity of SM-7338, a new carbapenem antimicrobial agent. *Antimicrob Agents Chemother* 1989;33:1232-1235.

Solberg CO, Sjursten H. Safety and efficacy of meropenem in patients with septicaemia: a randomised comparison with ceftazidime, alone or combined with amikacin. *J Antimicrob Chemother* 1995;36(Suppl A):157-166.

Wiseman LR, Wagstaff AJ, Brogden RN, Bryson HM. Meropenem: A review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1995;50:73-101.

Yourassowsky E, Van der Linden MP, Lismont MJ, Crokaert F. Bactericidal activity of meropenem against *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 1989;24(Suppl A):169-174.

Yourassowsky E, Van der Linden MP, Crokaert F. Antibacterial effect of meropenem and imipenem on *Proteus mirabilis*. *J Antimicrob Chemother* 1990;26:185-192.

Pediatrics

Klugman KP, Dagan R. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. *Antimicrob Agents and Chemother* 1995;1140-1146.

Parker EM, Hutchison M, Blumer JL. The pharmacokinetics of meropenem in infants and children: a population analysis. *J Antimicrob Chemother* 1995;36(Suppl A):63-71.

Schuler D. Safety and efficacy of meropenem in hospitalised children: randomized comparison with cefotaxime, alone and combined with metronidazole or amikacin. *J Antimicrob Chemother* 1995;36(Suppl A): 99-108.