Merodel 1 MG (Pack Insert)

℞

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

MEROPENEM INJECTION I.P.

MERODEL

For Intravenous Use Only

DESCRIPTION

MERODEL (Meropenem Injection I.P.) 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 $C_{17}H_{25}N_3O_5S3H_2O$ with a molecular weight of 437.52.

MERODEL 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, Each 1 g MERODEL vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq).

Each 500 mg of MERODEL vial will deliver 500 mg of meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).

Each 250 mg of MERODEL vial will deliver 250 mg of meropenem and 22.55 mg of sodium as sodium carbonate (0.98 mEq).

Each 125 mg of MERODEL vial will deliver 125 mg of meropenem and 11.275 mg of sodium as sodium carbonate (0.49 mEq).

INDICATIONS

MERODEL 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. thetaiotamicron and *Peptostreptococcus* species.

Bacterial Meningitis

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

Penicillin-resistant strains have not been studied in clinical trials.

MERODEL has been found to be effective in eliminating concurrent bacteremia in association with bacteria meningitis.

MERODEL 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.

RECONSTITUTION

For intravenous Bolus Administration

Constitute injection vials (125 mg, 250 mg, 500 mg & 1000 mg) with sterile water for injection. (see table below). Shake to dissolve and let stand until clear.

Vial Size	Amount of Diluent Added	Approximate Average Concentration (mg/mL)
125 mg	2.5 mL	50
250 mg	5 mL	50
500 mg	10 mL	50
1000 mg	20 mL	50

For Infusion: Constitute the injection vial with a compatible infusion fluid. Add the resulting solution to an I.V. Container and further dilute it with an appropriate infusion fluid.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of Merodel is 500 mg given every 8 hours for skin and skin structure infections and 1 gram given every 8 hours for intra-abdominal infections. When treating complicated skin and skin structure infections caused by P. aeruginosa, a dose of 1 gram every 8 hours is recommended.

Merodel should be administered by intravenous infusion over approximately 15 minutes to 30 minutes. Doses of 1 gram may also be administered as an intravenous bolus injection (5 mL to 20 mL) over approximately 3 minutes to 5 minutes.

Recommended MERODEL Dosage Schedule for Adults with Impaired Renal Function.

Creatinine Clearance (mL/min)	Dose (dependent on type of infection)	Dosing Interval
25-50	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 the serum creatinine is available, the following formula may be used to estimate the creatinine clearance.

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 MERODEL in patients on hemodialysis. There is no experience with the 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 the elderly patients with creatinine clearance values above 50 mL/min.

Use in Pediatric Patients: For the pediatric patients from 3 months of age and older, the MERODEL 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). Pediatric patients weighing over 50 kg should be administered. MERODEL at a dose of 1 g every 8 hours for intra-abdominal infections and 2 g every 8 hours for meningitis. MERODEL should be given similarly as in adults by intravenous infusion. There is no experience in pediatric patients with renal impairment.

CLINICAL PHARMACOLOGY

At the end of a 30 minute intravenous infusion of a single dose of MERODEL in normal volunteers, mean peak plasma concentrations are approximately 23 µg/mL (range14-26) for the 500 mg dose and 49 µg/mL (range39-58) for the 1 g dose. A 5-minute intravenous bolus injection of MERODEL in normal volunteers results in mean peak plasma concentrations of approximately 45 µg/mL (range18-65) for the 500mg dose and 112 µg/mL (range 83-140) for the 1 g dose. Following intravenous doses of 500mg, mean plasma concentrations of the meropenem usually decline to approximately 1 µg/mL at 6 hours after administration.

In subjects with normal renal function, the elimination half-life of MERODEL 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 grams administered every 6 hours in volunteers with normal renal function. Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid, achieving concentrations matching or exceeding those require to inhibit most susceptible bacteria.

The pharmacokinetics of MERODEL in pediatric patients 2 years of age or older is essentially similar to those in adults. The elimination half-life for meropenem was approximately 1.5 hours in pediatric patients of age 3 month to 2 years. The pharmacokinetic are linear over the dose range from 10 to 40 mg/kg.

Pharmacokinetics studies with MERODEL in patients with renal insufficiency have shown that the plasma clearance of meropenem corelates with creatinine clearance. In elderly patients with renal insufficiency it has been shown a reduction in plasma clearance of meropenem that corelates with age associated reduction in creatinine clearance.

MERODEL is hemodialyzable However, there is no information on the usefulness of hemodialysis to treat over dosage. A pharmacokinetic study with MERODEL in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

SIDE EFFECTS

Adult Patients

Local Adverse Reactions

Local adverse reactions that were reported irrespective of the relationship to therapy with meropenem injection was as follows: Inflammation at the injection site, Phlebitis/thrombophlebitis, Injection site reaction. Pain at the injection site, Edema at the injection site.

Systemic Adverse Reactions

Systemic adverse clinical reactions that were reported irrespective of the relationship to Meropenem injection occurring in greater than 1.0% of the patients were diarrhea (5%), nausea/vomiting (3.9%), headache (2.8%), rash (1.7%), pruritus

(1.6%), apnea (1.2%) and constipation (1.2%).

Additional adverse systematic clinical reactions occuring in less than 1.0% but greater than 0.1% of the patients are listed below within each body system in order of decreasing frequency.

Bleeding events: (Gastrointestinal hemorrhage, melena, epistaxix and hemoperitoneum) occurred in 0.7% of meropenem patients.

Body as a Whole: Pain, abdominal pain, chest pain, sepsis, shock, fever, abdominal enlargement, back pain, hepatic failure.

Cardiovascular: Heart Failure, Heart Arrest, tachycardia, hypertension, myocardial infarction, pulmonary emblous, bradycardia, hypotension, syncope.

Digestive: Oral moniliasis, anorexia, cholestatic jaundice/ jaundice, flatulence, ileus.

Hemic & Lymphatic: Anemia.

Metabolic & Nutritional: Peripheral edema, hypoxia.

Nervous System: Insomnia, agitation/delirium, confusion, dizziness, seizure, nervousness, paresthesia, hallucinations, somnolence, anxiety, depression.

Respiratory: Respiratory disorder, dyspnea.

Skin and Appendages: Urticaria, sweating.

Urogenital: Dysuria, kidney failure.

Adverse Laboratory Changes: Adverse Laboratory changes that were reported irrespective of relationship to meropenem injection occuring 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, prolonged prothrombin time, prolonged partial thromboplastin time, decreased platelets, positive direct or indirect coombs test, decreased hemoglobin, decreased hematocrit, decreased WBC, shortened prothrombin time, and shortened partial thromboplastin time.

Renal: Increased creatinine and increased BUN.

Urinalysis: Presence of urine red blood cells.

Pediatric Patients:

Clinical Adverse Reactions

The Types of clinical adverse events seen in pediatric patients are similar to the adults, with the most common adverse events

reported as possibly, probably, or definitely related to Meropenem injection.

DRUG INTERACTIONS

Probenecid completes 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 Systematic exposure (56%). Therefore, the coadministration of Probenecid with meropenem is not recommended. Other than probenecid no specific drug interaction studies were conducted.

WARNINGS / PRECAUTIONS

Before initiating therapy with MERODEL, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other b-lactams and other allergens. If an allergic reaction to MERODEL occurs, discontinue the drug immediately. Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steriods, and airway management, including intubation. Other therapy may also be administered as indicated.

Psedumembranous 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. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic -associated colitis".

Mild cases of *Psedumembranous colitis* usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and elecrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis*.

Seizures and other CNS adverse experiences have been reported during treatment with MERODEL. All meropenem-treated patients with seizures had preexisting contributing factors. Among these are included prior history of seizures or CNS abnormality and concomitant medications with seizure potential. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus or seizures occur, patients should be evaluated neurologically, place on anticonvulsant therapy if not already instituted, and the dosage of MERODEL 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.

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.

While MERODEL 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.

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. 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.

Pediatrics

The safety and effectiveness of MERODEL have been established for pediatric patients >3 months of age. Use of MERODEL in pediatric patients with bacterial meningitis is supported by evidence from adequate and well-controlled studies in the pediatric population. Use of MERODEL 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.

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 MERODEL is administered to a nursing woman.

OVERDOSE

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

Intentional overdosing of MERODEL 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 safely risks have been observed.

No specific information is available for the treatment of MERODEL overdosage. In the event of an overdose, MERODEL 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.

CONTRAINDICATIONS

MERODEL 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 reaction to beta-lactams.

HOW SUPPLIED

MERODEL is supplied in 5 mL, 10 mL, 10 mL and 20 mL injection vials containing sufficient meropenem to deliver 125 mg, 250 mg, 500 mg and 1 g for intravenous administration respectively.

STORAGE

Store below 25ºC. Protect from moisture.

Manufactured by :
VENUS REMEDIES LIMITED
Hill Top Industrial Estate, Jharmajri,
EPIP, Phase-I (Extn.), Bhatoli Kalan, Baddi,
Distt. Solan, Himachal Pradesh-173205, (INDIA)
www.venusremedies.com

Marketed by:
DELIGHT BIOPHARMA PVT LTD
Reg. Off.: 11-10-255/2, Street No.,
Road No. 2, Hyderabad
Corp. Off.: Khasra No. 741, GT Road,
Jamalpur, Roorkee-247667

D50/MM1000/3385-01,
D50/MM500/3409