RM-MEROPENEM TRIHYDRATE Line Insert (Back), V2

Stability in Infusion Vials:

Compatible Diluent	Hours Stable	
	at 15 to 25°C	at 2 to 8°C
Solutions (to provide meropenem concentrations ranging from **2.5 to 50 mg/mL**) prepared with:		
0.9% Sodium Chloride	2	18
5% Dextrose	1	8

Stability in IV Plastic Bags:

Compatible Diluent	Hours Stable	
	at 15 to 25°C	at 2 to 8°C
Solutions (to provide meropenem concentrations ranging from **1 to 20 mg/mL**) prepared with:		
0.9% Sodium Chloride	4	24
5% Dextrose	1	4
10% Dextrose	1	2
5% Dextrose + 0.9% Sodium Chloride	1	2

Stability in Plastic Syringes:

Compatible Diluent	Hours Stable
	at 2 to 8°C
Solutions (to provide meropenem concentrations ranging from **1 to 20 mg/mL**) prepared with:	
Sterile Water for Injection	48
0.9% Sodium Chloride	48

- Compatibility of meropenem with other drugs has not been established.
- Do not mix with or add to solutions containing other drugs.
- It is recommended to use freshly prepared solutions of IV meropenem.
- Do not freeze meropenem solutions.

CONTRAINDICATIONS
Known hypersensitivity reactions to any component of the product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactams.

WARNINGS AND PRECAUTIONS

- HYPERSENSITIVITY REACTIONS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON BETA-LACTAM THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN THOSE WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. A THOROUGH INQUIRY ABOUT THE PATIENT'S PREVIOUS HYPERSENSIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA-LACTAMS, AND OTHER ALLERGENS SHOULD BE MADE BEFORE INITIATING THERAPY WITH MEROPENEM.

  SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. OTHER THERAPY MAY ALSO BE ADMINISTERED AS INDICATED.

- Seizure Potential: Seizures and other adverse CNS experiences have been reported during meropenem therapy, particularly in patients with CNS disorders (e.g., brain lesions or history of seizures), bacterial meningitis, and/or compromised renal function.

  Do not exceed recommended dosage especially in those with known factors that predispose to seizures. Continue anticonvulsant therapy in those with known seizure disorders. If focal tremors, myoclonus, or seizures occur, evaluate the patient neurologically, initiate anticonvulsant therapy if necessary, and determine whether meropenem dosage should be decreased or the drug discontinued.

- Interaction with Valproic Acid: The concomitant use of meropenem and valproic acid or divalproex sodium is generally not recommended.

  Meropenem may reduce serum levels of valproic acid to subtherapeutic levels which can increase patient's predisposition to seizure (see INTERACTIONS WITH OTHER MEDICAMENTS).

- *Clostridium difficile-associated diarrhea (CDAD):* This has been reported with the use of nearly all antibacterial agents, including meropenem, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.

- Sodium Content: Meropenem contains sodium (see FORMULATIONS) which should be taken into consideration when treating patients requiring restricted sodium intake.

Other Precautions

- There is partial cross-allergenicity among beta-lactam antibiotics, including penicillins, cephalosporins, or other beta-lactams.
- Although meropenem has a low toxicity profile, the renal, hepatic, and hematopoietic status of patients undergoing prolonged treatment with the drug should be evaluated periodically.
- Prescribing meropenem in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

- Aminoglycosides: Concomitant administration with aminoglycosides may result in synergistic antibacterial effects against *Pseudomonas aeruginosa.*
- Oral Anticoagulants: Simultaneous administration of antibiotics with warfarin may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the antibiotic to the increase in international normalized ratio (INR) is difficult to assess. It is recommended to frequently monitor the INR during and shortly after concomitant administration.
- Probenecid: Probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem. Concomitant use is not recommended.
- Valproic acid: There have been case reports that concomitant administration of carbapenems, including meropenem, to patients on valproic acid or divalproex sodium results in a reduction (60 to 100%) in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range, therefore increasing the risk of breakthrough seizures. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction.

  Although the mechanism of this interaction is unknown, data from in vitro and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid.

Interference with Laboratory Tests:

- A positive direct or indirect Coombs' test may develop.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: (Pregnancy Category B) There are no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, meropenem should be used during pregnancy only when clearly needed.

Lactation: It is not known whether meropenem is excreted in human milk; thus it should be used with caution in breastfeeding women.

Children: The safety and efficacy of meropenem have not been established in children less than 3 months old.

Elderly: There are no substantial differences in safety and efficacy compared with younger adults. However, since elderly patients are more likely to have decreased renal function, care should be taken in dose selection and renal function should be monitored.

Renal Impairment: Dose adjustment is recommended in patients with creatinine clearance less than 51 mL/min. In patients with renal impairment, thrombocytopenia has been observed but no clinical bleeding has been reported.

Hepatic Impairment: Patients with pre-existing liver disorders should have their liver function monitored during treatment with meropenem.

Effects on Ability to Drive and Use Machines: Patients on meropenem on an outpatient basis may develop adverse events such as seizures, headaches and or paresthesias. Until it is reasonably established that meropenem is well tolerated, patients should be advised to avoid performing tasks which require complete mental alertness such as driving and operating machinery.

UNDESIRABLE EFFECTS
Adverse reactions reported in 1% or more of patients receiving meropenem include gastrointestinal (GI) effects (diarrhea, nausea, vomiting, constipation), local reactions (pain, edema and inflammation at injection site, phlebitis/thrombophlebitis), headache, anemia, rash, pruritus, sepsis, apnea, shock, glossitis, oral candidiasis, and thrombocytosis.

In children, the most common adverse events reported as possibly, probably, or definitely related to meropenem include diarrhea, rash (mostly diaper area moniliasis), nausea, vomiting, oral moniliasis, and glossitis

Additional adverse reactions that were reported irrespective of relationship to meropenem therapy include:
Body as a Whole: Abdominal enlargement, chills, fever, infection, pain (abdominal, back, chest, pelvic)

Hypersensitivity Reactions/Dermatologic: Angioedema, eosinophilia, erythema multiforme, exfoliative dermatitis, manifestations of anaphylaxis, skin ulcer, Stevens-Johnson syndrome, sweating, superinfection, toxic epidermal necrolysis, urticaria

Nervous System: Agitation/delirium, anxiety, asthenia, confusion, depression, dizziness, hallucinations, insomnia, mental disturbances, nervousness, neuropathy, paresthesia, seizure/convulsion, somnolence

Cardiovascular: Bradycardia, heart arrest, heart failure, hypertension, hypotension, myocardial infarction, peripheral vascular disorder, pulmonary embolus, syncope, tachycardia

Gastrointestinal: Anorexia, dyspepsia, flatulence, GI hemorrhage, hemoperitoneum, ileus, intestinal obstruction, melena, pseudomembranous colitis, tooth or tongue discoloration

Metabolic/Nutritional: Hypoglycemia, hypokalemia, hypomagnesemia, hypoxia, peripheral edema

Respiratory: Asthma, increased cough, dyspnea, epistaxis, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder

Genitourinary: Increased creatinine and blood urea nitrogen (BUN); dysuria, urinary incontinence, presence of red blood cells in urinalysis, kidney failure/renal impairment, vaginal candidiasis/moniliasis, vaginitis

For patients with varying degrees of renal impairment, the incidence of heart failure, kidney failure, seizure, and shock reported irrespective of relationship to meropenem increased in patients with moderately severe renal impairment.

Hepatic: Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), gamma-glutamyltransferase, and bilirubin; cholestatic jaundice/jaundice, hepatic failure, hepatitis

Hematologic: Increased platelets, eosinophils; decreased platelets, hemoglobin, hematocrit, white blood cells; abnormal/shortened prothrombin time and partial thromboplastin time; agranulocytosis, anemia, hemolytic anemia, hypervolemia, hypochromic anemia, leukocytosis, leukopenia, neutropenia, positive Coombs' test, thrombocythemia, thrombocytopenia (with bleeding)

Other Adverse Effects: Accidental injury, taste perversion

OVERDOSE AND TREATMENT
Intentional overdosing with meropenem is unlikely, although accidental overdosing might occur particularly in patients with reduced renal function.

The largest dose of meropenem administered in clinical studies involving patients with normal renal function has been 2 g IV given every 8 hours in adults (40 mg/kg body weight every 8 hours in children). No adverse pharmacological effects or increased safety risks were observed at this dosage.

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

No information is available for the treatment of meropenem overdosage. In the event of an overdose, discontinue the drug and give general supportive treatment until renal elimination takes place. Although meropenem is hemodialyzable, there is no information on the usefulness of hemodialysis to treat overdosage.

STORAGE CONDITIONS
Store at temperatures not exceeding 30°C.
Keep the product out of sight and reach of children.

AVAILABILITY
RiteMED® Meropenem Trihydrate Powder for Injection, USP 1g, in Type I clear glass vial. Box of 1's.
RiteMED® Meropenem Trihydrate Powder for Injection, USP 500 mg, in Type I clear glass vial. Box of 1's.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND RiteMED at (+632) 8-726-0835 or e-mail productsafety@ritemed.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by Savior Lifetec Corporation
(Tainan Branch Injection Plant)
4F, No. 12, 16, 8 & 5F, No. 12 Chuangye Rd.
Xinshi Dist. Tainan City 74144, Taiwan
Republic of China
Imported and distributed by RiteMED Phils., Inc.
56 Epifanio Delos Santos Ave., Mandaluyong, Metro Manila

Date of First Authorization: April 2018
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RiteMED® Meropenem 500 mg: DR-XY46320
RiteMED® Meropenem 1 g: DR-XY46321
RTM700105IN02

Reg. IPOPHIL

SIZE : 210 mm X 297 mm

PRINT COLOR
Pantone 2756 C

• *F.A. Revision Date: 26 January 2023*

RM-MEROPENEM TRIHYDRATE Line Insert (Front), V2

RiteMED®

MEROPENEM

500 mg and 1 g Powder for I.V. Injection

ANTIBACTERIAL (Carbapenem)

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FORMULATIONS
Each vial contains:
Meropenem (as trihydrate), USP.....500 mg or 1 g
Sodium carbonate (as excipient)*

**When reconstituted, each Meropenem 500 mg injection contains 45.1 mg sodium as 105.6 mg sodium carbonate (1.96 mEq); each Meropenem 1 g injection contains 90.2 mg sodium as 211.2 mg sodium carbonate (3.92 mEq).*

PRODUCT DESCRIPTION
Meropenem (500 mg or 1 g) is a sterile, pyrogen-free, white to light yellow crystalline powder. When reconstituted, solutions of meropenem range from colorless to yellow.

PHARMACODYNAMICS
Meropenem is a synthetic carbapenem beta-lactam antibiotic that is structurally related to imipenem. It is more stable to renal dehydropeptidase 1 (DHP 1) than imipenem and therefore does not require concomitant administration with a DHP 1 inhibitor such as cilastatin. It has a broad spectrum antibacterial activity. Meropenem is active against Gram-positive, Gram-negative and some anaerobic bacteria. It readily penetrates the bacterial cells and interferes with the synthesis of the peptidoglycan layer, an important structure of the cell wall, which leads to cell death. Meropenem is highly resistant to hydrolysis by a variety of beta-lactamases (including penicillinases, cephalosporinases and extended-spectrum beta-lactamases).

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Meropenem is active against most strains of the following microorganisms both *in vitro* and in clinical infections:

Gram-positive	Gram-negative	Anaerobes
Enterococcus faecalis (vancomycin-susceptible isolates only) *Staphylococcus aureus (methicillin-susceptible isolates only)* *Streptococcus agalactiae* *Streptococcus pneumoniae (Penicillin-susceptible isolates only)* *Viridans group streptococci* *Escherichia coli*	*Haemophilus influenzae* *Klebsiella pneumoniae* *Neisseria meningitidis* *Pseudomonas aeruginosa* *Proteus mirabilis*	*Bacteroides fragilis* *Bacteroides thetaiotaomicron* *Peptostreptococcus spp.*

Meropenem is active *in vitro* against the following microorganisms; however, clinical significance is unknown:

Gram-positive	Anaerobes
Staphylococcus epidermidis (methicillin-susceptible isolates only)	*Bacteroides distasonis* *Bacteroides ovatus* *Bacteroides uniformis* *Bacteroides urealyticus* *Bacteroides vulgatus* *Clostridium difficile* *Clostridium perfringens* *Eubacterium lentum* *Fusobacterium spp.* *Prevotella bivia* *Prevotella intermedia* *Prevotella melaninogenica* *Porphyromonas asaccharolytica* *Propionibacterium acnes*
Gram-negative	
Aeromonas hydrophila *Campylobacter jejuni* *Citrobacter koseri (formerly diversus)* *Citrobacter freundii* *Enterobacter cloacae* *Hafnia alvei* *Klebsiella oxytoca* *Moraxella catarrhalis* *Morganella morganii* *Pasteurella multocida* *Proteus vulgaris* *Serratia marscescens*	

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS
Intravenous (IV) bolus injection of single dose meropenem 500 mg or 1 g over 5 minutes in normal adults results in peak plasma concentrations (C_{max}) of about 50 and 112 mcg/mL, respectively. The same doses infused over a period of 30 minutes produce C_{max} of 23 and 49 mcg/mL, respectively.

Meropenem is distributed into a wide range of body fluids and tissues, including bronchial mucosa, lungs, bile, gynecologic tissue (endometrium, myometrium, ovary, cervix, fallopian tube), muscle, heart valves, skin, interstitial and peritoneal fluids, and cerebrospinal fluid.

Approximately 70% of the IV dose is eliminated in urine as unchanged drug by tubular secretion and glomerular filtration. A further 28% is recovered as the microbiologically inactive metabolite. Plasma protein binding is approximately 2%. Urinary concentration in excess of 10 mcg/mL is maintained for up to 5 hours after a 500 mg dose. No accumulation of meropenem in plasma or urine was observed after 500 mg and 1 g doses administered every 8 and 6 hours, respectively, in adults with normal renal function.

The plasma half-life ($t_{1/2}$) of meropenem is approximately 1 hour in adults with normal renal function and 1.5 hours in children 3 months to 2 years old. Plasma $t_{1/2}$ is increased and clearance is decreased with renal impairment; thus, dosage adjustments are necessary in patients with renal impairment. Hepatic impairment has no effect on the pharmacokinetics of meropenem and therefore no dosing adjustment is necessary.

INDICATIONS
For the treatment of the following infections caused by susceptible microorganisms:
- Skin and skin structure infections
- Intra-abdominal infections (e.g., complicated appendicitis, peritonitis)
- Bacterial meningitis (Note: There is limited adult efficacy data for meropenem in the treatment of bacterial meningitis. Support for meningitis indication in adults is largely provided by pediatric data.)
- Lower respiratory tract infections (e.g., community-acquired pneumonia, healthcare-associated pneumonia), including patients with cystic fibrosis
- Complicated urinary tract infections
- Gynecological infections (e.g., endometritis, pelvic inflammatory disease, postpartum infections)
- Septicemia
- Empiric treatment of patients with febrile neutropenia, used as monotherapy or in combination with other antimicrobial drugs.

DOSAGE AND ADMINISTRATION
» Meropenem is administered by intravenous (IV) bolus injection or IV infusion.
» IV bolus injection (5 to 20 mL) is given over approximately 3 to 5 minutes.
» There are limited safety data available to support the administration of a 2 g dose in adults or a 40 mg/kg body weight in children, as an IV bolus injection.
» IV infusion is given over approximately 15 to 30 minutes.

Usual Adult Dose: 500 mg to 1 g IV every 8 hours, depending on the type and severity of infection, the known or suspected susceptibility of the pathogens and the condition of the patient.

Recommended Dose for Specific Infections in Adults

Infections	Meropenem Adult Dose To be administered IV every 8 hours
Skin and skin structure infections	500 mg
Intra-abdominal infections	1 g
Bacterial meningitis	2 g
Lower respiratory tract infections	
Community-acquired pneumonia	500 mg
Healthcare-associated pneumonia	1 g
In cystic fibrosis	Up to 2 g
Complicated urinary tract infections	500 mg
Gynecological infections	500 mg
Septicemia	1 g
Febrile episodes in neutropenic patients	1 g

» As with other antibiotics, caution may be required in using meropenem as monotherapy in critically ill patients with known or suspected Pseudomonas aeruginosa lower respiratory tract infections.
» When treating infections known or suspected to be caused by P. aeruginosa, a dose of at least 1 g three times a day in adults (maximum approved dose: 6 g/day given in 3 divided doses) is recommended. This dose is based on pharmacokinetic/pharmacodynamic modeling and probability of target attainment simulation for susceptible strains of P. aeruginosa (MIC = 2 mcg/mL).

Adults with Renal Impairment:
The dose of meropenem should be reduced in patients with creatinine clearance less than 51 mL/min.

Creatinine Clearance (mL/min)	Dose (dependent on the type of infection)	Dosing Interval
26 to 50	Usual recommended dose	Every 12 hours
10 to 25	½ usual recommended dose	Every 12 hours
<10	½ usual recommended dose	Every 24 hours

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

There are no established dose recommendations for patients receiving peritoneal dialysis.

When only serum creatinine is available, the following formula may be used to estimate creatinine clearance in adults. Serum creatinine should represent a steady state of renal function:

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

Women: 0.85 x value calculated using the above formula

Usual Pediatric Dose:
Children = 3 months old up to 12 years old (weighing = 50 kg): 10 to 40 mg/kg body weight every 8 hours, depending on the type and severity of infection, known or suspected susceptibility of the pathogens and condition of the patient (see table below).

Recommended Dose for Specific Infections in Children:

Infections	Meropenem Pediatric Dose To be administered IV every 8 hours
Complicated urinary tract infections	10 mg/kg body weight/dose
Complicated intraabdominal infections	20 mg/kg body weight/dose
Febrile episodes in neutropenic patients	20 mg/kg body weight/dose
Skin and skin structure infections	10 to 20 mg/kg body weight/dose
Lower respiratory tract infections	
Community-acquired pneumonia	10 to 20 mg/kg body weight/dose
In cystic fibrosis	40 mg/kg body weight/dose
Meningitis	40 mg/kg body weight/dose

» When treating infections known or suspected to be caused by P. aeruginosa, a dose of at least 20g/kg body weight three times a day in children (maximum approved dose: 120 mg/kg body weight/day given in three divided doses) is recommended.

Children > 50 kg: Follow usual adult dosing

Children with Renal Impairment: There are no data on appropriate doses for pediatric patients with renal impairment.

Usual Duration of Treatment: 7 to 14 days depending on the type and severity of infection.

Or, as prescribed by a physician.

Directions for Use, Compatibility and Stability:
» Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.
» Shake the reconstituted solution before use.
» Observe strict aseptic technique when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.

For IV Bolus Administration
To reconstitute, dissolve meropenem powder for injection in the required amount of sterile Water for Injection as shown below. Shake to dissolve and let stand until clear.

Meropenem Dosage Format	Amount of sterile Water for Injection to be added	Approximate Average Concentration
500 mg	10 mL	50 mg/mL
1 g	20 mL	50 mg/mL
Reconstituted solution (up to 50 mg/mL) are stable for up to 2 hours at controlled room temperature (15 to 25°C) **OR** for up to 12 hours at 2 to 8°C.		

For IV Infusion
Meropenem for IV infusion may be directly reconstituted with a compatible infusion fluid. Alternatively, an injection vial may be reconstituted (as above for IV Bolus), then the resulting solution added to an IV container and further diluted with an appropriate infusion fluid.

SIZE : 210 mm X 297 mm

PRINT COLOR

Pantone 2756 C

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