Instruction of Meropenem Medis for Injection

Please read the instruction carefully and follow the guidance of the doctor

Drug name Meropenem Medis for Injection
Composition The main ingredient of this product is Meropenem. Each vial contains Meropenem trihydrate equivalent to 1.0g of anhydrous Meropenem ($C_{17}H_{25}N_3O_5S$).
Properties: This product is white to slightly yellow powder.
Indications
Meropenem Medis is suitable for both adults and children who are infected by one or more types of bacteria sensitive to Meropenem, including pneumonia (includ-ing inpatients with acquired infection), urinary tract infection, gynecological infection (such as endometritis and pelvic inflammation), skin soft-tissue infection, meningitis and septicemia. For empirical treatment, adult patients who have febrile neutropenia can be treated with this product alone or in combination with antiviral drugs or antifungal agents. Meropenem alone or in combination with other antimicrobial agents can be used for multiple infec-tions.
There is no experience in infant patients with neutrope-nia or primary or secondary immunodeficiency.
Specification:1.0g based on the content of $C_{17}H_{25}N_3O_5S$.
Administration and Dosage:
Usage:
Meropenem Medis should be given as intravenous bolus injection over 5 minutes or as intravenous infusion over approximately 15 minutes to 30 minutes. Meropenem to be used for intravenous bolus injection should be reconstituted with sterile Water for Injection (every 5 ml contains 250 mg meropenem). This provides an approximate available concentration of 50 mg/mL.
Meropenem can be re-constituted with the following compatible infusion fluids:
Sodium Chloride Injection 0.9%, Glucose Injection 5% and Glucose and Sodium Chloride Injection.

Dosage:
Adult patients:
The administration dose and interval should be based on the type and severity of infection and the condition of the patients.
Recommended daily dosage:
The recommended dose of meropenem is 500mg given every 8 hours for pneumonia, urinary tract infection, gynecological infection (such as endometritis), and skin and soft tissue infection, which should be administered by intravenous infusion. Meropenem for injection should be administered by intravenous infusion at a dose of 1g every 8 hours for nosocomial pneumonia, peritonitis, and neutropenia with concurrent infection and septicaemia. And dose of 2g every 8 hours for meningitis should be administered as an intravenous infusion or intravenous bolus injection.

Use in Adult patients with renal impairment:
Dosage should be reduced in patients with creatinine clearance less than 51 mL/min. (See dosing table below.)

Creatinine clearance (ml/min)	Dose (dependent on type of infection)	Dosing interval
26~50	Recommended dose	Every 12 hours
10~25	One-half recommended dose	Every 12 hours
10	One-half recommended dose	Every 24 hours

Note:
Freshly prepared solutions of Meropenem for Injection should be used immediately and should be administered within 15-30 minutes. Shake to dissolve and let stand until clear before using it. However, in special case if it cannot be used immediately, it should be constituted only with Normal Saline, the reconstituted solution may be stored up to 6 hours at controlled room temperature. (Solutions of Meropenem for injection should not be frozen.)

Adverse reaction
Main adverse reactions: rash, diarrhea, loose stool, nausea and vomiting.
Adverse laboratory changes: increased AST, GPT, ALP and eosinophil.
Serious adverse reactions in patients after using Mero-penem: anaphylactic shock, sever renal impairment such as acute kidney failure, severe colonitis accompanied by bloody stools such as pseudomembranous colitis, interstiti-tial pneumonia, PZF syndrome, convulsion, consciousness disorders and other nervous system symptoms, toxic epidermal necrolysis (LYELL syndrome), Stevens-Johnson syndrome, pancytopenia, agranulocytosis, decreased WBC, liver dysfunction and jaundice. There are also reports of Hemolytic anemia and Thrombophlebitis in similar drugs.

Other adverse reactions in using Meropenem Medis:
1. Allergic reaction: nettle rash, feverish, erythema, pruritus, fever and flush.
2. Hematologic: granulocytopenia, increased platelets, decreased platelets, achroacytosis, increased eosinophils and decreased erythrocyte, decreased hemoglobin and decreased hematocrit.
3. Nervous system: headache and paraesthesia.
4. Hepatic: increased LDH, γ-GTP, bilirubin, urobilinogen and jaundice
5. Renal: increased β2-microblobulin, BUN, and Cr.
6. Digestive system: stomachache, anorexia, stomatitis, oral moniliasis, Vitamin K deficiency and Hypovitaminosis B.

Contraindication
1. Meropenem for Injection is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class.
2. Meropenem or injection is contraindicated in patients who are using valproic Acid.

Precautions
Patients who are allergic to penicillin or other beta lactam antibiotics can also be allergic to this product and should be used with caution.
Patients with severe hepatic and renal impairment should be careful in using this product.
Those patients who can not intake food normally or who are using para-oral nutrition, patients with poor overall conditi on and elderly people should be careful in using this product.
Patients with history of seizures or CNS abnormality should be careful in using this product.
Patients with pre-existing liver disorders should have liver function monitored during treatment with mero-penem.
As with other broad-spectrum antibacterial drugs, prolonged use of meropenem may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential.
This product is not recommended for methicillin-resis-tant Staphylococcus infections.

Pseudomembranous colitis has been observed with practically all antibiotics and may vary in severity from slight to life-threatening. It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea or aggravated stom-achache when using Meropenem. Although studies indicate that a toxin produced by Clostridium difficile is one of the main causes of antibiotic-associated colitis, other causes should be considered.
Routine antimicrobial susceptibility testing should be performed when treating Pseudomonas infections such as Pseudomonas aeruginosa.
This product can be removed by hemodialysis. If it is necessary to use this product continuously, it is recom-mended to give the full dose after hemodialysis based on the disease conditions so as to gain the effective plasma concentration.
There is inadequate information regarding the use of Meropenem for injection in patients on peritoneal dialysis.
In patients with hepatic insufficiency, dosage adjust-ment is not necessary.

Meorpenem Medis should not be frozen, shake it prior to administration, and freshly prepared solutions of this product should be used up once. The preparation and use of this product should be strictly in accordance with aseptic operation requirements.
Keep this product out of the reach of children.
There is no data available for reference on the impact of this product on the ability of drivers and mechanical operators.

Administration for pregnant women and nursing mothers
Meropenem Medis should not be used in pregnancy unless the potential benefit justifies the potential risk to the foetus.

Meropenem Medis should not be used in nursing mothers unless the potential benefit justifies the potential risk to the baby.

Administration for pediatric patients
Pediatric patients: For pediatric patients over 3 months and up to 12 years of age, the recommended intrave-nous dose is 10-20mg/kg every 8 hours depending on type and severity of infection, the known or suspected susceptibility of the pathogen(s) and the condition of the patient. In pediatric patients over 50 kg weight, adult dosage should be administered. For pediatric patients with meningitis, the dose should be 40 mg/kg every 8 hours. There is no experience in pediatric patients with renal impairment.
Infants: Efficacy and tolerability in infants under 3 months of age have not been established; therefore, meropenem is not recommended for use below this age. There is no experience in infants patients with hepatic and renal impairment.

Administration for geriatric patients
Geriatric patients: No dosage adjustment is required for elderly patients with normal renal function or creatinine clearance values above 50ml/min. However, elderly patients may develop adverse reaction due to the decreased physiologic function. And meanwhile, bleeding may occur in the elderly patients caused by vitamin K deficiency. Therefore, this product should be used with caution in the elderly patients.

Drug Interactions
When Meropenem Medis is used with drugs with potential renal toxicity, should pay attention to the following: Probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem with the effect of increasing elimination half-life and plasma concentrations of meropenem. Co-administration of probenecid with meropenem is not recommended.
Co-administration of Meropenem with valproic acid reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures.
Meropenem Medis cannot be used concomitantly with valeric acid glycerides.
Meropenem should not be mixed with other medicines.

Overdosage
If adverse events occur following dosage, especially in patients with renal impairment, the generated symptoms should be treated in time (the adverse event profile described in the Adverse Reactions section). In individuals with normal renal function, rapid renal elimination takes place. For patients with renal impairment, meropenem and its metabolite are readily dialyzable and effectively removed by hemodialysis.

Pharmacology and toxicology
Pharmacologic action
Meropenem Medis is a synthetic, broad-spectrum, carbapen-em antibiotics. The bactericidal activity of meropenem results from the inhibition of cell wall synthesis. Meropenem penetrates the cell wall of most Gram-pos-itive and Gram-negative bacteria to reach penicillin-binding-protein
(PBP) targets. Meropenem has significant stability to the hydrolysis by most β-lactamases (including the penicillinases and cephalosporinase produced by gram-positive and gram-negative bacteria), except metalβ-lactamase. Meropenem should not be used to treat methicillin-resistant staphylococcal infection.

And cross-resistance is sometimes observed with isolates resistant to other carbapenems. In-vitro tests show Meropenem to act synergistically with aminoglycoside antibacterials against some isolates of pseudomonas aeruginosa.

Meropenem Medis has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections:
1. Gram-positive aerobes: Streptococcus pneumoniae (penicillin-susceptible isolates only) and viridans group streptococci.
2. Gram-negative aerobes: Escherichia coli, haemophilus influenzae (β- lactamase positive bacterial strain and β- lactamase negative bacterial strain), Klebsiella pneumoniae, Pseudomonas aeruginosa, Neisseria meningitides.
3. Anaerobes: Bacteroides fragilis, Bacteroides thetaiotaomicron and peptostreptococcus.

Meropenem has in vitro antibiotic activity against the following bacteria, but the clinical significance is uncertain:
1. Gram-positive aerobes: Staphylococcus aureus (β- lactamase positive bacterial strain and β- lactamase negative bacterial strain), Staphylococcus epidermidis (β- lactamase positive bacterial strain and β- lactamase negative bacterial strain). (Note: Those staphylococci resistant to meticillin /oxacillin should be considered to be resistant to Meropenem.)
2. Gram-negative aerobes: Acinetobacter, Aeromonas hydrophila, Campylobacter jejuni, Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, haemophilus influenzae (bacterial strain resistant to ampicillin and β- lactamase negative bacterial strain), Moraxella catarrhalis (β- lactamase positive and negative bacterial strains) Morganella morganii, Proteus mirabilis, Proteus vulgaris, Salmonella, Serratia marcescens, Shigella etc..
3. Anaerobes: Bacteroides distasonis, Bacteroides ovatus, Bacteroides uniformis, Bacteroides ureolyticus, Bacteroides vulgatus, clostridium difficile, clostridium perfringens, Eubacterium lentum, Bacillus fusiformis, Porphyromonas asaccharolytica, Propionibacterium acnes.

Toxicologic research:
Genetic toxicity: 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.
Reproductive toxicity: Reproductive studies were performed with meropenem in rats at doses up to 1000mg/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 and these studies revealed no evidence of impaired fertility or harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (on the basis of AUC comparisons, 0.4 times the human exposure at a dose of 1 gram every 8 hours) and above in rats.

Pharmacokinetics
It is reported in the literature: A 5-minute intravenous bolus injection of a single dose of Meropenm in healthy volunteers, mean peak plasma concentrations of Meropenem are 52ug/ml for the 500 mg dose group and 112ug/ml for the 1 g dose group.
At the end of a 2, 3 and 5-minute intravenous infusion of Meropenem in healthy volunteers, mean peak plasma concentrations of Meropenem are 110, 91 and 94ug/ml for the 1 g dose respectively.
Following intravenous doses of 500mg,mean plasma concentrations of meropenem usually decline to approximately 1ug/ml at 6 hours after administration, and no accumulation of Meropenem in plasma was observed when the healthy volunteers with normal renal function are given different doses of Meropenem every 3 hours.
In volunteers with normal renal function, the elimination half-life of meropenem is approximately 1 hour. Meropenem is primarily excreted unchanged by the kidneys. Approximately 70% of the dose is excreted unchanged within 12 hours. Urinary concentrations of meropenem is of 10μg/ml are maintained for up to 5hours after a 500mg dose. No accumulation of Meropenem in plasma or urine was observed with regimens using 500mg administered every 8 hours or 1g administered every 6 hours in healthy volunteers.
Meropenem penetrates well into most body fluid and tissues including cerebrospinal fluid of patients with bacterial meninigitis, achieving an effective concentration.
The pharmacokinetics of meropenem for injection in pediatric patients less than 2 years of age, are similar to those in adults. The elimination half-life of meropenm was approximately 1.5-2.3 hours, in pediatric patients less than 2 years of age.
The pharmacokinetic parameters showed a good linear relationship within a dose range of 10-40 mg/kg.
Pharmacokinetic studies with meropenem for injection in patients with renal impairment have shown that the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment.
A pharmacokinetic study with meropenem for injection in elderly patients showed a reduction in plasma clearance of meropenem that correlates with age-associated reduction in creatinine clearance.
A pharmacokinetic study with meropenem for injection in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Storage: Sealed up and kept at a dry and cool place away from light (away from light with the temperature less than 30°C).
Shelf life:24 months
Manufacturer and Market authorization holder :
Shenzhen Haibin Pharmaceutical Co., Ltd.
Address: No. 2003, Shenyan Road, Shenzhen City, Yantian District, Guangdong Province, P.R. China Post Code:518081, China
Zip code: 518081
Tel: 0755-25229666
Fax: 0755-25227635