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the Ministry of Health
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MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

Patient Information Leaflet

MEROPENEM-TF (МЕРОПЕНЕМ-ТФ) Powder for solution for intravenous injection/ infusion 500 mg, 1000 mg.

Invented trade name: Meropenem -TF

International Non-proprietary Name: Meropenem

Pharmaceutical form: powder for solution for intravenous injection/ infusion

Description: White to pale yellowish white powder.

Qualitative and quantitative composition:

1 vial contains:
Meropenem – 500 mg or 1000 mg
(as meropenem and sodium carbonate)

Pharmacotherapeutic group: Antibacterials for systemic use. Carbapenems.

ATC-code: J01DH02.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Meropenem-TF is a broad-spectrum bactericidal antibiotic that shows reduced susceptibility to hydrolysis by human dehydropeptidase-I. Meropenem-TF exerts a bactericidal action by inhibiting bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all serine beta-lactamases and its marked affinity for the penicillin binding proteins explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria.

The antimicrobial spectrum of Meropenem-TF includes virtually all clinically significant Gram-positive and Gram-negative aerobic and anaerobic microorganisms. The antibiotic is *in vitro* active against the microorganisms given below.

Meropenem- TF is active against the following *Gram-positive aerobic bacteria*: *Enterococcus faecalis*, *Staphylococcus aureus* (both penicillinase-producing and non- penicillinase-producing strains), coagulase-negative staphylococci, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (Group B), *Streptococcus pyogenes* (Group A), *Streptococcus milleri*; *Gram-negative aerobic bacteria*: *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae* (including beta-lactamase producing strains and ampicillin-resistant strains), *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Serratia marcescens*; *anaerobic bacteria*: *Clostridium perfringens*, *Peptoniphilus asaccharolyticus*, *Peptostreptococcus* species, *Bacteroides fragilis*, *Bacteroides caccae*, *Prevotella bivia*, *Prevotella disiens*, *Enterococcus faecium*, *Acinetobacter* spp., *Bucholderia cepacia*, *Pseudomonas aeruginosa* *may be resistant* to Meropenem-TF.

Stenotrophomonas maltophilia, *Legionella* species, *Chlamydia psittaci*, *Coxiella burnetii*, *Mycoplasma pneumoniae* are resistant to Meropenem-TF.

Meropenem-TF was shown to be effective as a monotherapy, or in combination with other antimicrobial agents in the treatment of polymicrobial infections.

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Pharmacokinetics

Distribution

An intravenous infusion of a single dose of Meronem results in peak plasma levels of approximately 23 microgram/ml for the 500 mg dose and 49 microgram/ml for the 1g dose.

An intravenous bolus injection of Meronem results in peak plasma levels of approximately 52 microgram/ml for the 500 mg dose and 112 microgram/ml for the 1g dose.

Plasma protein binding of meropenem is approximately 2%.

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.

Metabolism and elimination

Meropenem is metabolised in the liver generating a sole microbiologically inactive metabolite.

Approximately 70% of the administered dose is recovered as unchanged meropenem in the urine over 12 hours. No accumulation of meropenem in plasma or urine was observed in volunteers with normal renal function. The elimination half-life of Meropenem-TF is approximately 1 hour.

Pharmacokinetics in special populations

Comparison showed the pharmacokinetics in infants and children similar to that observed in adults.

The elimination half-lives in pediatric patients under 2 years of age are approximately 1.5 – 2.3 hours; at doses of 10 to 40 mg/kg, linear dependency is observed.

Pharmacokinetic studies in patients with renal insufficiency have shown the plasma clearance of meropenem correlates with creatinine clearance. Dosage adjustments are necessary in subjects with renal impairment. Pharmacokinetic studies in patients with liver disease have shown no effects of liver disease on the pharmacokinetics of meropenem.

Therapeutic indications

Meropenem-TF is indicated for the treatment of the following infections caused by susceptible strains of microorganisms in adults and children over 3 months of age: lower respiratory tract infections (including pneumonia, including nosocomial pneumonia), broncho-pulmonary infections in cystic fibrosis, complicated urinary tract infections, complicated intra-abdominal infections, intra- and post-partum infections, skin and soft tissue infections, meningitis. Meropenem may be used as an empiric therapy in the management of neutropenic adults with fever that is suspected to be due to a bacterial infection; as a monotherapy or in combination with antiviral or antifungal drugs.

Contraindications

The drug product is contraindicated in patients who have had previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, or other beta-lactam antibiotics. The drug product is contraindicated in children under 3 months of age.

Caution should be taken, when using Meropenem-TF in combination with potentially nephrotoxic drugs.

It is important to consider the diagnosis of pseudomembranous colitis in the case of patients who develop diarrhoea in association with the use of Meronem (especially individuals with a history of gastro-intestinal complaints, particularly colitis). The studies indicate that a toxin produced by *Clostridium difficile* is one of the main causes of antibiotic-associated colitis.

Special warnings and precautions for use

Use in pregnancy and lactation

Clinical safety of Meropenem-TF during pregnancy has not been established. Meropenem -TF should not be used during pregnancy except when the potential benefit justifies the potential risk. In each case, the drug must be used under the direct supervision of a physician.

If Meropenem -TF is to be administered to a nursing woman, the breastfeeding discontinuation should be considered.

Special warnings

Use of Meronem in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels. When using Meropenem-TF as a monotherapy for known or suspected *Pseudomonas aeruginosa* infection of the lower respiratory tract, periodic susceptibility testing should be done when clinically appropriate.

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As with other antibiotics, prolonged use of Meropenem-TF may result in overgrowth of nonsusceptible organisms. Thus careful supervision is required during therapy.

Effects on ability to drive and use machines weren't studied.

Posology and method of administration

FOR INTRAVENOUS ADMINISTRATION ONLY!

The dosing schedule and duration of therapy should be determined according to the susceptibility of the causative organisms, the severity and type of the infection, and the condition of the patient.

A dose of up to 2 g three times daily in adults and adolescents and a dose of up to 40 mg/kg three times daily in children may be particularly appropriate when treating some types of infections, such as *nosocomial infections due to Pseudomonas aeruginosa or Acinetobacter spp.*

The recommended daily doses for adults are as follows:

500 mg or 1 g intravenously every 8 hours in the treatment of *pneumonia, complicated urinary tract infections, intra-abdominal infections, intra- and post-partum infections, skin and soft tissue infections.*

1 g intravenously every 8 hours in the treatment of *nosocomial pneumonias, peritonitis, presumed bacterial infections in neutropenic patients.*

In meningitis and broncho-pulmonary infections in cystic fibrosis, doses up to 2 g every 8 hours should be used.

In patients with impaired renal function, the dose adjusted according to the creatinine clearance: creatinine clearance of 26-50 ml / min - 500 mg-1000 mg 2 times a day; 10-25 ml / min - 250 mg-500 mg 2 times a day; less than 10 ml / min - 250 mg-500 mg once a day.

Meropenem is cleared by haemodialysis and hemofiltration; if continued treatment with Meronem is necessary, it is recommended that the unit dose (based on the type and severity of infection) is administered at the completion of the haemodialysis procedure to restore therapeutically effective plasma concentrations.

There is no experience with the use of Meronem in patients under peritoneal dialysis.

No dosage adjustment is required for the *elderly* with normal renal function or creatinine clearance values above 50 ml/min. No dosage adjustment is necessary in patients with *hepatic insufficiency.*

For *children over 3 months and up to 12 years of age*, the recommended dose is 10 to 20 mg/kg every 8 hours depending on type and severity of infection, susceptibility of the pathogen and the condition of the patient. In *meningitis* the recommended dose is 40 mg/kg every 8 hours.

In children over 50 kg weight, adult dosage should be used.

Instructions for preparation and administration of the solution

Meropenem-TF can be given as an intravenous bolus injection over approximately 5 minutes, after the contents of a vial is dissolved in an amount of 5 ml of solvent per every 250 mg of the drug product, or as an intravenous infusion over 15-30 minutes, after the contents of a vial is dissolved in 50 -250 ml of solvent. The solvent to be used is sterile water for injection or a compatible infusion fluid (0.9% sodium chloride, 5% or 10% glucose solution, 0.9% sodium chloride, 5% glucose solution, 2.5% or 10% mannitol solution).

This medicinal product must not be mixed with other medicinal products.

Standard aseptic techniques should be used for solution preparation and administration.

The solution should be shaken before use.

Do not freeze the reconstituted solution.

Undesirable effects

Meropenem is generally well tolerated. Serious adverse reactions are rare.

Allergic reactions: pruritus, rash, urticaria, rarely - multiforme (exudative) erythema, Stevens-Johnson syndrome and toxic epidermal necrolysis, rarely - angioedema, anaphylactic reactions.

Gastrointestinal disorders: abdominal pain, nausea, vomiting, diarrhea; in certain cases – a reversible increase in bilirubin, transaminases, alkaline phosphatase and lactate dehydrogenase levels alone or in combination; in some cases – pseudomembranous colitis.

Blood and lymphatic system disorders: reversible thrombocytosis, eosinophilia, thrombocytopenia, leukopenia and neutropenia (including very rare cases of agranulocytosis). In some patients a positive direct or indirect Coombs test is reported; also the cases of decreased partial thromboplastin time were reported.

Nervous system disorders: headache, dizziness, paresthesias, insomnia, drowsiness, irritability, agitation, anxiety, depression, alteration of consciousness, hallucinations, epileptiform seizures, convulsions.

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Cardiovascular disorders: the development or exacerbation of congestive heart failure, cardiac arrest, tachycardia and bradycardia, decreased and elevated blood pressure, fainting, myocardial infarction, embolism of the pulmonary artery branches.

General disorders and administration site conditions: inflammation, thrombophlebitis, pain at the injection site.

Undesirable effects due to the biological action: oral candidiasis, vaginal candidiasis.

Overdose

Accidental overdose could occur during therapy, particularly in patients with renal impairment.

Treatment: symptomatic treatment is applied. In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite in patient with impaired renal function.

Interaction with other medicinal products and other forms of interaction

Probenecid increases the elimination half-life of Meropenem-TF and its plasma concentrations.

Storage conditions and shelf-life

Store in a dry and dark place at the temperature not above 25°C.

Keep out of reach of the children.

2 years. Do not use beyond the labeled expiration date.

Prescription status

Prescription only medicine.

Presentation

500 mg in a 10 ml vial.

5 vials in a pack or 36 vials in a box (for inpatient facilities).

1000 mg in a 20 ml vial.

5 vials in a pack or 25 vials in a box (for inpatient facilities).

Manufacturing company

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