MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

INSTRUCTION
for Medical Use of Medicinal Product

MEROPENEM-TF

powder for solution for intravenous administration 500 mg, 1000 mg

Stamp: [APPROVED
by the MINISTRY OF HEALTH
OF THE REPUBLIC OF BELARUS
Order of the Ministry of Health
of the Republic of Belarus
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Trade name: Meropenem-TF.
International non-proprietary name: Meropenem.
Pharmaceutical form: Powder for solution for intravenous administration 500 mg, 1000 mg.
Description: White or white to yellowish powder.
One vial contains:
Active substance:
Meropenem (as meropenem trihydrate) – 500 mg or 1000 mg.
Excipient: sodium carbonate.
Pharmacotherapeutic group: Antibacterials for systemic use. Other beta-lactam antibacterials. Carbapenems.
ATC code: J01DH02.
Pharmacological properties
Pharmacodynamics
Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins (PBPs).
Pharmacokinetic/Pharmacodynamic (PK/PD) relationship
Meropenem is relating to antibacterial agents with time-dependent effect. The time (T) that meropenem concentrations exceed the minimum inhibitory concentrations (T>MIC) for certain pathogen has been shown to best correlate with efficacy.
Mechanism of resistance
Bacterial resistance to meropenem may result from: decreased permeability of the outer membrane of Gram-negative bacteria (due to diminished production of porins), reduced affinity of the target PBPs, increased expression of efflux pump components, and production of beta-lactamases that can hydrolyse carbapenems.
There is no target-based cross-resistance between meropenem and agents of the quinolone, aminoglycoside, macrolide and tetracycline classes. However, bacteria may exhibit resistance to more than one class of antibacterial agents when the mechanism involved include impermeability and/or an efflux pump(s).
Breakpoints
European Committee on Antibacterial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing is presented below[*]:

Microorganism	Susceptibility (S), (mg/l)	Resistance (R), (mg/l)
Enterobacteriaceae	≤ 2	> 8
Pseudomonas spp.	≤ 2	> 8
Acinetobacter spp.	≤ 2	> 8
Streptococcus groups A, B, C and G	note 6	note 6
Streptococcus pneumoniae[1]	≤ 2	> 2

[*] EUCAST, Version 3.1 dated 11.02.2013.

Microorganism	Susceptibility (S), (mg/l)	Resistance (R), (mg/l)
Viridans group *streptococci*[2]	≤ 2	> 2
Enterococcus spp.	–	–
Staphylococcus spp.	note 3	note 3
Haemophilus influenzae[1,2] and *Moraxella catarrhalis*[2]	≤ 2	> 2
Neisseria meningitidis[2,4]	≤ 0.25	> 0.25
Gram-positive anaerobes except *Clostridium difficile*	≤ 2	> 8
Gram-negative anaerobes	≤ 2	> 8
Listeria monocytogenes	≤ 0.25	> 0.25
Non-species related breakpoints[5]	≤ 2	> 8

[1] Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25 mg/l (Susceptible) and 1 mg/l (Resistant).

[2] Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

[3] Staphylococci susceptibility to carbapenems is inferred from the cefoxitin susceptibility.

[4] Meropenem breakpoints for *Neisseria meningitidis* relate to meningitis only.

[5] Non-species related breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

[6] The beta-lactam susceptibility of streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

"–" Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product. Isolates may be reported as R without prior testing.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Meropenem is active against the following microorganisms:

Gram-positive aerobes: *Enterococcus faecalis*[7], *Staphylococcus aureus* (methicillin-susceptible)[8], *Staphylococcus* spp. (methicillin-susceptible), including *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (Group B), *Streptococcus pyogenes* (Group A), *Streptococcus milleri* group *(S. anginosus, S. constellatus, S. intermedius)*.

Gram-negative aerobes: *Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria meningitidis Proteus mirabilis, Proteus vulgaris, Serratia marcescens.*

Gram-positive anaerobes: *Clostridium perfringens, Peptoniphilus asaccharolyticus, Peptostreptococcus* spp. (including *P. micros, P. anaerobius, P. magnus*).

Gram-negative anaerobes: *Bacteroides fragilis* group*, Bacteroides caccae, Prevotella bivia, Prevotella disiens.*

Species for which acquired resistance may be a problem

Gram-positive aerobes: *Enterococcus faecium*[7].

Gram-negative aerobes: *Acinetobacter* spp., *Burkholderia cepacia, Pseudomonas aeruginosa*.

Inherently resistant organisms

Gram-negative aerobes: *Stenotrophomonas maltophilia, Legionella* spp.

Other microorganisms: *Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Mycoplasma pneumoniae*.

[7]Species that show natural intermediate susceptibility.

[8]All methicillin-resistant staphylococci are resistant to meropenem.

Glanders and melioidosis: Use of meropenem in humans is based on *in vitro B. mallei* and *B. pseudomallei* susceptibility data and on limited human data. Treating physicians should refer to

national and/or international consensus documents regarding the treatment of glanders and melioidosis.

Pharmacokinetics

In healthy subjects the mean plasma half-life is approximately 1 hour; the mean volume of distribution is approximately 0.25 l/kg (11-27 l) and the mean clearance is 287 ml/min at 250 mg falling to 205 ml/min at 2 g.

There is no absolute proportional dependence of the maximum concentration (C_{max}) and the area under the pharmacokinetic curve "concentration-time" (AUC) on the administered dose. Doses of 500, 1000 and 2000 mg infused over 30 minutes give mean C_{max} values of approximately 23, 49 and 115 μg/ml respectively, corresponding AUC values were 39.3, 62.3 and 153 μg×h/ml. After infusion over 5 minutes C_{max} values are 52 and 112 μg/ml after 500 and 1000 mg doses respectively. When multiple doses are administered 8-hourly to subjects with normal renal function, accumulation of meropenem does not occur.

A study of 12 patients administered meropenem 1000 mg 8-hourly post-surgically for intra-abdominal infections showed a comparable C_{max} and half-life to normal subjects but a greater volume of distribution 27 L.

Distribution

The average plasma protein binding of meropenem was approximately 2% and was independent of concentration. After rapid administration (5 minutes or less) the pharmacokinetics are biexponential but this is much less evident after 30 minutes infusion. Meropenem has been shown to penetrate well into several body fluids and tissues: including lung, bronchial secretions, bile, cerebrospinal fluid, gynecological tissues, skin, fascia, muscle, and peritoneal exudates.

Biotransformation

Meropenem is metabolized by hydrolysis of the beta-lactam ring generating microbiologically inactive metabolite. *In vitro* meropenem shows reduced susceptibility to hydrolysis by human dehydropeptidase-I (DHP-I) compared to imipenem and there is no requirement to co-administer a DHP-I inhibitor.

Elimination

Meropenem is primarily excreted unchanged by the kidneys; approximately 70 % (50-75 %) of the dose is excreted unchanged within 12 hours. A further 28% is recovered as the microbiologically inactive metabolite. Faecal elimination represents only approximately 2% of the dose. The measured renal clearance and the effect of probenecid show that meropenem undergoes both filtration and tubular secretion.

Pharmacokinetics in special populations

Renal insufficiency

In patients with renal insufficiency the clearance of meropenem correlates with creatinine clearance (CC). Dose adjustment is recommended for patients with moderate and severe renal impairment. Meropenem is cleared by haemodialysis with clearance during haemodialysis being approximately 4 times higher than in anuric patients.

Hepatic insufficiency

Liver diseases have no effect on the pharmacokinetics of meropenem.

Elderly

Pharmacokinetic studies in healthy elderly subjects (65-80 years) have shown a reduction in plasma clearance, which correlated with age-associated reduction in creatinine clearance, and a smaller reduction in non-renal clearance. No dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

Paediatric population

Pharmacokinetic parameters in children at the dose of 10, 20 and 40 mg/kg showed C_{max} values approximating to those in adults following 500, 1000 and 2000 mg doses respectively. Comparison showed consistent pharmacokinetics between the doses and half-lives similar to those observed in adults in all but the youngest subjects (<6 months $T_{1/2}$ 1.6 hours). Approximately 60% of the dose is excreted in urine over 12 hours as meropenem with a further 12% as metabolite. Meropenem concentrations in the cerebro-spinal fluid of children with meningitis are approximately 20% of concurrent plasma levels although there is significant

interindividual variability. The pharmacokinetics of meropenem in neonates requiring anti-infective treatment, showed greater clearance with an overall average half-life of 2.9 hours.

Preclinical safety data

Animal studies indicate that meropenem is well tolerated by the kidney. Histological evidence of renal tubular damage was seen in mice and dogs only at doses of 2000 mg/kg and above after a single administration and in monkeys at 500 mg/kg in a 7-day study.

Meropenem is generally well tolerated by the central nervous system. Effects were seen in acute toxicity studies in rodent at doses exceeding 1000 mg/kg. The IV LD50 of meropenem in rodents is greater than 2000 mg/kg.

In repeat dose studies of up to 6 months duration only minor effects were seen including a decrease in red cell parameters in dogs.

There was no evidence of mutagenic potential in a conventional test battery and no evidence of reproductive toxicity including teratogenic potential in studies in rats up to 750 mg/kg and in monkeys up to 360 mg/kg.

There was no evidence of increased sensitivity to meropenem in juveniles compared to adult animals. The intravenous formulation was well tolerated in animal studies. The sole metabolite of meropenem had a similar profile of toxicity in animal studies.

Therapeutic indications

Meropenem-TF is indicated for treatment of the following infections in adults and children aged 3 months and older:

- severe pneumonia, including hospital and ventilator-associated pneumonia;
- broncho-pulmonary infections in cystic fibrosis;
- complicated urinary tract infections;
- complicated intra-abdominal infections;
- intra- and post-partum infections;
- complicated skin and soft tissue infections;
- acute bacterial meningitis;
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem-TF may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Contraindications

Hypersensitivity to any of the components of the medicinal product.

Hypersensitivity to any other carbapenem antibacterial agent.

Severe hypersensitivity (e.g., anaphylaxis, severe skin reaction) to any other type of beta-lactam antibacterial agents (e.g. penicillins or cephalosporins).

Special warnings and precautions for use

Use during pregnancy and breastfeeding

The safety of meropenem in human *pregnancy* has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Meropenem-TF should not be used in pregnancy unless the potential benefit exceeds the potential risk to the fetus.

If administering Meropenem-TF during lactation is required, consideration should be given to stopping breastfeeding.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving or operating machines, the possibility of headache, paresthesia and seizures should be considered when using Meropenem-TF and their effect on the ability to drive vehicles and work with mechanisms.

Special warnings

The selection of Meropenem-TF to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on severity of the infection, the

prevalence of resistance to other antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Prescribers are advised to take into account the local prevalence of resistance in *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter* spp. to carbapenems.
As with all beta-lactam antibiotics, serious and occasionally fatal *hypersensitivity reactions* (anaphylactic reactions) have been reported. Patients who have a history of hypersensitivity to carbapenems, penicillins or other beta-lactam antibiotics may also be hypersensitive to meropenem. Before initiating therapy with meropenem, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactam antibiotics and other allergens.
Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM) and acute generalised exanthematous pustulosis (AGEP) have been reported in patients receiving meropenem.
If a severe allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken!
Antibiotic-associated colitis and *pseudomembranous colitis* have been reported with nearly all antibacterial agents, including meropenem, and may range in severity from mild to life threatening. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem. Discontinuation of therapy with Meropenem-TF and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.
Seizures have infrequently been reported during treatment with carbapenems, including meropenem.
Hepatic function should be closely monitored during treatment with meropenem due to the risk of *hepatic toxicity* (hepatic dysfunction with cholestasis and cytolysis).
Patients with *pre-existing hepatic disorders* should have liver function monitored during treatment with meropenem. There is no dose adjustment necessary.
A positive *direct or indirect Coombs test* may develop during treatment with meropenem.
The concomitant use of meropenem and valproic acid or sodium valproate is not recommended!
Paediatric population
Meropenem is used for children over 3 months of age. There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.
Meropenem-TF 500 mg contains approximately 2.0 mEq *sodium* , Meropenem-TF 1000 mg contains approximately 4.0 mEq *sodium,* which should be taken into account by patients on a controlled sodium diet.

Posology and method of administration

Meropenem-TF is prescribed for intravenous administration only!
General recommendations for the dosage of the medicinal product are given in Table 1.
The dose of meropenem administered and the duration of treatment should take into account the type of infection to be treated, including its severity, and the clinical response.
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 nosocomial infections some types of infections, such as infections due to less susceptible bacterial species (*Enterobacteriaceae, Acinetobacter* spp. and *Pseudomonas aeruginosa)* or very severe infections.
Additional considerations for dosing are needed when treating patients with *renal insufficiency.*
Table 1. Recommended daily doses for *adults and children from 12 years of age:*

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	500 mg or 1 g
Broncho-pulmonary infections in cystic fibrosis	2 g

Complicated urinary tract infections	500 mg or 1 g
Complicated intra-abdominal infections	500 mg or 1 g
Intra- and post-partum infections	500 mg or 1 g
Complicated skin and soft tissue infections	500 mg or 1 g
Acute bacterial meningitis	2 g
Management of febrile neutropenic patients	1 g

Meropenem-TF is usually given by intravenous infusion over approximately 15 to 30 minutes
Alternatively, doses up to 1 g can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 2 g dose in adults as an intravenous bolus injection.
In patients with *renal impairment* with ClCR <51 ml/min, a dose adjustment is required in accordance with the table 2.
Table 2. Recommended doses for *adults and children from 12 years of age with impaired renal function*

Creatinine clearance (ml/min)	Dose (based on "unit" dose)*	Frequency
26-50	one unit dose	every 12 hours
10-25	half of one unit dose	every 12 hours
<10	half of one unit dose	every 24 hours

* The standard dose is determined according to table 1. Data confirming the use of doses of the medicinal product adjusted for the standard dose of 2 g is limited.

Meropenem-TF is cleared by haemodialysis and hemofiltration; therefore the unit dose is recommended to be administered at the completion of the haemodialysis procedure.
There are no established dose recommendations for patients receiving peritoneal dialysis.
No dose adjustment is required in patients with *hepatic impairment.*
No dosage adjustment is necessary for the *elderly* with normal renal function or creatinine clearance values above 50 ml/min.
Paediatric population
The safety and efficacy of meropenem in *children under 3 months of age* have not been established and the optimal dose regimen has not been identified. However, limited pharmacokinetic data suggest that 20 mg/kg every 8 hours may be an appropriate regiment.
For children from 3 months to 12 years of age and up to 50 kg body weight the recommended dose regimens are shown in the table 3.
Table 3.

Infection	Dose to be administered every 8 hours
Severe pneumonia including hospital and ventilator-associated pneumonia	10 or 20 mg/kg
Broncho-pulmonary infections in cystic fibrosis	40 mg/kg
Complicated urinary tract infections	10 or 20 mg/kg
Complicated intra-abdominal infections	10 or 20 mg/kg
Complicated skin and soft tissue infections	10 or 20 mg/kg
Acute bacterial meningitis	40 mg/kg
Management of febrile neutropenic patients	20 mg/kg

In *children over 50 kg body weight*, the adult dose should be administered.
There is no experience in children with renal impairment.
Preparation and administration of solution

Meropenem-TF is usually given by intravenous infusion over approximately 15 to 30 minutes. Alternatively, doses up to 20 mg/kg can be given as an intravenous bolus injection over approximately 5 minutes. There are limited safety data available to support the administration of a 40 mg/kg dose in children as an intravenous bolus injection.
Standard aseptic techniques should be used for Meropenem-TF solution preparation.
A solution for *bolus injection* is prepared by reconstitution of the contents of the vial of Meropenem-TF with water for injection to a final concentration of 50 mg/ml. The solution should be shaken until clear.
The reconstituted solution of Meropenem-TF should be diluted immediately after recovery!
A solution *for infusion* is prepared by dissolving the contents of the vial Meropenem-TF in either 0.9% sodium chloride solution for infusion or 5% dextrose solution for infusion to a final concentration of 1 to 20 mg/ml.
The solution should be shaken before use!
The diluted solution of Meropenem-TF should be used immediately!
To avoid the introduction of a dose less than the required one, the medicinal product must be completely dissolved. The prepared solution must be completely transferred from the vial!
Do not freeze Meropenem-TF solution!

Undesirable effects

In a review of 4,872 patients with 5,026 meropenem treatment exposures, meropenem-related adverse reactions most frequently reported were diarrhoea (2.3%), rash (1.4%), nausea/vomiting (1.4%) and injection site inflammation (1.1%). The most commonly reported meropenem-related laboratory adverse events were thrombocytosis (1.6%) and increased hepatic enzymes (1.5-4.3%).
The list of adverse reactions is presented according to system organ class classification and frequency of occurrence: very common (≥1/10); common (from ≥1/100 to <1/10); uncommon (from ≥1/1000 to <1/100); rare (from ≥1/10000 to <1/1000); very rare (<1/10000); unknown (cannot be established from the available data). Within each grouping undesirable effects are presented in order of descending seriousness.
Infections and infestations: uncommon - oral and vaginal candidiasis.
Blood and lymphatic system disorders: common - thrombocytaemia; uncommon - eosinophilia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis, haemolytic anemia.
Immune system disorders: uncommon - angioedema, anaphylaxis.
Nervous system disorders: common - headache; uncommon - paresthesia; rare - convulsions, delirium.
Gastrointestinal disorders: common - diarrhea, nausea, vomiting, abdominal pain; uncommon - antibiotic-associated colitis.
Hepatobiliary disorders: common - transaminases increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased; uncommon - blood bilirubin increased.
Skin and subcutaneous tissue disorders: common - rash, pruritis; uncommon - urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme; unknown - drug reactions with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis.
Renal and urinary disorders: uncommon - blood creatinine increased, blood urea increased.
General disorders and administration site conditions: common - inflammation, pain; uncommon - thrombophlebitis, pain in the injection site.
Paediatric population
There is no evidence of an increased risk of any adverse drug reaction in children based on the limited available data. All reports received were consistent with events observed in the adult population.
Reporting of adverse reactions
It is important to report suspected adverse reactions after drug product registration in order to ensure continuous monitoring of the benefit-to-risk ratio. Healthcare providers are encouraged to report any suspected adverse drug reactions through national ADR systems.

If any adverse reactions occur, patients are advised to consult a doctor or report adverse reactions to the Adverse Drug Reactions Information Database.
This recommendation applies to any possible adverse reactions, including those not listed in the instructions for medical use, including reports of ineffectiveness of the drug product. Adverse reaction reports provide more information on the safety of a medicinal product.

Overdose

Relative overdose may be possible in patients with renal impairment if the dose is not adjusted as described in section “Posology and method of administration”. Limited post-marketing experience indicates that if adverse reactions occur following overdose, they are consistent with the adverse reaction profile and are generally mild in severity and resolve on withdrawal or dose reduction. Symptomatic treatments should be considered.
In individuals with normal renal function, rapid renal elimination will occur. Haemodialysis will remove meropenem and its metabolite.

Interactions with other medical products

No specific medicinal product interaction studies other than probenecid were conducted.
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 meropenem. Caution is required if probenecid is co-administered with Meropenem-TF.
The protein binding is so low that no interactions with other compounds would be expected on the basis of this mechanism.
Decreases in blood levels of *valproic acid* have been reported when it is co-administered with carbapenem agents resulting in a 60-100% decrease in valproic acid levels in about two days. Due to the rapid onset and the extent of the decrease, co-administration of valproic acid/sodium valproate/valpromide with Meropenem-TF should be avoided.
There have been many reports of increases in the anti-coagulant effects of *orally administered anti-coagulant agents*, including *warfarin* in patients who are concomitantly receiving antibacterial agents. 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 INR (international normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of antibiotics with an oral anti-coagulant agent.
Paediatric population
Interaction studies have only been performed in adults.

Storage and shelf-life

Keep protected from moisture and light at a temperature not exceeding 25 °C.
Keep out of the reach of children.
Shelf-life is 2 years. Do not use beyond the labeled expiration date.

Prescription status

Prescription only medicinal product.

Packaging

500 mg in 10 ml vial for injection or 1000 mg in 20 ml vial for injection. Vials are corked with rubber stoppers and plugged up by aluminum caps with plastic covers with inscription "FLIP OFF" or without inscription.
5 vials with the instruction for medical use are placed in a pack.
36 vials for 500 mg dosage or 25 vials for 1000 mg dosage with the instructions for medical use are placed in a cardboard box (package for inpatient hospitals).

Information about manufacturer
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by the MINISTRY OF HEALTH
OF THE REPUBLIC OF BELARUS
Order of the Ministry of Health
of the Republic of Belarus]