MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

PACKAGE LEAFLET

FOSFOMYCIN-TF
Powder for concentrate for solution for infusion 2.0 g

Trade name: Fosfomycin-TF.
International nonproprietary name: Fosfomycin.
Dosage form: Powder for concentrate for solution for infusion.
Description: White or almost white highly hygroscopic powder.
Reconstituted solution: clear colorless or light-yellow solution.
Diluted solution: clear colorless or light-yellow solution.
Composition per 1 vial
Active ingredient:
Fosfomycin (in the form of fosfomycin sodium) – 2.0 g.
Excipients: succinic acid – for pH adjustment to 7.4-7.8.
Pharmacotherapeutic group: Antibacterials for systemic use. Other antibacterials.
ATC-code: J01XX01.
Pharmacological properties
Pharmacodynamics
Mechanism of action
Fosfomycin takes a bactericidal effect on proliferating pathogenic microorganisms by preventing enzymatic synthesis of bacterial cell walls. Fosfomycin inhibits the first stage of bacterial cell wall synthesis by blocking peptidoglycan synthesis.
Fosfomycin is actively transported into a bacterial cell by means of two different transport systems: sn-glycerol-3-phosphate and hexose-6.
Pharmacokinetic/ pharmacodynamic (PK/PD) relationship
Limited data points at possible dependence of Fosfomycin effect on time.
Mechanism of resistance
The main mechanism of resistance is chromosome mutation resulting in the change of the bacterial systems of Fosfomycin transport. Other mechanisms of resistance transferred by means of plasmids or transposons induce enzyme inactivation of Fosfomycin by binding its molecule with glutathione or by carbon-phosphorus bond cleavage in the Fosfomycin molecule, respectively.
Cross-resistance
Cross resistance between Fosfomycin and antibiotics of other classes is not found.
Fosfomycin antimicrobial spectrum (in vitro)
The data obtained during the *in vitro* studies allows to forecast possible susceptibility of microorganisms to Fosfomycin only.
Minimum inhibitory concentration (MIC) breakpoints
The European Committee on Antimicrobial Susceptibility Testing (EUCAST, version 10 dated 01.01.2020) established the following MIC breakpoints for Fosfomycin (for intravenous administration) to identify susceptible and resistant pathogens:

Microorganisms	Susceptibility, mg/ l	Resistance, mg/ l
Enterobacteriaceae	≤32	>32
Staphylococcus spp.	≤32	>32

The prevalence of the acquired resistance of particular species can vary in different geographic regions and in the course of time so it is recommended to have local information concerning resistance, especially upon treatment of severe infections.
The information provided below gives only approximate indications concerning susceptibility of microorganisms to Fosfomycin.
Fosfomycin is active for the following microorganisms:
Aerobic gram-positive microorganisms: *Staphylococcus aureus.*
Aerobic gram-negative microorganisms: *Citrobacter freundii, Citrobacter koseri, Escherichia coli, Haemophilus influenzae, Neisseria meningitidis, Salmonella enterica.*
Anaerobic microorganisms: *Fusobacterium* spp., *Peptococcus* spp., *Peptostreptococcus* spp.
Microorganisms which can acquire resistance:
Aerobic gram-positive microorganisms: *Staphylococcus epidermidis, Streptococcus pneumoniae, Enterococcus* spp.
Aerobic gram-negative microorganisms: *Enterobacter cloacae, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens.*
Anaerobic gram-positive microorganisms: *Clostridium* spp.
Species with natural resistance:
Aerobic gram-positive microorganisms: *Staphylococcus saprophyticus, Streptococcus pyogenes.*
Aerobic gram-negative microorganisms: *Legionella pneumophila, Morganella morganii, Stenotrophomonas maltophilia*.
Anaerobic gram-negative microorganisms: *Bacteroides* spp.
Other microorganisms: *Chlamydia* spp., *Chlamydophila* spp., *Mycoplasma* spp.

Pharmacokinetics

Absorption
Following single intravenous administration of 4 g and 8 g of Fosfomycin by young healthy men, the maximum concentrations in serum (C_{max}) made up about 200 and 400 μg/ ml, respectively. The serum elimination half-life made up about 2 hours. The individual intravenous doses of 8 g of Fosfomycin administered by elderly and/ or seriously ill men and women led to the average value of C_{max} and plasma elimination half-life equal to about 350-380 μg/ ml and 3.6-3.8 hours, respectively.
Distribution
The apparent volume of Fosfomycin distribution makes up about 0.30 l/ kg of body weight. Fosfomycin easily penetrates to body tissues. High concentrations of Fosfomycin are achieved in eye tissues, bones, wound drainage, muscles, skin, subcutaneous tissue, lung tissue and bile. The concentration of Fosfomycin in cerebrospinal fluid of patients with inflammation of the meninges achieves the rate at about 20-50% of the corresponding serum concentrations. Fosfomycin penetrates through the placental barrier. Small amounts were found in breast milk (about 8% of the serum concentration). Binding with plasma proteins is insignificant.
Metabolism
Fosfomycin is not metabolized by the liver and is not subject to enterohepatic circulation so Fosfomycin accumulation in patients with hepatic insufficiency is not expected.
Elimination
80-90% of Fosfomycin administered by healthy adult volunteers is eliminated via the kidneys within 12 hours following single intravenous administration. A small amount of the antibiotic is eliminated with fecal masses (0.075%). Fosfomycin is not metabolized, which means it is eliminated in the form of the biologically active compound. 50-60% of the cumulative dose of Fosfomycin in patients with normal kidney function as well as in patients with mild or moderate renal insufficiency (creatinine clearance ≥40 ml/ min) is eliminated within the first 3-4 hours.

Linearity
Pharmacokinetics of Fosfomycin is linear following intravenous administration in therapeutic doses.
Pharmacokinetics in special medical cases
Data on administration in special population is very limited.
No dose adjustment is required for *elderly patients* with normal kidney function. However, it is necessary to estimate the renal function and decrease the dose if there are signs of renal insufficiency (see "Posology and Administration").
The elimination half-life in patients with *renal impairment* increases proportionally to the degree of renal insufficiency. Patients with the values of creatinine clearance equal to or less than 40 ml/ min need dose adjustment (see "Posology and Administration").
The data obtained during the studies with participation of 12 patients undergoing continuous veno-venous hemofiltration (CVVH) with polyethylene sulfone hemofilters with the membrane area equal to 1.2 m^2 and average speed of ultrafiltration equal to 25 ml/ min, is available. In the described clinical conditions, the average values of clearance and plasma elimination half-life made up 100 ml/ min and 12 hours, respectively.
There is no change in pharmacokinetics of Fosfomycin in patients with *hepatic insufficiency* so no dose adjustment is required.
Pediatric population
Pharmacokinetics of Fosfomycin in children and adolescents at the age from 3 till 15 years old as well as in term newborn infants with normal kidney function is overall similar with the same of healthy adults. However, the glomerular filtration rate of newborn infants and children aged under 12 months with normal kidney function is physiologically lower in comparison with children aged above 12 months old and adults. It causes extension of Fosfomycin elimination half-life depending on the stage of renal aging.

Preclinical safety data

According to the preclinical data based on the standard safety pharmacology, repeated-dose toxicity, genotoxicity or reproductive toxicity studies, no special hazard for humans was revealed.
No data on carcinogenicity upon administration of Fosfomycin is available.

Therapeutic indications

Fosfomycin-TF is indicated for administration by patients of all age groups in cases when antibacterials that are usually recommended for the initial therapy of the infections listed below demonstrate ineffectiveness, or their administration is considered unreasonable:

- complicated urinary tract infections;
- infective endocarditis;
- infections of bones and articulations;
- hospital-acquired pneumonia, including ventilator-associated pneumonia;
- complicated skin and soft tissue infections;
- bacterial meningitis;
- complicated intra-abdominal infections;
- bacteremia possibly associated with any of the infections listed above.

Official recommendations on proper administration of antibacterials should be taken into consideration.

Contraindications

Hypersensitivity to the active ingredient or excipient contained in the composition of the medicinal product (see "Composition per 1 vial" section).

Precautions for use

Use in pregnancy and breastfeeding

No data on intravenous administration of Fosfomycin by pregnant women is available. Fosfomycin penetrates through the placenta. According to the data obtained during the studies in animals, no direct or indirect adverse effect of Fosfomycin on the reproductive system was revealed. Fosfomycin-TF can be prescribed to pregnant women provided that the expected benefit from the therapy for the mother exceeds the potential risk for the fetus.

Following administration of Fosfomycin, its small amounts were found in breast milk. Data on administration of Fosfomycin in breastfeeding is limited so it is not recommended as the first choice therapy for lactating women, especially in breastfeeding of a preterm or newborn infant. No specific risk for a baby on breastfeeding was revealed, however, as well as upon administration of other antibiotics, the potential risk of changing the intestinal flora in infants should be taken into consideration.

No data on effect on *fertility* in humans is available. Oral administration of Fosfomycin in doses up to 1,000 mg/ kg/ day didn't decrease fertility in male and female rats.

Effects of the medicinal product on ability to drive and use machines

No special studies were carried out, however, patients must be informed about possible occurrence of confused consciousness and asthenia. It can influence on ability to drive and use machines.

Special warnings

Risk of resistance development and necessity in combined therapy

During the *in vitro* studies, quick *selection of resistant mutant pathogens* was observed upon administration of Fosfomycin. Moreover, intravenous administration of Fosfomycin as monotherapy was connected with selection of the resistant microflora in the clinical studies. Whenever possible, it is recommended to introduce Fosfomycin as a part of a combined antibacterial treatment regimen in order to reduce the risk of selection of resistant pathogens.

Limited clinical data

Clinical data supporting intravenous administration of Fosfomycin for treatment of some therapeutic indications listed is limited by absence of adequate randomized controlled studies. Moreover, the data obtained during the clinical trials did not provide convincing proof of any of the studied dosing regimen of Fosfomycin for intravenous administration. It is recommended to prescribe Fosfomycin for treatment of the listed therapeutic indications provided that use of antibacterials recommended for the initial therapy is considered unreasonable.

Hypersensitivity reactions

Severe, sometimes fatal *hypersensitivity reactions*, including anaphylaxis and anaphylactic shock, can occur upon therapy with Fosfomycin. Upon occurrence of such reactions, treatment with Fosfomycin-TF should be terminated immediately, and adequate emergency measures should be taken.

Clostridioides difficile-associated diarrhea

It was reported about development of *C.difficile*-associated colitis and pseudomembranous colitis (from mild to life-threatening severity) upon therapy with Fosfomycin. It is important to take this diagnosis into account for patients with diarrhea developed during or following administration of Fosfomycin-TF. In such cases some consideration should be given to discontinuation of Fosfomycin-TF and prescription of specific treatment for the infection caused by *C.difficile.* Medicinal products that inhibit intestinal peristalsis should not be prescribed.

Sodium and potassium levels and risk of sodium overload

The sodium and potassium levels should be controlled on a regular basis in patients receiving Fosfomycin, especially upon long-term treatment.

1 g of Fosfomycin (equivalent to 1.32 g of fosfomycin sodium) contains 14 mmol (320 mg) of sodium which is equivalent to 16% of the recommended by the World Health Organization level of sodium consumption for adults that makes up 2 g of sodium per day. One vial of the medicinal product "Fosfomycin-TF" contains 28 mmol (640 mg) of sodium which should be taken into consideration by patients on diet with low content of sodium.

In consideration of high content of sodium, the risk of hypernatremia and fluid overload should be estimated prior to treatment, especially in patients with past medical history of congestive cardiac failure or with concurrent diseases such as nephrotic syndrome, hepatic cirrhosis, hypertension, hyperaldosteronism, pulmonary edema or hypoalbuminemia, as well as in newborn infants with sodium limitation. Upon treatment, it is recommended to keep to a diet with low content of sodium. Some consideration should also be given to extension of the infusion period and/ or reduction of the individual dose (with more frequent administration). Fosfomycin can decrease the level of potassium in serum or plasma so some consideration should be given to additional administration of potassium by the patient.

Haematological reactions (including agranulocytosis)

It was reported about development of haemotological reactions, including neutropenia or agranulocytosis, in patients receiving Fosfomycin by intravenous administration. Leukocytes with differential should be controlled on a regular basis, and upon development of haemotological reactions adequate treatment should be prescribed.

Renal insufficiency

It is necessary to adjust the dose depending on the degree of renal insufficiency in patients with renal impairment (see "Posology and Administration" section).

Posology and Administration

The daily dose of Fosfomycin-TF is determined in accordance with the therapeutic indications, severity of the disease and localization of the pathological process, susceptibility of the pathogen (-s), age and condition of the kidney function of the patient. The age and body weight of the children are also taken into account.

Adults and children above 12 years old (≥40 kg)

Table 1. General recommendations on dosing for adults and children above 12 years old with creatinine clearance >80 ml/ min

Therapeutic indication	Daily dose
Complicated urinary tract infections	12-24 g[a] in 2-3 divided doses
Infective endocarditis	12-24 g[a] in 2-3 divided doses
Infections of bones and articulations	12-24 g[a] in 2-3 divided doses
Hospital-acquired pneumonia, including ventilator-associated pneumonia	12-24 g[a] in 2-3 divided doses
Complicated skin and soft tissue infections	12-24 g[a] in 2-3 divided doses
Bacterial meningitis	16-24 g[a] in 3-4 divided doses
Complicated intra-abdominal infections	12-24 g[a] in 2-3 divided doses
Bacteremia possibly associated with any of the infections listed above	12-24 g[a] in 2-3 divided doses

The individual dose should not exceed 8 g.

[a] The regimen of high doses in 3 divided doses should be applied for severe infections which is known to be caused by less responsive bacteria.

Data on safety of high dose administration, in particular, doses exceeding 16 g/ day, is limited. Upon prescription of such doses, special precautions should be taken.

Therapy duration

The therapy duration is determined in accordance with the type and severity of the infection as well as with the clinical response of the patient. Upon determination of the therapy duration, corresponding therapeutic recommendations should be followed.

Administration by patients with renal impairment

No dose adjustment is recommended in patients with calculated creatinine clearance from 40 till 80 ml/ min. However, in such cases special precautions should be taken, especially upon prescription of the doses within the upper recommended range.

The dose of Fosfomycin is required to be adjusted in accordance with the degree of renal insufficiency based on the values of creatinine clearance in patients with renal impairment.

Table 2. Dose adjustment in patients with creatinine clearance <40 ml/ min

Creatinine clearance of the patient	Creatinine clearance of the patient/ Normal creatinine clearance	Recommended daily dose[a]
40 ml/ min	0.333	70% (in 2-3 divided doses)
30 ml/ min	0.250	60% (in 2-3 divided doses)
20 ml/ min	0.167	40% (in 2-3 divided doses)
10 ml/ min	0.083	20% (in 1-2 divided doses)

[a] The dose is expressed as a part of the recommended dose for patients with normal kidney function calculated according to the Cockroft-Gault formula.

The first (loading) dose should be increased by 100% but should not exceed 8 g.

Patients receiving substitutive renal therapy

Patients on chronic discontinuous dialysis treatment (every 48 hours) should administer 2 g of Fosfomycin at the end of each dialysis session.

Fosfomycin is effectively eliminated during continuous veno-venous hemofiltration (CVVH) in the post-dilution mode. No dose adjustment is required in such patients.

Administration by patients with hepatic impairment

No dose adjustment is required in patients with hepatic impairment.

Administration by elderly patients

The recommended doses for adults should be used for elderly patients. Special precautions should be taken upon administration of the doses within the upper recommended range (see "Administration by patients with renal impairment").

Pediatric population

Recommendations on dosing regimen are based on very limited data.

Newborn infants and children under 12 years old (<40 kg)

The dose of Fosfomycin for children should be determined in accordance with the age and body weight (BW).

Table 3. Doses for children and newborn infants

Age/ Body weight	Daily dose
Preterm newborn infants (age [a] <40 weeks)	100 mg/ kg of BW in 2 divided doses
Newborn infants (age [a] 40-44 weeks)	200 mg/ kg of BW in 3 divided doses
Children at the age from 1 till 12 months old (to 10 kg of BW)	200-300 [b] mg/ kg of BW in 3 divided doses
Children at the age from 1 till 12 years old (10-40 kg of BW)	200-400 [b] mg/ kg of BW in 3-4 divided doses

[a] The sum of gestational and postnatal age.

[b] The regimen of high doses can be applied for severe and/ or serious infections (such as meningitis), especially in cases when the infection is caused by the established or suspected infecting agent with moderate hypersensitivity.

No dosing recommendations for children with *renal insufficiency* are available.

Method of administration

Fosfomycin-TF is intended for intravenous administration only!

The infusion period should be at least 15 minutes for 2 g dose, at least 30 minutes for 4 g dose and at least 60 minutes for 8 g dose.

Separate reports from the literature data specify that extension of the infusion period to 4 hours can reduce the risk of development of hypokalemia. Some consideration can be given to the extended infusion period (to 4 hours for 4 g and 8 g doses) for patients with the high risk of hypokalemia.

Only clear solution of the medicinal product is allowed to administration!

Noci-influence is possible upon unintentional intra-arterial administration of the medicinal products which are not recommended for intra-arterial therapy. *It is necessary to make sure that Fosfomycin-TF is administered intravenously only!*

Rules of solution preparation and administration

Prior to administration, the medicinal product Fosfomycin-TF should be reconstituted and diluted. Water for injection, 5% glucose solution for infusion or 10% glucose solution for infusion can be used as a solvent for reconstitution. *Solvents containing sodium chloride are not allowed to use due to additional sodium loading (see "Precautions for use" section)!*

Reconstitution

It is necessary to shake the vial till reconstitution in order to loosen the powder. Add 20 ml of the solvent into the vial with 2 g of the medicinal product under aseptic conditions. Shake carefully till complete dissolution.

The exothermic reaction is possible upon dissolution of the medicinal product Fosfomycin-TF.

Reconstituted solutions are not allowed to use for infusion!

The medicinal product reconstituted in a vial with the help of *water for injection* under aseptic conditions reserves its physical and chemical stability within 24 hours, subject to protecting from light and storing at the temperature of 25°C. From the microbiological point of view, the prepared medicinal product should be administered immediately, otherwise the responsibility for the storage period and conditions during the administration process is rested on the customer.

The reconstituted solution in a vial should be clear colorless or light-yellow.

The medicinal product reconstituted in a vial with the help of *5%* or *10% glucose solutions* is subject to further dilution *immediately after reconstitution*.

Dilution

The following solvents can be used for preparation of solution for infusion: water for injection, 5% glucose solution for infusion or 10% glucose solution for infusion.

Transfer the reconstituted content of **2 g** vial into an infusion container with **30 ml** of the compatible solvent.

Upon infusion of **4 g** dose, the corresponding amount of the reconstituted solution is dissolved in the compatible solvent till the final volume of **100 ml**.

Upon infusion of doses exceeding **4 g**, the corresponding amount of the reconstituted solution is dissolved in the compatible solvent till the final volume of **200 ml**.

The solution diluted for infusion should be clear colorless or light-yellow.

Solutions diluted for infusion should be administered immediately after preparation!

Side effects

The most common adverse reactions in the course of treatment are erythematous skin rash, ion imbalance, administration site reactions, dysgeusia and gastrointestinal disorders. Other important adverse reactions include anaphylactic shock, antibiotic-associated colitis and decrease of the leukocyte number.

Adverse reactions are provided in accordance with the system organ classification and frequency of occurrence. The following categories are used for frequency determination: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), unknown frequency (it is not possible to determine the frequency based on the data available).

Blood and lymphatic system disorders: unknown frequency – transient agranulocytosis, leukopenia, thrombocytopenia, neutropenia.

Immune system disorders: very rare – anaphylactic reactions, including anaphylactic shock and hypersensitivity.

Nervous system disorders: common – dysgeusia; uncommon – headache.
Respiratory, thoracic and mediastinal disorders: uncommon – dyspnea; unknown frequency – asthma attack.
Gastrointestinal disorders: uncommon – nausea, emesis, diarrhea; unknown frequency – antibiotic-associated colitis.
Hepatobiliary disorders: uncommon – transient increase of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl transpeptidase of blood; unknown frequency – hepatitis.
Skin and subcutaneous tissue disorders: common – erythematous rash; uncommon – rash; unknown frequency – angioneurotic edema, pruritus, urticarial.
General disorders and administration site conditions: common – site administration phlebitis; uncommon – asthenia.
Laboratory and instrumental studies: common – hypernatremia, hypokalemia.
Description of particular adverse reactions
Hypokalemia can lead to diffuse symptoms such as weakness, lassitude or oedema and/ or muscular twitching. Severe forms can cause hyporeflexia and heart beat disorder. Hypernatremia can cause hypertension and such signs of hypervolemia as oedema. Severe forms can cause confused consciousness, hyperreflexia, convulsions and coma.
Pediatric population
Data on safety of administration of Fosfomycin by children is limited. It can be expected that frequency, type and severity of adverse reactions will be similar with the same of adults.
Reports of adverse reactions
It is important to report about suspected adverse reactions after registration of the medicinal product in order to ensure continuous monitoring of the benefit-risk profile. Medical specialists are recommended to report about any suspected adverse reactions to the medicinal product by means of the national system of reporting about adverse reactions.
Upon occurrence of any adverse reactions, patients are recommended to consult with a medical specialist or report about the adverse reactions to the information data base of adverse reactions to medicinal products. This recommendation covers any possible adverse reactions, including to the medicinal products not listed in the package leaflet, including reports of ineffectiveness of the medicinal product. Reports of adverse reactions allow to receive more data on the medicinal product safety.

Overdose

Data on Fosfomycin overdose is limited. It was reported about cases of hypotension, somnolence, electrolytic imbalance, thrombocytopenia and hypoprotrombinemia upon parenteral administration of Fosfomycin. In case of overdose, the patient's state should be controlled (especially the electrolyte level in plasma/ blood serum), and symptomatic and supportive treatment should be carried out. Fluid balance recovery is recommended which ensures urine elimination of the medicinal product. Fosfomycin is effectively eliminated from the organism upon hemodialysis with the average elimination half-life of about 4 hours.

Interaction with other medicinal products

It was reported about numerous cases of increase in activity of oral anticoagulants in patients receiving antibacterial therapy. The risk factors were severity of the infection or inflammatory process as well as the age and general state of the patient. In such cases it is difficult to estimate the effect on disbalance of the international normalised ratio (INR) of the infection itself and its treatment. However, some classes of antibiotics have a more active effect, in particular, fluoroquinolones, macrolides, cyclins, co-trimoxazole and some cephalosporins.

Storage conditions and shelf life
In the original package (to protect from light) at a temperature not exceeding 25°C.
Keep out of reach of children.
Shelf life is 3 years. Do not use upon expiry of the shelf life indicated on the package.
The solution in a vial reconstituted with the help of *water for injection* reserves its physical and chemical stability within 24 hours, subject to protecting from light and storing at the temperature of 25°C. From the microbiological point of view, the prepared medicinal product should be administered immediately, otherwise the responsibility for the storage period and conditions during the administration process is rested on the customer.
Prescription status
Prescription medicinal product only.
Package
2.0 g of the active ingredient in vials for injection with the volume of 20 ml. 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 package leaflet in a boxboard pack.
25 vials with package leaflets in a boxboard package (package for inpatient facilities).
Information about the manufacturer
“TriplePharm” JLLC, Minskaya street, building 2B, 223141, Logoysk, Minsk region, Republic of Belarus, tel./ fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com