For the use of Registered Medical Practitioner, Hospital or Laboratory only

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# Fosfomycin for Injection 4 gm

## FOSFOMYWIN-4

**COMPOSITION:**
Each vial contains:
Fosfomycin Sodium (Sterile)
Equivalent to Anhydrous
Fosfomycin ..... 4 g
(A Sterile Lyophilized Powder)

**DESCRIPTION**

**Fosfomywin** is a sterile, powder for solution for intravenous infusion that contains Fosfomycin sodium. Chemical name of Fosfomycin sodium is disodium (2R, 3S)-(3-methyloxiran-2-yl) phosphonate, The molecular formula is $C_3H_3Na_2O_4P$ and the molecular weight is 182.02 g/mol. Fosfomycin sodium is very soluble in water, sparingly soluble in methanol and practically insoluble in ethanol and methylene chloride.

**CLINICAL PHARMACOLOGY**

**PHARMACODYNAMICS**

Mode of action

Fosfomycin exerts a bactericidal effect on proliferating pathogens by preventing the enzymatic synthesis of the bacterial cell wall. Fosfomycin inhibits the first stage of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems).

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship:

Limited data indicate that Fosfomycin most likely acts in a time-dependent manner.

Resistance mechanism

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems, Further resistance mechanisms, which are plasmid- or transposon-borne, cause enzymatic inactivation of Fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus-bond in the fosfomycin molecule, respectively.

The risk of the occurrence of resistant mutants is effectively reduced by combination therapy with other antibiotics.

Cross-resistance

The mode of action of Fosfomycin differs from that of all other antibiotic classes. Fosfomycin was generally found to be active in-vitro against clinical isolates of methicillin-resistant staphylococci, vancomycin-resistant enterococci, penicillin- and erythromycin-resistant streptococci and multi-resistant *Pseudomonas*.

Antimicrobial spectrum of Fosfomycin(in vitro)

The data predict only the probability of micro-organism susceptibility to fosfomycin. For intravenous Fosfomycin, the susceptibility breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *Staphylococci, Enterobacteriaceae and Pseudomonas.* spp, is as follows:

≤ 32 µg/ml = susceptible
> 32 µg/ml = resistant.

In-vitro activity spectrum of Fosfomycin and resistance

The following table is based on the breakpoint according to EUCAST and comprises organisms relevant for the approved indications:

| **Commonly susceptible species** | |
|---|---|
| **Aerobic Gram-positive microorganisms**<br>*Staphylococcus aureus*<br>*Streptococcus pyogenes*<br>*Streptococcus pneumoniae* | **Aerobic Gram-negative microorganisms**<br>*Citrobacter* spp,<br>*Edwardsiella* spp,<br>*Enterobacter cancerogenus*<br>*Escherichia coli*<br>*Haemophilus influenzae*<br>*Klebsiella oxytoca*<br>*Neisseria* spp,<br>*Proteus mirabilis*<br>*Proteus penneri*<br>*Providencia rettgeri* |
| **Anaerobic microorganisms**<br>*Peptococcus spp.*<br>*Peptostreptococcus spp.* | |
| **Species in which acquired resistance may be a problem** | |
| **Gram-positive microorganisms**<br>*Enterococcus faecalis*<br>*Staphylococcus epidermidis* | **Gram-negative microorganisms**<br>*Enterobacter cloacae*<br>*Klebsiella pneumoniae*<br>*Proteus inconstans*<br>*Pseudomonas aeruginosa*<br>*Serratia marcescens* |
| **Inherently resistant species** | |
| **Gram-negative microorganisms**<br>*Morganella morganii* | **Anaerobic microorganisms**<br>*Bacteroides spp.* |

The physiologically important apathogenic anaerobic species, *Lactobacillus* and *Bifidobacterium*, are not susceptible to fosfomycin.

**PHARMACOKINETICS**

A single intravenous infusion of 4 g and 8 g of Fosfomycin in young healthy males resulted in maximum serum concentrations ($C_{max}$) of approx. 200 and 400 µg/ml, respectively. The serum half-life was approx. 2 hours. In elderly and/or critically ill male and female subjects, single intravenous doses of 8 g of fosfomycin resulted in mean $C_{max}$ and half-lives in plasma of approximately 350-380 µg/ml and 3,6-3,8 h, respectively.

Distribution

The apparent volume of distribution of Fosfomycin is approx. 0,30 l/kg body weight. Fosfomycin is distributed well to tissues. High concentrations are reached in eyes, bones, wound secretions, musculature, cutis, subcutis, lungs and bile. In patients with inflamed meninges, cerebrospinal fluid concentrations reach approx. 20-50% of the corresponding serum levels. Fosfomycin passes the placental barrier, Low quantities were found in human milk (about 8 % of the serum concentrations). The plasma protein binding is negligible.

Metabolism

Fosfomycin is not metabolized by the liver and does not undergo enterohepatic circulation. No accumulation is therefore to be expected in patients with hepatic impairment.

Elimination

80-90% of the quantity of Fosfomycin administered to healthy adults is eliminated renally within 10 hours after a single intravenous administration. Fosfomycin is not metabolized, i.e. the biologically active compound is eliminated. In patients with normal or mildly to moderately impaired renal function (creatinine clearance ≥ 40 ml/min), approximately 50-60% of the overall dose is excreted within the first 3-4 hours.

Linearity

Fosfomycin shows linear pharmacokinetic behavior after intravenous infusion of therapeutically used doses.

**Special populations**

*Pregnancy*

No clinical data on pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. **Fosfomywin** should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

*Lactation*

After the administration, low quantities of fosfomycin were found in human milk. **Fosfomywin** should therefore not be administered during lactation, unless the benefit outweighs the risk.

*Elderly*

No dose adjustment is necessary based on age alone, However, renal function should be assessed and the dose should be reduced if there is evidence of renal impairment.

*Paediatric population*

The pharmacokinetics of Fosfomycin in children and adolescents aged 3-15 years as well as in term newborns with normal renal function are generally similar to those of healthy adult subjects. However, in renally healthy neonates and infants up to 12 months, the glomerular filtration rate is physiologically decreased compared to older children and adults. This is associated with a prolongation of the elimination half-life of fosfomycin in dependence on the stage of renal maturation.

*Renal insufficiency*

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Patients with creatinine clearance values of 40 ml/min or less require dose adjustments.

*Hepatic insufficiency*

There is no requirement for dosage adjustments in patients with hepatic insufficiency since the pharmacokinetics of fosfomycin remains unaffected in this patient group.

**INDICATIONS**

**Fosfomywin** is indicated for the treatment of the following infections in adults and children including neonates:

- Acute osteomyelitis
- Complicated urinary tract infections
- Nosocomial lower respiratory tract infections
- Bacterial meningitis
- Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

**Fosfomywin** should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of the infections listed above, or when these alternative antibacterial agents have failed to demonstrate efficacy.

**DOSAGE AND ADMINISTRATION**

The daily dose of **Fosfomywin** is determined based on the indication, severity and site of the infection, susceptibility of the pathogen(s) to Fosfomycin and the estimated creatinine clearance. In children, it is also determined by age and body weight.

**Adults and adolescents ≥ 12 years of age (> 40 kg):**

Fosfomycin is primarily excreted renally unchanged.

The general dosage guidelines for adults with estimated creatinine clearance > 80 ml/min are as follows:

| Indication | Daily dose |
|---|---|
| Acute osteomyelitis | 12-24 g [a] in 2-3 divided doses |
| Complicated urinary tract infection | 12-16 g [b] in 2-3 divided doses |
| Nosocomial lower respiratory tract infection | 12-24 g [a] in 2-3 divided doses |
| Bacterial meningitis | 16-24 g [a] in 3-4 divided doses |

Individual doses must not exceed 8 g.

[b]The high-dose regimen in 3 divided doses should be used in severe infections expected or known to be caused by less susceptible bacteria.

[c]There are limited safety data in particular for doses in excess of 16 g/day. Special caution is advised when such doses are prescribed.

Dosage in renal insufficiency

It is unclear if dose reductions are necessary for patients with an estimated creatinine clearance between 40-80 ml/min, Great caution should be exercised in these cases, particularly if doses at the higher end of the recommended range are considered.

In patients with impaired renal function the dose of **Fosfomywin** must be adjusted to the degree of renal impairment.

Dose titration should be based on creatinine clearance values. In adults, creatinine clearance may be calculated according to the following formula by Cockroft and Gault:

$$\text{Creatinine clearance } (CL_{CR}) \text{ in men [ml/min]} = \frac{(140 - \text{age [years]}) \times \text{body weight [kg]}}{72 \times \text{serum creatinine [mg/dl]}}$$

In order to calculate $CL_{CR}$ in women, the result of this formula is multiplied by 0,85.

Dosage table for patients with impaired renal function:

| $CL_{CR}$ patient | $CL_{CR}$ patient / $CL_{CR}$ normal | Daily dosage recommended [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 proportion of the dose that would have been considered appropriate if the patient's renal function were normal

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

Patients undergoing renal replacement therapy

Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of **Fosfomywin** at the end of each dialysis session.

During continuous veno-venous hemofiltration (post-dilution CVVHF), Fosfomycin is effectively eliminated, Patients undergoing post-dilution CVVHF will not require any dose adjustment. In a study investigating 12 patients under CVVHF customary polyethylene sulfone haemofilters with a membrane surface of 1,2 $m^2$ and a mean ultrafiltration rate of 25 ml/min were employed. In this clinical setting, the mean values of plasma clearance and elimination half-life in plasma were 100 ml/min, and 12h, respectively.

No clinical data exist for intravenous Fosfomycin in patients undergoing pre-dilution CVVHF or other forms of renal replacement therapy.

Neonates, infants and children < 12 years of age (< 40 kg)

The dosage of **Fosfomywin** in children should be based on age and body weight (BW):

| Age/weight | Daily dose |
|---|---|
| Premature neonates(age [a]<40 weeks) | 100 mg/kg in 2 divided doses |
| Neonates (age [a] 40-44 weeks) | 200 mg/kg in 3 divided doses |
| Infants 1-12 months (up to 10 kg) | 200-300 [b] mg/kg in 3 divided doses |
| Infants and children aged 1-12 year (10-40 kg) | 200-400 [b] mg/kg in 3-4 divided doses |

[a]Sum of gestational and postnatal age,

[b]The high-dose regimen may be considered for severe infections and or serious infections (such as meningitis), in particular when known or suspected to be caused by organisms with moderate susceptibility.

No dose recommendations can be made for children with renal impairment.

Preparation of the solution for infusion

Withdraw 20 ml Sterile Water for Injections from 100 ml Infusion bag (containing Sterile Water for Injections 100 ml). Then, transfer 20 ml Sterile Water for Injections in to the vial; shake the vial for about 30 seconds. Transfer the whole content immediately back to the infusion bag. Final concentration should be approximately 40 mg/ml. A slight degree of warming occurs when the powder is dissolved.

*Method of administration*

**Fosfomywin** is intended for intravenous administration. The duration of infusion should be at least 30 minutes for **Fosfomywin** 4 g. Use only clear solutions.

As damaging effects can result from inadvertent intra-arterial administration of products not specifically recommended for intra-arterial therapy, it is essential to ensure that **Fosfomywin** is only administered into veins.

*Duration of treatment*

The duration of treatment depends on the individual response of the pathogens and the patient's clinical outcome. Therapy should be continued for a few more days after fever and other symptoms have subsided.

**CONTRAINDICATIONS**

**Fosfomywin** is contraindicated in persons with known hypersensitivity to the active substance, Fosfomycin, or to any of the excipients.

**WARNINGS AND PRECAUTIONS**

Caution is advised when **Fosfomywin** is used in patients with cardiac insufficiency, hypertension, hyperaldosteronism, hypernatraemia or pulmonary oedema.

A high sodium load associated with the use of **Fosfomywin** may result in decreased levels of potassium in serum or plasma. A low-sodium diet is recommended during **Fosfomywin** treatment. The substitution of potassium may be necessary in some cases. Serum electrolyte levels and water balance must be monitored during therapy with .

Acute, potentially life-threatening hypersensitivity reactions (anaphylactic shock) may occur in very rare cases. At the first signs (including sweating, nausea, cyanosis), the infusion of **Fosfomywin** must be immediately discontinued. The intravenous line should be left in place. Depending upon the clinical situation, appropriate emergency measures may need to be initiated.

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all antibacterial agents including Fosfomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of **Fosfomywin** Discontinuation of therapy with Fosfomycin and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

In patients with severe renal insufficiency (creatinine clearance ≤ 40ml/min), the elimination of Fosfomycin is substantially slowed.

**DRUG INTERACTIONS**

No drug-drug interaction studies have been performed with **Fosfomywin** To date, no clinically relevant pharmacological interactions between Fosfomycin and other agents (drugs, stimulants or food stuffs) have been reported.

Combination with other antibiotics

In-vitro tests have shown that the combination of Fosfomycin with a β-lactam antibiotic such as penicillin, ampicillin, cefazolin or the class of carbapenems, usually shows an additive to synergistic effect. The same applies to the combination of Fosfomycin with most anti-staphylococcal (linezolid, quinupristin/dalfopristin, moxifloxacin) agents in the treatment of staphylococcal infections. The combination of Fosfomycin with aminoglycosides has predominantly indifferent to additive effects.

**ADVERSE REACTIONS**

Undesirable effects are listed by body system and frequency in accordance with the following classification: Very common: ≥ 1/10 Common: ≥ 1/100 to <1/10 Uncommon: ≥ 1/1,000 to <1/100 Rare: ≥ 1/10,000 to <1/1,000 Very rare: < 1/10,000 Not known: cannot be estimated from the available data.

| System Organ Class | Frequency Category | Adverse Drug Reactions |
|---|---|---|
| Blood and lymphatic system disorders | Rare | Aplastic anaemia, eosinophilia |
| | Frequency not known | Agranulocytosis, granulocytopenia, leucopenia, pancytopenia, thrombocytopenia |
| Immune system disorders | Very rare | Anaphylactic shock |
| Metabolism and nutrition disorders | Uncommon | Decreased appetite, hypernatraemia and/or hypokalaemia |
| Psychiatric disorders | Frequency not known | Confusion |
| Nervous system disorders | Uncommon | Dysgeusia, headache |
| Eye disorders | Very rare | Visual impairment |
| Ear and labyrinth disorders | Uncommon | Vertigo |
| Cardiac disorders | Frequency not known | Tachycardia |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Dyspnoea |
| | Frequency not known | Asthmatic attack |
| Gastrointestinal disorders | Common | Retching, stomach ache |
| | Uncommon | Nausea, vomiting, diarrhoea |
| | Frequency not known | Pseudomembranous colitis |
| Hepatobiliary disorders | Uncommon | Blood alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase increased (transient) |
| | Very rare | Fatty liver (completely reversible after discontinuation) |
| | Frequency not known | Hepatitis, cholestatic hepatitis, icterus |
| Skin and subcutaneous tissue disorders | Uncommon | Rash |
| | Frequency not known | Angioedema, facial oedema, pruritus, urticaria |
| General disorders and administration site conditions | Common | Injection site phlebitis |
| | Uncommon | Fatigue |

**OVERDOSAGE**

To date, no cases of accidental overdose with clinically relevant intolerances have been reported, If an overdose is believed to have taken place, the patient must be monitored (particularly for plasma/serum electrolyte levels) and treated symptomatically, Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

**PRESENTATION**

**Fosfomywin** is available as 4g vial

**SHELF-LIFE**

Please see Manufacturing date and Expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

**STORAGE: Store below 25°C, protected from light.**

Keep all medicine out of reach of children.

After reconstitution: From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless reconstitution has taken place in controlled and validated aseptic conditions. A reconstituted solution that has been produced under aseptic conditions is chemically stable in a refrigerator (at 2-8°C or room temperature) for at least 24 hours, if protected from light.

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