

CRIFOS 4 GM Injection (Fosfomycin sodium)

Composition

CRIFOS 4 GM

Each vial contains:

Fosfomycin Sodium BP equivalent to

Fosfomycin.....4 g

Excipients.....q.s.

Dosage Form

Powder for solution for infusion

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 multiresistant *Pseudomonas*.

Antimicrobial spectrum of fosfomicin (in vitro)

The data predict only the probability of micro-organism susceptibility to fosfomicin.

For intravenous fosfomicin, 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.

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

In-vitro activity spectrum of fosfomicin 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
<i>Staphylococcus aureus</i>
<i>Streptococcus pyogenes</i>
<i>Streptococcus pneumonia</i>
Aerobic Gram-negative microorganisms
<i>Citrobacter spp.</i>
<i>Edwardsiella spp.</i>
<i>Enterobacter cancerogenus</i>
<i>Escherichia coli</i>
<i>Haemophilus influenza</i>
<i>Klebsiella oxytoca</i>
<i>Neisseria spp.</i>
<i>Proteus mirabilis</i>
<i>Proteus penneri</i>
<i>Providencia rettgeri</i>
Anaerobic microorganisms
<i>Peptococcus spp.</i>
<i>Peptostreptococcus spp.</i>
Species in which acquired resistance may be a problem
Gram-positive microorganisms

<i>Enterococcus faecalis</i>
<i>Staphylococcus epidermidis</i>
Gram-negative microorganisms
<i>Enterobacter cloacae</i>
<i>Klebsiella pneumonia</i>
<i>Proteus inconstans</i>
<i>Pseudomonas aeruginosa</i>
<i>Serratia marcescens</i>
Inherently resistant species
Gram-negative microorganisms
<i>Morganella morganii</i>
Anaerobic microorganisms
<i>Bacteroides spp.</i>

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

Pharmacokinetics

Absorption

A single intravenous infusion of 4 g and 8 g of fosfomycin in young healthy males resulted in a 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 metabolised 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

Very limited data are available in special populations.

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 (Please see “**DOSAGE AND ADMINISTRATION**” for further details).

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

Fosfomycin 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
- Bacteremia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Fosfomycin 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.

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

Dosage and Administration

Dosage

The daily dose of Fosfomycin 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 \geq 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.

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

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

Paediatric

Dose recommendations are based on very limited data.

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

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

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

Geriatric

The recommended doses for adults should be used in elderly patients. Caution is advised when considering the use of doses at the higher end of the recommended range.

Hepatic Impairment

There are no data indicating that dose adjustment is necessary in patients with hepatic impairment.

Renal Impairment

The dose recommendations for patients with renal impairment are based on pharmacokinetic modelling and limited clinical data; safety and efficacy have not yet been evaluated in clinical trials.

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 fosfomycin 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 Cockcroft and Gault:

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

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.

Patients undergoing renal replacement therapy

Patients undergoing chronic intermittent dialysis (every 48 hours) should receive 2 g of fosfomycin 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 m² 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.

Method of Preparation and Administration

Aseptically add 20 ml of sterile water for injection, shake the vial for about 30 seconds. Transfer whole content immediately to 100 ml sterile water for injection. Final concentration should be 40 mg/ml. Final infusion can be stored up to 24 hours at room temperature or in a refrigerator (at 2-8°C). A slight degree of warming occurs when the powder is dissolved. The duration of infusion should be at least 30 minutes for fosfomycin for injection 4 g. Use only clear solutions.

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

Hypersensitivity to the active substance, fosfomycin, or to any of the excipients.

Warnings and Precautions

General

Caution is advised when fosfomycin is used in patients with cardiac insufficiency, hypertension, hyperaldosteronism, hypernatraemia or pulmonary oedema. One vial with 4 g of fosfomycin contains 56 mmol (1280 mg) sodium.

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

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 fosfomycin 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 diarrhea during or subsequent to the administration of fosfomycin. 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 \leq 40ml/min), the elimination of fosfomycin is substantially slowed.

Drug Interactions

No drug-drug interaction studies have been performed with fosfomycin. To date, no clinically relevant pharmacological interactions between fosfomycin and other agents (drugs, stimulants or foodstuffs) 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.

Very limited data are available in special populations.

Renal Impairment

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. (See **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

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

Fertility

To date, in humans no reduction in fertility after therapy with fosfomycin has been reported. In male and female rats, reduced fertility was observed after the oral administration of fosfomycin at supra-therapeutic doses.

Pregnancy

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

Lactation

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

Paediatric

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.

Geriatrics

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 (see **DOSAGE AND ADMINISTRATION**).

Effects on Ability to Drive and Use Machines

Occasionally, even if the product is correctly administered, side effects may occur which impair the ability to drive and use machines.

Undesirable Effects

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
	Rare	Aplastic anaemia, eosinophilia
Blood and lymphatic system disorders	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
	Common	Retching, stomach ache
Gastrointestinal disorders	Uncommon	Nausea, vomiting, diarrhea
	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 of fosfomycin)
	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.

Incompatibility

Although no chemical/pharmaceutical incompatibilities have been found, fosfomycin solutions should not be mixed together with other parenteral preparations with the exception of water for injection.

Storage and Handling Instructions

Before Opening

Store below 25°C, Protect from light. Keep all medicine out of reach of children.

Reconstituted Solutions

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.

Final infusion that has been produced under aseptic conditions can be stored up to 24 hours at room temperature or in a refrigerator (at 2-8°C), if protected from light.

Packaging Information

CRIFOS 4 GM: Vial of 50 mL

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