

## FOSFOCINA INYECTABLE

### TECHNICAL SPECIFICS

#### NAME OF MEDICATION

**Fosfocina Intramuscular 1g**

**Fosfocina Intravenosa 1g**

**Fosfocina Intravenosa 4g**

#### 1. QUANTATIVE AND QUALITATIVE COMPOSITION

**Fosfocina Intramuscular 1g**

Disodium Fosfomycin.....1g per vial

Lidocaine Chlorhydrate.....30mg per ampoule of dissolvent

**Fosfocina Intravenosa 1g**

Disodium Fosfomycin.....1g per vial

**Fosfocina Intravenosa 4g**

Disodium Fosfomycin.....4g per vial

#### PHARMACEUTICAL FORM

**Fosfocina Intramuscular 1g:** Powder and dissolvent for injectable solution.

**Fosfocina Intravenosa 1g:** Powder and dissolvent for injectable solution.

**Fosfocina Intravenosa 4g:** Powder for injectable solution.

#### 2. THERAPEUTIC INDICATIONS.

**Fosfocina Intramuscular** is recommended for the treatment of genitourinary tract infections, respiratory tract infections, and soft tissue abscesses caused by micro-organisms sensitive to fosfomycin.

**Fosfocina Intravenosa** is recommended in the treatment of grave or complicated urinary, dermatological, gynaecological, respiratory, surgical and septicaemic infections, as well as infections of the locomotive apparatus, endocarditis and meningitis, caused by micro-organisms susceptible to fosfomycin. In cases of severe hospital infections (septicaemia, endocarditis, meningitis) it is essential to use fosfomycin in conjunction with other antibiotics (see 4.4 “Warnings and special precautions of use”) Fosfomycin can be used, in conjunction with other drugs, against methicillin-resistant Staphylococcal meningitis.

#### 3. DOSAGE AND FORM OF ADMINISTRATION

**Fosfocina Intramuscular** is administered exclusively in deep muscle tissue, after aspiration to ensure the needle doesn't pierce a blood vessel.

**Adults:** 1-2g every 8 hours. In serious infections up to 8g a day can be administered.

**Children more than 2½ years old:** 500-1000mg every 8 hours.

When higher doses are necessary, they must be given intravenously.

**Fosfocina Intravenosa** is administered exclusively as an intravenous drip of 1 hour duration.

**Adults:** 4g every 6-8 hours

**Children:** 200-400 mg/kg/day, over 2-3 daily administrations.

**Renal insufficiency:** The dose should remain at a constant 4g, with the interval between administrations varying according to the creatine clearance rate.

Creatinine clearance	Doses	Hours between doses
40-20 ml/min	4 g	12 h
20-10 ml/min	4 g	24 h
≤ 10 ml/min	4 g	48 h

**Patients on haemodialysis:** A perfusion of 2-4g after every haemodialysis session.

#### 4. COUNTERINDICATIONS

Known hypersensitivity to fosfomicin or any of the components of this product. Fosfocina Intramuscular should not be administered to patients with a history of hypersensitivity to lidocaine or to children under 2 ½.

#### Warnings and special precautions of use

Before administering fosfomicin, the possible previous existence of hypersensitivity to fosfomicin (and lidocaine in the case of Fosfocina Intramuscular) should be investigated. (See 4.8 Adverse reactions)

In cases of severe hospital infections it is essential to use fosfomicin in conjunction with other antibiotics, to avoid to the maximum the selection of resistant mutants (acquired chromosomal resistance).

In patients with severe or moderate renal failure interval between doses should be adapted in accordance with the creatine clearance rate (see 4.2 Posology and form of administration)

It must be taken into account that each gram of fosfomicin contains 330mg of sodium. When fosfomicin is administered at high doses for long periods of time, in patients who require a restricted sodium intake (cardiopathy, hypertension, acute pulmonary edema, etc), sodium chloride consumption should be restricted and the level of sodium, potassium and chorine ions in the blood should be checked periodically.

Fosfocina Intramuscular contains lidocaine in the dissolvent, in order to increase its local tolerance. In consequence it must not be administered intravenously, or in children younger than 2½ , or to anyone with a history of hypersensitivity to lidocaine.

Fosfocina intramuscular contains an ingredient which can give a positive result in a doping test.

#### Interactions with other medication and other forms of interaction

Fosfomicin can prove to be synergic with betalactamic antibiotics, aminoglucoisides, vancomycine, colistin, chloramphenicol, tetracycline, erythromycin and trimetroprime.

Antagonism is not produced in associations with tetracycline, chloramphenicol and erythromycin despite the fact that those antibiotics can produce antagonism with betalactamics which, like fosfomycin, act by inhibiting the synthesis of the bacterial wall.

### **Pregnancy and breastfeeding**

Studies conducted on animals have shown no evidence of teratogenic effects, but the possible effects of fosfomycin on pregnant women are not known. A small quantity of fosfomycin passes into breast milk.

### **Effects on capacity to drive or operate machinery**

None have been observed.

## **5. ADVERSE REACTIONS**

The following adverse reactions to fosfomycin have been observed:

Hypersensitive reactions: Cases of urticaria, cold sores, angioedema and severe hypersensitivity (anaphylaxis) have been observed.

Stomach upsets: Rarely, vomiting, dyspepsia, diarrhoea, nausea.

Alterations in hepatic function: Temporary increases in transaminase and alkaline phosphatase have been observed.

Haematological alterations: Rare cases of light increases in eosinophilis and platelets have been observed. Rarely, aplastic anaemia has been described.

Other adverse reactions: Cases of visual disturbance, loss of appetite, brochospasm and headaches have been reported. On occasion reinfection by resistant bacteria has been described.

Adverse reactions related lidocaine, relevant in the case of FOSFOCINA IM 1g. They principally affect the central nervous system, and are short term and dose dependent.

Neurological/Psychological Reactions: Drowsiness, dizziness, disorientation, confusion, trembling, psychosis, nervousness, euphoria, nausea, sickness, headaches, hallucinations. There is a risk of loss of consciousness and convulsions if administered too rapidly.

Cardiovascular reactions: Normal doses of lidocaine do not produce adverse cardiovascular effects, patients with elevated plasmatic levels of lidocaine or with myocardial conduction defects may develop hypertension, arrhythmia and brachycardia. In exceptional cases, cardiovascular collapse, which can cause cardiac arrest.

Respiratory reactions: Respiratory depression when administered too rapidly.

Ocular reactions: Blurred vision, double vision.

Other adverse reactions attributable to lidocaine: Phlebitis, vein thrombosis at the point of injection, fever. Risk of malign hyperthermia.

## Overdoses

No cases of overdose of injectable fosfomycin have ever been described. If this should occur, signs of sodium overload may appear. It may be necessary to treat this with natriuretics.

## 6. PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties.

Fosfomycin acts to inhibit the synthesis of the bacterial wall. It penetrates the bacterial cell through two active transport systems: the alphaglycerophosphate path, constitutive in sensitive bacteria, and the hexose phosphate path, operative through induction in some bacterial species, especially through the glucose-6-phosphate. Afterwards it selectively and irreversibly inhibits the UDP-N-acetyl-glucosamine: transferase phosphoenolpyruvate, the enzyme which catalyzes the first stage of synthesis in the bacterial wall.

Fosfomycin acts as a bactericide and works over a wide spectrum of gram-positive and gram-negative bacteria.

Gram-positives: *Staphylococcus spp.* (including methicillin resistant strains), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus faecalis*.

Gram-negatives: *Escherichia coli*, *Citrobacter spp.*, *Enterobacter spp.*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus rettgeri*, *Serratia marcescens*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Salmonella spp.*, *Shigella spp.*, *Campylobacter spp.*, and *Yersinia enterocolitica*.

*Klebsiella spp* and *providencia* are **moderately sensitive**.

*Bacteroides*, *Brucella*, *Corynebacterium*, *Mycoplasma*, *Chlamydia*, *Treponema*, *Borrelia* and *Mycobacterium* **are resistant**.

### Pharmacokinetic properties

Fosfomycin, administered intramuscularly, reaches maximum seric concentrations after 1 hour. These are 17mcg/ml and 28mcg/ml for doses of 0.5g and 1g respectively. 6 hours after a 1g dose, seric concentrations are still 8mcg/ml. Around 90% of the administered dose is eliminated within 24 hours through the urine, in which there are concentrations higher than 100mcg/ml up to 12 hours after a 0.5g dose.

The administration of intravenous 0.5g or 1g doses of fosfomycin provide, within 15 minutes, seric concentrations of 28mcg/ml of 46mcg/ml respectively. These drop within half an hour to approximately half that figure (distribution phase), later falling more slowly. In a constant infusion of 500mg/h (12g/day) or of 650 mg/h (16 g/h) continuous plasma levels of 60mcg/ml, and 80mcg/ml, respectively, are reached. In 30 minute intravenous infusions of 4g diluted in 125ml of distilled water (repeated every 6 hours) maximum concentrations of 195mcg/ml, and 253mcg/ml, respectively, are achieved after 30 minutes. After six hours concentrations are 5.000-6.000 mcg/ml.

Fosfomycin shows good tissular and humeral diffusion and crosses the placentary and haematoencephalic barriers; it reaches therapeutic levels in urine, sputum, lymph,

pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, aqueous humour, kidney, lungs and bone. In milk, bile and vitreous humour it is found at very low levels.

Fosfomicin does not fix in plasma proteins and has an elimination half-life of 1.5-2 hours in patients with normal renal function, which is lengthened in cases of renal insufficiency.

When administered parenterally, the elimination of fosfomicin is primarily renal, via glomerular filtration. Fosfomicin administered in this way is largely unmetabolized (85-95% of the dose is expelled via the urine within 24 hours).

### **Pre-clinical safety data**

The preclinical data shows no evidence of any special risk for humans, in accordance with conventional tests for safety, acute toxicity, chronic toxicity, mutagenicity, and reproductive toxicity.

## **7. PHARMACEUTICAL DATA**

### **List of excipients**

Fosfocina Intramuscular 1g: Recrystallized succinic acid (vial): teraglycol, 1-2 propylenglycol and water for injection (dissolvent ampoule)

Fosfocina Intravenosa 1g: Recrystallized succinic acid (vial): water for injection (dissolvent ampoule)

Fosfocina intravenosa 4g: Recrystallized succinic acid (vial): water for injection (dissolvent ampoule)

### **Incompatibilities**

Fosfocina Intravenosa is physically incompatible with aqueous solutions of sodium ampicillin, cephalothin, erythromycin lactobionate, gentamicin, oxytetracycline, and rifampicin.

Fosfocina Intramuscular is physically incompatible with the same drugs as Fosfocina Intravenosa. It is also incompatible with aqueous solutions of streptomycin sulphate and kanamycin sulphate.

### **Period of validity**

Fosfocina Intramuscular: 1g: 36 months

Fosfocina Intravenosa 1g and 4g: 36 months

### **Special precautions for storage:**

Fosfocina Intramuscular and Fosfocina Intravenosa don't require any special storage conditions; they should be kept in a cool dry place, at room temperature.

Once open, Fosfocina Intramuscular can be kept at room temperature for 2-3 days without loss of effectiveness.

Fosfocina Intravenosa glucosate serum solution is stable for 24 hours.

Fosfocina Intravenosa is compatible with the following perfusion solutions:

Simple chlorinated	Glucosaline
Ringer	1.4% Bicarbonate of soda
Lactate 1/6 M	Levulose, from 5-10%

Ringer Lactate                      Elkinton's solution  
Darrow's solution                    10%, 30%, and 50% Dextrose

**Nature and Content of pack**

Fosfocina Intramuscular 1g: Type I glass vial with rubber cap and type I ampoule

Fosfocina Intravenosa 1g: Type I glass vial with rubber cap and type I ampoule

Fosfocina Intravenosa 4g: Type I glass vial

**Instructions for use and handling**

**Fosfocina Intramuscular 1g:** Reconstitute the solution using the entire contents (4ml) of the dissolvent ampoule. Shake until dissolution.

**Fosfocina Intravenosa 1g:** Dissolve the contents of the vial with the contents 10ml dissolvent ampoule.

Dilute in water for injection or in a glucosate serum at 4ml for every ml of the solution already prepared, and put in a 1hr drip. Ensure the volume corresponds to the correct dosage.

**Fosfocina Intravenosa 4g:** Dissolve the contents of the 4g vial with 20ml of the injection water or glucosate serum. Transfer to a container of 200ml of injection water or glucosate serum and place in a 1 hour drip.

**TITULAR AUTHORIZED FOR COMMERCIALIZATION**

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