SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fosfocina Intramuscular 1 g
Fosfocina Intravenosa 1 g
Fosfocina Intravenosa 4 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fosfocina Intramuscular 1 g
Fosfomycin (DOE) disodium ……..…… 1 g per vial
Lidocaine hydrochloride …… 30 mg per solvent vial

Fosfocin Intravenosa 1 g
Fosfomycin (DOE) disodium ……..… 1 g per vial

Fosfocin Intravenosa 4 g
Fosfomycin (DOE) disodium ……..…… 4 g per vial

3. PHARMACEUTICAL FORM

Fosfocina Intramuscular 1 g: Powder and solvent for solution for injection.
Fosfocina Intravenosa 1 g: Powder and solvent for solution for injection.
Fosfocina Intravenosa 4 g: Powder for solution for injection.

4. CLINICAL DATA

4.1 Therapeutic indications

Fosfocina Intramuscular is indicated for the treatment of infections of the genitourinary tract, respiratory tract and tissues caused by micro-organisms that are sensitive to fosfomycin.

Fosfocina Intravenosa is indicated for the treatment of complicated or serious infections of the urinary tract, dermatological, gynecological, respiratory, musculoskeletal, surgical, sepsis, endocarditis and meningitis caused by micro-organisms that are sensitive to fosfomycin. In cases of serious hospital infections (sepsis, endocarditis, meningitis), it is essential to use fosfomycin combined with other drugs (see 4.4 “Special warnings and precautions for use”). Fosfomycin can be used for methicillin-resistant staphylococcal meningitis, associated with other antibiotic drugs.

4.2 Posology and method of administration

Fosfocina Intramuscular must be injected exclusively via deep intramuscular injection, after previous aspiration to make sure the needle has not penetrated a vessel.

Adults: 1-2 g every 8 hours. In severe infections, up to 8 grams a day can be used.

Children over the age of 2½ years: 500-1000 mg every 8 hours.

When higher doses are required, this must be done by intravenous administration, using Fosfocina Intravenosa.

Fosfocina Intravenosa shall be administered exclusively by intravenous (IV) drip of 1 hour in duration.

Adults: 4 g every 6-8 hours.

Children: 200-400 mg/kg/day, distributed in 2-3 daily administrations.

Renal failure: A constant rate of dosage of 4 grams per administration must be maintained, increasing the interval between the same according to the creatinine clearance.

Clearance of creatinine	Dose	Interval between doses
40-20 ml/min.	4 g	12 hours
20-10 ml/min.	4 g	24 hours
≤ 10 ml/min.	4 g	48 hours

Patients on hemodialysis: A perfusion of 2-4 grams after each hemodialysis session.

4.3 Contraindications

Known hypersensitivity to fosfomycin or to any of the components of this product.
Fosfocina Intramuscular must not be administered to patients with a history of hypersensitivity to lidocaine or in children less than 2 years and a half old.

4.4 Special warnings and precautions for use

Before the administration of fosfomycin, the patient must be researched for prior episodes of hypersensitivity to fosfomycin (and to lidocaine, in the case of Fosfocina Intramuscular). (See section 4.8 "Undesirable effects")

In cases of serious hospital infections, it is essential to use fosfomycin combined with other drugs to avoid as much as possible the selection of resistant mutants (acquired resistance of chromosomal nature).

In patients with moderate or severe renal failure, the interval between doses will be adapted according to the creatinine clearance (see 4.2 "Posology and method of administration").

It must be taken into account that each gram of fosfomycin disodium contains 330 mg of sodium. For these patients that require sodium restriction (heart disease, hypertension, acute pulmonary edema, etc.), when administering high and prolonged doses, the intake of sodium chloride must be reduced and the blood concentration of sodium, potassium and chloride ions must be regularly monitored.

Fosfocina Intramuscular contains lidocaine in the solvent to increase its local tolerance. Accordingly, it must not be administered intravenously to children under the age or 2 and a half years nor to patients with a history of hypersensitivity to the lidocaine.

Fosfocina Intramuscular contains a component that can give a positive analytical result in a doping control.

4.5 Interaction with other medicinal products and other forms of interaction

Fosfomycin may show a synergistic behaviour in association with beta-lactam antibiotics, aminoglycosides, vancomycin, colistin, chloramphenicol, tetracycline, erythromycin and trimethoprim.

There is no antagonism when it is used together with tetracycline, chloramphenicol or erythromycin, despite the fact that such antibiotics can be antagonists with the beta-lactam antibiotics which, as fosfomycin, act by inhibiting the synthesis of the bacterial wall.

4.6 Pregnancy and lactation

Studies in animals have not shown any teratogenic effects, but not enough is known about the possible effect of Fosfomycin on pregnant women. A small amount of fosfomycin passes into breast milk.

4.7 Effects on the ability to drive and use of machinery

They have not been described.

4.8 Undesirable effects

4.8.1. The following undesirable effects of fosfomycin have been communicated:

Hypersensitivity reactions. Cases of exanthema, urticaria and angioedema and serious hypersensitivity reactions (anaphylaxis) have been observed (see section 4.4. “Special warnings and precautions for use”).

Digestive disorders. Rarely, vomiting, diarrhea, dyspepsia, nausea.

Alterations of the liver function. Temporary increases in transaminases and alkaline phosphatase have been reported.

Hematological alterations. Rare cases have been described of slight increases of eosinophils and platelets, as well as some mild petechial reactions. Aplastic anaemia has rarely been described.

Local effects. The injection of fosfomycin produces a more or less intense pain in the area where injected. With Fosfocina Intravenosa, the cases of phlebitis have been rare.

Other undesirable effects. There have been reports of cases of visual disturbances, inappetence, dyspnea, bronchospasm and headaches. Sometimes superinfections by resistant bacteria have been described.

4.8.2. Adverse reactions of lidocaine when Fosfocina IM 1g is administered. These mainly affect the Central Nervous System, are of short duration and dose-dependent.

Neurological/psychological reactions: drowsiness, dizziness, disorientation, confusion, tremors, psychosis, nervousness, euphoria, nausea, dizziness, headache, hallucinations. Risk of convulsions and loss of consciousness if the administration is too fast.

Cardiovascular reactions: Normal doses of lidocaine do not cause adverse cardiovascular effects; patients with elevated concentrations of lidocaine in plasma or with defects in myocardial conduction may develop hypotension, arrhythmia and bradycardia. Exceptionally, a cardiovascular collapse that may cause a cardiac arrest.

Respiratory reactions: respiratory depression, if the administration is too fast.

Eye reactions: blurred vision or diplopia.

Digestive reactions: vomiting.

Other undesirable effects related to lidocaine: phlebitis, venous thrombosis at the injection site, fever. Risk of malignant hyperthermia.

4.9 Overdose

There are no described cases of overdose with injectable fosfomycin. If they occur, there can be signs of excessive sodium overload that may be necessary to treat with natriuretic products.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fosfomycin inhibits the synthesis of the bacterial wall. It enters the bacterial cell by two active transport systems: via alpha-glycerophosphate, constitutive in sensitive bacteria, and via hexose-phosphate, operational in some bacterial species after their induction, especially by glucose-6-phosphate. Then, it selectively and irreversibly inhibits UDP-N-acetyl-glucosamine:phosphoenolpyruvate transferase, an enzyme that catalyses the first stage of the synthesis of the bacterial wall.

The action of fosfomycin is bactericidal and it is exercised over a broad spectrum of gram-positive and gram-negative bacteria.

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

Gram-negative: *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 *Providence* are moderately sensitive.

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

5.2 Pharmacokinetic properties

Intramuscularly administered fosfomycin provides maximal serum concentrations after 1 hour of 17 mcg/ml and 28 mcg/ml, with doses of 0.5 g and 1 g respectively. 6 hours after administering a dose of 1 gram, serum concentrations are still 8 mcg/ml. About 90% of the administered dose is eliminated in 24 hours through the urine, where concentrations above 100 mcg/ml can be found up to 12 hours after the administration of 0.5 grams.

The intravenous administration of dose of 0.5 and 1 g of fosfomycin in 15 minutes provides serum concentrations of 28 mcg/ml and 46 mcg/ml respectively, which in half an hour fall to approximately half (distribution phase) and then decrease more slowly later. With a constant infusion of 500 mg/h (12 g/day) or 650 mg/h (~ 16 g/day) the continuous plasma levels reached are 60 mcg/ml and 80 mcg/ml respectively. The intravenous infusions of 4 g diluted in 125 ml of distilled water during 30 minutes, repeated every 6 hours, give serum concentrations of 195 mcg/ml and 253 mcg/ml respectively after 30 minutes. 6 hours later, urinary concentrations are 5,000-6,000 mcg/ml.

Fosfomycin has a good humoral and tissue diffusion and crosses the placental barrier as well as the hematoencephalic one; it provides therapeutic levels in urine, sputum, lymph fluid, pleural, peritoneal, pericardial effusion and synovial fluids, the aqueous humour, the kidneys, lungs and bones. In milk, bile and vitreous humour very low concentrations are reached.

Fosfomycin is not set to plasma proteins and has an elimination half-life of 1.5 hours in subjects with normal renal function, which is longer for those with kidney failure.

Administered parenterally, the elimination of the fosfomycin is primarily renal, by glomerular filtration, in an active way, without metabolising and in a large proportion (85%-95% of the dose in the urine within 24 hours).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans, according to the results of conventional studies regarding safety, acute toxicity, chronic toxicity, mutagenicity and toxicity on reproduction.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Fosfocina Intramuscular 1 g: recrystallized succinic acid (vial); tetraglycol, 1-2 propylene glycol and water for injection (ampoule of solvent).

Fosfocina Intravenosa 1 g: recrystallized succinic acid (vial); water for injection (ampoule of solvent).

Fosfocina Intravenosa 4 g: recrystallized succinic acid.

6.2 Incompatibilities

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

Fosfocina Intramuscular is physically incompatible, in addition to the above mentioned, with aqueous solutions of streptomycin sulfate and kanamycin sulfate.

6.3 Shelf life

Fosfocina Intramuscular 1 g: 48 months.
Fosfocina Intravenosa 1 g and 4 g: 48 months.

6.4 Special precautions for storage

Fosfocina Intramuscular and Fosfocina Intravenosa do not require special precautions for storage; keep them in a cool and dry place at room temperature.

Prepared solutions for injection of Fosfocina Intramuscular can be kept at room temperature for 2-3 days without loss of activity.

The solution of Fosfocina Intravenosa in dextrose serum stays stable for 24 hours.

Fosfocina Intravenosa is compatible with the following infusion solutions:

Chlorinated simple	Glucosaline
Ringer's	1.4% sodium bicarbonate
Lactate 1/6 M	5% and 10% levulose
5% Glucose - 10% Dextran	Glucose-potassium solution
Lactated Ringer's	Elkinton Solution
Darrow solution	10%, 30% and 50% Dextrose

6.5 Nature and contents of container

Fosfocina Intramuscular 1 g: Type I glass vial with a bromobutyl plug and type I glass ampoule.
Normal container: 1 vial + 1 ampoule of solvent
Clinical container: 100 vials + 100 ampoules of solvent

Fosfocina Intravenosa 1 g: Type I glass vial with a bromobutyl plug and type I glass ampoule.
Normal container: 1 vial + 1 ampoule of solvent
Clinical container: 50 vials + 50 ampoules of solvent

Fosfocina Intravenosa 4 g: Type I glass vial.
Normal container: 1 vial
Clinical container: 50 vials

6.6 Instructions of use/handling

Fosfocina Intramuscular 1 g. Reconstitute the solution using the entire content (4 ml) of the solvent ampoule. Shake until dissolution.

Fosfocina Intravenosa 1 g. Dissolve the content of the vial into the 10 ml of the ampoule of solvent. Dilute in water for injection or dextrose serum at a rate of 4 ml per ml of the previously prepared solution and drip for 1 hour. Take the volume corresponding to the appropriate dose.

Fosfocina Intravenosa 4 g. Dissolve the content of the 4 g vial into 20 ml of water for injection or dextrose serum. Transfer to a container with 200 ml of water for injection or dextrose serum and drip for 1 hour.

Fosfomycin, upon dissolution, produces an exothermic reaction, with the consequent production of heat, that makes the vial is slightly warm.

6.7 Name or corporate name and permanent address or registered office of the holder of the marketing authorization

LABORATORIOS ERN, S.A.
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7. DATE OF APPROVAL OF THE SUMMARY OF PRODUCT CHARACTERISTICS

April 2003