

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Product Information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS

Powder for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition]

<Invented name> is indicated in all age groups for the treatment of the following infections when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment (see sections 4.2, 4.4 and 5.1):

- complicated urinary tract infections
- infective endocarditis
- bone and joint infections
- hospital-acquired pneumonia, including ventilator-associated pneumonia
- complicated skin and soft tissue infection
- bacterial meningitis
- complicated intra-abdominal infections
- bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

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

4.2 Posology and method of administration

[This section should read as follows:]

Posology

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 renal function. In children, it is also determined by age and body weight.

[This section should read as indicated below. The table below should only include posology information of approved indications in line with section 4.1 above.]

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

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

Table 1 – dosing in adults and adolescents with CrCl >80 ml/min

Indication	Daily dose
Complicated urinary tract infection	12–24 ^a g in 2–3 divided doses
Infective endocarditis	12–24 g ^a in 2–3 divided doses
Bone and joint infections	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
Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above	12–24 g ^a in 2–3 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.

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

[This section should read as follows:]

Duration of treatment

Treatment duration should take into account the type of infection, the severity of the infection as well as the patient's clinical response.

Elderly patients

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 (see also recommendations on dosage for patients with impaired renal function).

Renal impairment

No dose adjustment is recommended in patients within estimated creatinine clearance between 40–80 ml/min. However, 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.

Table 2 shows the recommended dose adjustments for patients with a CrCL less than 40 mL/min:

Table 2 – Dose adjustments for patients with a CrCL less than 40 mL/min

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 as calculated according to Cockcroft-Gault formula.

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

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 (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

Paediatric population

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):

Table 13 – Dosing in children and neonates

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.

Method of administration

<Invented name> is intended for intravenous use.

The duration of infusion should be at least 15 minutes for the 2 g pack size, at least 30 minutes for the 3, 4 and 5 g pack size and at least 60 minutes for the 8 g pack size.

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 fosfomycin is only administered into veins.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Section 4.3 Contraindications

[This section should read as follows:]

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Section 4.4 Special warnings and precautions for use

[This section should read as follows:]

Risk of selecting for resistance and the need for combination therapy

In vitro, fosfomycin has been found to rapidly select for resistant mutants. Also, the use of intravenous fosfomycin alone has been associated with selection of resistance in clinical studies. Whenever possible, it is recommended that fosfomycin is administered as part of a combination antibacterial drug regimen to reduce the risk of selecting for resistance.

Limitations of the clinical data

The clinical data to support the use of intravenous fosfomycin for treatment of some of the listed indications is limited by a lack of adequate randomised controlled trials. Furthermore, various dose regimens have been used and no single intravenous dose regimen has been strongly supported by clinical trial data. It is recommended that fosfomycin is selected to treat the listed indications only when it is considered inappropriate to use antibacterial agents that are commonly recommended for their initial treatment.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see sections 4.3 and 4.8). If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

Clostridioides difficile-associated diarrhea

Clostridioides difficile-associated colitis and pseudo-membranous colitis have been reported with fosfomycin and may range in severity from mild to life-threatening (see section 4.8). 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 *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sodium and potassium levels and risk of sodium overload

Sodium and potassium levels should be monitored regularly in patients receiving fosfomycin, in particular during prolonged treatment. Given the high content of sodium (0.32 grams) per gram of fosfomycin, the risk of hypernatraemia and fluid overload should be assessed before starting treatment, especially in patients with a history of congestive heart failure or underlying comorbidities such as nephrotic syndrome, liver cirrhosis, hypertension, hyperaldosteronism, pulmonary oedema or hypoalbuminemia as well as in neonates under sodium restriction. A low-sodium diet is recommended during treatment. An increase in the infusion length and/or a reduction to the individual dose (with more frequent administration) could also be considered. Fosfomycin may decrease potassium levels in serum or plasma, therefore potassium supplementation should be always considered.

Haematological reactions (including agranulocytosis)

In patients receiving fosfomycin intravenously haematological reactions including neutropenia or agranulocytosis have occurred (see section 4.8). Therefore, the leukocyte count should be monitored at regular intervals and if such reactions occur, an adequate medical treatment should be initiated.

Renal impairment

In patients with impaired renal function, adjust the dosage according to the grade of renal insufficiency (see section 4.2).

Excipients

[A warning about any excipient that would result in unwanted undesirable effects in patients with specific metabolism disorders (e.g. fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies (e.g against the colouring agent sunset yellow (E110)) should be added in this section. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

Section 4.5 Interaction with other medicinal products and other forms of interaction

[This section should read as follows:]

Specific concerns relating to INR imbalance:

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. The severity of the infection or inflammation, patient age and general state of health appear to be risk factors. Under these circumstances, it is difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly: fluoroquinolones, macrolides, cyclins, cotrimoxazole, and certain cephalosporins.

Section 4.6 Fertility, pregnancy and lactation

[This section should read as follows:]

Pregnancy:

There are no data from the use of intravenously administered fosfomycin in pregnant women. Fosfomycin crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Fosfomycin should therefore not be prescribed to pregnant women unless the benefit outweighs the risk.

Breast-feeding:

After the administration of fosfomycin, low quantities were found in human milk. Only scarce information about fosfomycin use during breastfeeding is available, therefore this treatment is not recommended as first choice for a breastfeeding woman, especially if she is breastfeeding a premature or new-born baby. No specific risk for a breastfed child was demonstrated, however, as with any other antibiotics a potential risk of changes in infant bowel flora should be taken into consideration.

Fertility:

No data in humans are available. In male and female rats oral administration of fosfomycin up to 1000 mg/kg/day did not impair fertility (see section 5.3).

Section 4.7 Effects on ability to drive and use machines

[This section should read as follows:]

No specific studies have been performed but patients should be informed that confusion and asthenia have been reported. This may influence some patients' ability to drive and use machines (see section 4.8).

Section 4.8 Undesirable effects

[This section should read as follows:]

Summary of the safety profile

The most commonly reported adverse reactions during treatment are erythematous skin eruption, ion disbalances (see section 4.4), injection site reactions, dysgeusia and gastrointestinal disturbances. Other important adverse reactions include anaphylactic shock, antibiotic associated colitis and decreases in white blood cell counts (see section 4.4).

Tabulated list of adverse reactions

Undesirable effects are listed by body system and frequency using the following convention:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Very rare: $< 1/10,000$

Not known: cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known	Agranulocytosis (transient), leucopenia, thrombocytopenia, neutropenia
Immune system disorders	Very rare	Anaphylactic reactions including anaphylactic shock and hypersensitivity (see section 4.4)
Nervous system disorders	Common	Dysgeusia,
	Uncommon	Headache
Investigations	Common	Hypernatremia, hypokalemia* (see section 4.4)
Gastrointestinal disorders	Uncommon	Nausea, vomiting, diarrhea
	Not known	Antibiotic-associated colitis (see section 4.4)
Hepatobiliary disorders	Uncommon	Blood alkaline phosphatase increased (transient), Transaminases increased (ALAT, ASAT), gamma-GT increased
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Common	Erythematous eruption
	Uncommon	Rash
	Not known	Angioedema, pruritus, urticaria

General disorders and administration site conditions	Common	Injection site phlebitis
	Uncommon	Asthenia

* see section below (Description of selected adverse reactions)

Description of selected adverse reactions:

Hypokalemia may result in diffuse symptoms such as weakness, tiredness or oedema and/or muscle twitching. Severe forms may cause hyporeflexia and cardiac arrhythmia. Hyponatremia may be associated with thirst, hypertension and signs of fluid overload such as oedema (see section 4.4). Severe forms may cause confusion, hyperreflexia, seizures and coma.

Paediatric population

Limited safety information is available from the paediatric population. Frequency, type and severity of adverse reactions may be expected to be similar to the adult population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Section 4.9 Overdose

[This section should read as follows:]

Experience regarding the overdose of fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin. In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

Section 5.1 Pharmacodynamic properties

[This section should read as follows:]

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials

ATC-Code: J01XX01

Mechanism 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/pharmacodynamic relationship

Limited data indicate that fosfomycin acts in a time-dependent manner.

Mechanism of resistance

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.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 10):

Species	susceptible	resistant
<i>Enterobacterales</i>	≤ 32 mg/L	> 32 mg/L
<i>Staphylococcus</i> spp.	≤ 32 mg/L	> 32 mg/L

Susceptibility

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.

The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to fosfomycin or not.

Commonly susceptible species

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.

Species in which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

Staphylococcus epidermidis

Streptococcus pneumoniae

Enterococcus spp.

Aerobic Gram-negative microorganisms

Enterobacter cloacae

Klebsiella aerogenes

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

*Pseudomonas aeruginosa**

Serratia marcescens

Anaerobic Gram-positive microorganisms

Clostridium spp.

Inherently resistant species

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 mikroorganisms

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Section 5.2 Pharmacokinetic properties

[This section should read as follows:]

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 approximately 200 and 400 $\mu\text{g/ml}$, respectively. The serum half-life was approximately 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 $\mu\text{g/ml}$ and 3.6–3.8 h, respectively.

Distribution

The apparent volume of distribution of fosfomycin is approximately 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 approximately 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 12 hours after a single intravenous administration. A small amount of the antibiotic is found in faeces (0.075%). Fosfomycin is not metabolised, 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 behaviour 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 (see section 4.2).

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 (see also section 4.2. "Renal impairment" for further details).

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.

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.

Section 5.3 Preclinical safety data

[This section should read as follows:]

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for Fosfomycin.

Fosfomycin trometamol granules for oral solution (3g)

4.1 Therapeutic indications

[This section should read as follows. Indications should only be implemented if the product was already approved for the condition]

<Invented name> is indicated for (see section 5.1):

- the treatment of acute, uncomplicated cystitis in women and female adolescents
- perioperative antibiotic prophylaxis for transrectal prostate biopsy in adult man

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

4.2 Posology and method of administration

[This section should read as follows:]

Posology

Acute, uncomplicated cystitis in women and female adolescents (>12 years of age): 3 g fosfomycin once

Perioperative antibiotic prophylaxis for transrectal prostate biopsy: 3 g fosfomycin 3 hours prior to the procedure and 3 g fosfomycin 24 hours after the procedure.

Renal impairment:

Use of <Invented name> is not recommended in patients with renal impairment (creatinin clearance < 10 ml/min, see section 5.2).

Paediatric population

The safety and efficacy of <Invented name> in children aged below 12 years of age have not been established.

Method of administration

For oral use.

For the indication of acute, uncomplicated cystitis in women and female adolescents it should be taken on an empty stomach (about 2-3 hours before or 2-3 hours after a meal), preferably before bedtime and after emptying the bladder.

The dose should be dissolved into a glass of water and taken immediately after its preparation.

4.3 Contraindications

[This section should read as follows:]

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

[This section should read as follows:]

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see sections 4.3 and 4.8). If such reactions occur, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

Clostridioides difficile-associated diarrhea

Clostridioides difficile-associated colitis and pseudo-membranous colitis have been reported with fosfomycin and may range in severity from mild to life-threatening (see section 4.8). 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 *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Paediatric population

The safety and efficacy of <Invented name> in children below 12 years of age have not been established. Therefore, this medicine should not be used in this age group (see section 4.2).

Persistent infections and male patients

In case of persistent infections, a thorough examination and a re-evaluation of the diagnosis is recommended as this is often due to complicated urinary tract infections or the prevalence of resistant pathogens (e.g. *Staphylococcus saprophyticus*, see section 5.1). In general, urinary tract infections in male patients have to be considered as complicated UTIs for which this medicinal product is not indicated (see section 4.1).

Excipients

[A warning about any excipient that would result in unwanted undesirable effects in patients with specific metabolism disorders (e.g. fructose intolerance, glucose-galactose malabsorption, sucrase/isomaltase deficiency) or allergies (e.g against the colouring agent sunset yellow (E110)) should be added in this section. Each MAH will need to mention any relevant excipient(s) and related warning(s) for their formulation(s).]

4.5 Interaction with other medicinal products and other forms of interaction

[This section should read as follows:]

Metoclopramide:

Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations of fosfomycin and should be avoided.

Other medicinal products that increase gastrointestinal motility may produce similar effects.

Food effect:

Food may delay the absorption of fosfomycin, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicinal product on an empty stomach or about 2 – 3 hours after meals.

Specific problems concerning the alteration in INR:

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. Risk factors include severe infection or inflammation, age and poor general health.

Under these circumstances, it is difficult to determine whether the alteration in INR is due to the infectious disease or its treatment. However, certain classes of antibiotics are more often involved and in particular: fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

[This section should read as follows:]

Pregnancy:

Only limited data on the safety of fosfomycin treatment during 1st trimester of pregnancy (n=152) are available. These data do not raise any safety signal for teratogenicity so far. Fosfomycin crosses the placenta.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

<Invented name> should only be used during pregnancy, if clearly necessary.

Breast-feeding:

Fosfomycin is excreted in human milk in low quantities. If clearly necessary, a single dose of oral fosfomycin can be used during breast-feeding.

Fertility:

No data in humans are available. In male and female rats oral administration of fosfomycin up to 1000 mg/kg/d did not impair fertility.

4.7 Effects on ability to drive and use machines

[This section should read as follows:]

No specific studies have been performed but patients should be informed that dizziness has been reported. This may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

[This section should read as follows:]

Summary of the safety profile

The most common adverse reactions following the single-dose administration of fosfomycin trometamol involve the gastrointestinal tract, mainly diarrhoea. These events are usually self-limited in duration and resolve spontaneously.

Tabulated list of adverse reactions

The following table displays adverse reactions that have been reported with the use of fosfomycin trometamol from either clinical-trial or post-marketing experiences.

Undesirable effects are listed by body system and frequency using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Adverse drug reactions		
	Common	Uncommon	Not known
Infections and infestations	Vulvovaginitis		
Immune system disorders			Anaphylactic reactions including anaphylactic shock, hypersensitivity (see section 4.4)
Nervous system disorders	Headache, dizziness		
Gastrointestinal disorders	Diarrhoea, nausea, dyspepsia, abdominal pain	Vomiting	Antibiotic-associated colitis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritus	Angioedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

[This section should read as follows:]

Experience regarding the overdose of oral fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin.

In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

5.1 Pharmacodynamic properties

[This section should read as follows:]

Pharmacotherapeutic group: Antibacterials for systemic use; Other antibacterials.

ATC code: J01XX01

Mechanism 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/pharmacodynamic relationship

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

Mechanism of resistance

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.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known.

Susceptibility testing breakpoints

The susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 10):

Species	susceptible	resistant
<i>Enterobacterales</i>	≤ 32 mg/L	> 32 mg/L

Prevalence of acquired resistance

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.

The following table is based on data from surveillance programs and studies. It comprises organisms relevant for the approved indications:

Commonly susceptible species

Aerobic Gram-negative microorganisms

Escherichia coli

Species in which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

Enterococcus faecalis

Aerobic Gram-negative microorganisms

Klebsiella pneumonia

Proteus mirabilis

Inherently resistant species

Aerobic Gram-positive microorganisms

Staphylococcus saprophyticus

5.2 Pharmacokinetic properties

[This section should read as follows:]

Absorption

After single-dose oral administration, fosfomycin trometamol has an absolute bioavailability of about 33-53%. Rate and extent of absorption are reduced by food, but the total amount of active substance excreted in the urine over time is the same. Mean urinary fosfomycin concentrations are maintained above an MIC threshold of 128 µg/mL for at least 24 h post 3 g oral dose in either the fasting or fed state, but the time to reach maximal concentrations in urine are delayed by 4 h. Fosfomycin trometamol undergoes enterohepatic recirculation.

Distribution

Fosfomycin does not appear to be metabolised. Fosfomycin is distributed to tissues including the kidneys and bladder wall. Fosfomycin is not bound to plasma proteins and crosses the placental barrier.

Elimination

Fosfomycin is excreted unchanged mainly via the kidneys by glomerular filtration (40-50% of the dose is found in the urine) with an elimination half-life of about 4 hours after oral use and to a lesser extent in faeces (18-28% of the dose). Even if food delays drug absorption, the total amount of drug excreted in the urine over time is the same.

Special populations

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Urinary concentrations of fosfomycin in patients with impaired renal function remain effective for 48 hours after a usual dose if creatinine clearance is above 10 ml/min.

In older people fosfomycin clearance is reduced in line with the age related reduction in renal function.

5.3 Preclinical safety data

[This section should read as follows:]

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for Fosfomycin.

Fosfomycin calcium for oral use

4.1 Therapeutic indications

[This section should read as follows:]

<Invented name> is indicated for treatment of uncomplicated urinary tract infections in women.

4.2 Posology and method of administration

[Section 4.2 should only retain posology information pertinent for the use of Fosfomycin calcium in adults]

PACKAGE LEAFLET

Note: The existing package leaflet shall be amended to reflect the wording below.

Powder for solution for infusion

1. What <invented name> is and what it is used for

[This section should read as indicated below. Indications should only be implemented if the product was already approved for the condition]

<Invented name> contains the active substance fosfomicin. It belongs to a group of medicines called antibiotics. It works by killing certain types of germs (bacteria) that cause serious infectious diseases. Your doctor has decided to treat you with <Invented name> to help your body fight an infection. It is important that you receive effective treatment for this condition.

<Invented name> is used in adults, adolescents and children to treat bacterial infections of:

- the urinary tract
- the heart - sometimes called 'endocarditis'
- the bones and joints
- the lungs called "pneumonia"
- the skin and tissues below the skin
- the central nervous system
- the abdomen,
- the blood, when caused by any of the conditions listed above

2. What you need to know before you use <invented name>

[This section should read as follows:]

Do not use <Invented name>:

- if you are allergic to fosfomicin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using <Invented name> if you suffer from one of the following disorders:

- heart problems (cardiac insufficiency), especially if digitalis medicine is taken (due to possible hypokalaemia)
- high blood pressure (hypertension)
- a certain disorder of the hormone system (hyperaldosteronism)
- high levels of blood sodium (hypernatraemia)
- fluid accumulation in the lungs (pulmonary oedema)

- kidney problems. Your doctor may need to change the dose of your medicine (see section 3 of this leaflet).
- previous episodes of diarrhea after taking or receiving any other antibiotics

Conditions you need to look out for

<Invented name> can cause serious side effects. These include allergic reactions, inflammation of the large intestine and a decreasing number of white blood cells. You must look out for certain symptoms while you are taking this medicine, to reduce the risk of any problems. See "Serious side effects" in Section 4.

Other medicines and <Invented name>

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

- anticoagulants, as their ability to prevent your blood from clotting might be altered by fosfomycin and other antibiotics.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Fosfomycin may pass to the baby in the womb or through breast milk. If you are pregnant or breast-feeding your doctor will only give you this medicine when it is clearly needed.

Driving and using machines

When <Invented name> is given, there may be side effects such as confusion and weakness. If these occur, you should not drive or operate machinery.

3. How to use <Invented name>

[This section should read as follows:]

<Invented name> is given to you into a vein (a drip) by a doctor or a nurse.

Dosage

The dose you will be given and the frequency of the dose will depend on:

- The type and severity of infection you have
- Your kidney function.

In children, it also depends on

- The child's weight
- The child's age

If you have problems with your kidneys or require dialysis, your doctor may need to reduce your dose of this medicine

Route and method of administration

For intravenous use.

<Invented name> is given to you into a vein (a drip) by a doctor or a nurse. The infusion will normally take 15 to 60 minutes, depending on your dose. Usually this medicine is given 2, 3 or 4 times a day.

Duration of treatment

Your doctor will decide how long your treatment should last depending on how fast your condition will improve. When treating bacterial infections it is important to complete the full course of treatment. Even after the fever has passed and the symptoms have abated, treatment should be continued for a few days more.

Certain infections, such as infections of the bones, may require an even longer treatment period after the symptoms have subsided.

If you are given more <Invented name> than you should

It is unlikely that your doctor or nurse will give you too much medicine. Ask them immediately if you think that you have been given too much of this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

Signs of a serious allergic reaction (very rare: may affect up to 1 in 10,000 people,). These may include: breathing or swallowing problems, sudden wheezing, dizziness, swelling of eyelids, face, lips or tongue, rash or itching.

- Severe and persistent diarrhea, which may be associated with abdominal pain or fever (the frequency is unknown). This may be a sign of a serious bowel inflammation. Do not take medicines against diarrhea that inhibit the bowel movements (antiperistaltics).
- Yellowing of the skin or the whites of your eyes (jaundice, the frequency is unknown). This can be an early sign of liver problems.
- Confusion, muscle twitching or abnormal heart rhythm. This could be caused by high levels of blood sodium or low levels of blood potassium (common: may affect up to 1 in 10 people).

Tell your doctor or nurse as soon as possible if you notice any of the following side effects:

- Pain, burning, redness or swelling along the vein which is used during infusion of this medicine (common: may affect up to 1 in 10 people).
- You bleed or bruise more easily or get more infections than usual. This could be because you have a low number of white blood cells or blood platelets (the frequency is unknown).

Other side effects can include:

Common side effects (may affect up to 1 in 10 people)

- Taste disturbances

Uncommon side effects (may affect up to 1 in 100 people)

- Feeling sick, vomiting, or mild diarrhea

- Headache
- High levels of blood liver enzymes, possibly associated with liver problems.
- Rash
- Feebleness

Side effects with not known frequency (frequency cannot be estimated from the available data)

- Liver problems (hepatitis),
- Itching, hives

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

Fosfomycin trometamol granules for oral solution

1. What <invented name> is and what it is used for

[This section should read as follows:]

<Invented name> contains the active substance fosfomycin (as fosfomycin trometamol). It is an antibiotic that works by killing bacteria which can cause infections.

<Invented name> is used to treat uncomplicated infection of the bladder in women and female adolescents.

<Invented name> is used as antibiotic prophylaxis for transrectal prostate biopsy in adult man.

2. What you need to know before you take <Invented name>

[This section should read as follows:]

Do not take <Invented name> if you:

- are allergic to fosfomycin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using <Invented name> if you suffer from one of the following disorders:

- persistent infections of the bladder,
- previously had diarrhea after taking any other antibiotics.

Conditions you need to look out for

<Invented name> can cause serious side effects. These include allergic reactions and an inflammation of the large intestine. You must look out for certain symptoms while you are taking this medicine, to reduce the risk of any problems. See "Serious side effects" in Section 4.

Children and adolescents

Do not give this medicine to children less than 12 years of age, as its safety and efficacy have not been established in this age group.

Other medicines and <Invented name>

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

This is especially important if you are taking:

- **metoclopramide** or other medicinal products that increase the movement of food through the stomach and intestines, because they may reduce the uptake of fosfomycin by your body,
- **anticoagulants**, as their ability to prevent your blood from clotting might be altered by fosfomycin and other antibiotics.

<Invented name> with food

Food may delay the absorption of fosfomycin. Therefore, this medicinal product should be taken on an empty stomach (2-3 hours before or 2-3 hours after a meal).

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant your doctor will only give you this medicine when it is clearly needed.

Breast-feeding mothers can take a single oral dose of this medicine.

Driving and using machines

You may experience side effects, such as dizziness, which may affect your ability to drive or use machines.

3. How to take <Invented name>

[This section should read as follows:]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

In case of treatment of uncomplicated infection of the bladder, in women and female adolescents the recommended dose is 1 sachet of <Invented name> (3 g Fosfomycin).

When used as antibiotic prophylaxis for transrectal prostate biopsy the recommended dose is 1 sachet of <Invented name> (3 g fosfomycin) 3 hours prior to the procedure and 1 sachet of <Invented name> (3 g fosfomycin) 24 hours after the procedure.

Use in patients with renal impairment

This medicine should not be used in patients with severe renal impairment (creatinin clearance < 10 ml/min).

Use in children and adolescents

This medicine should not be used in children less than 12 years of age.

Method of administration

For oral use.

Take this medicine by mouth, on an empty stomach (2-3 hours before or 2-3 hours after a meal), preferably before going to bed after emptying the bladder.

Dissolve the content of one sachet in a glass of water and drink immediately.

If you take more <Invented name> than you should

If you accidentally take more than your prescribed dose, contact your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

[This section should read as follows:]

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

While taking <Invented name>, if you develop any of the following symptoms you should stop taking the medicine and contact your doctor immediately:

- anaphylactic shock, a life threatening type of allergic reaction (the frequency is unknown). Symptoms include a sudden onset of rash, itching or hives on the skin and or shortness of breath, wheezing or difficulty in breathing,
- swelling of the face, lips, tongue or throat with breathing difficulties (angioedema) (the frequency is unknown),
- moderate to severe diarrhea, abdominal cramps, bloody stools-and/or fever may mean that you have an infection of the large intestine (antibiotic-associated colitis) (the frequency is unknown). Do not take medicines against diarrhea that inhibit the bowel movements (antiperistaltics).

Other side effects

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- diarrhea
- nausea
- indigestion
- abdominal pain
- infection of the female genital organs with symptoms like inflammation, irritation, itching (vulvovaginitis).

Uncommon (may affect up to 1 in 100 people):

- vomiting
- rash
- urticaria
- itching

Not known (frequency cannot be estimated from the available data):

- allergic reactions.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

Fosfomycin calcium for oral use

1. What <invented name> is and what it is used for

[Information on indication should be updated as follows:]

<Invented name> is used to treat uncomplicated infection of the bladder in women.

3. How to take <Invented name>

[For Fosfomycin calcium capsules the information on posology should be updated as follows:]

For the treatment of uncomplicated infection of the bladder, in women, the recommended dose is 500mg – 1g (1 or 2 capsules) every 8 hours.

[For Fosfomycin calcium oral suspension the information on posology should be updated as follows:]

For the treatment of uncomplicated infection of the bladder, in women, the recommended dose is 2 spoons of 5ml (500mg of Fosfomycin) or 4 spoons of 5ml (1g of Fosfomycin) every 8 hours.