SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

UROFAST 3 g ADULTS, granules for oral solution in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fosfomycin trometamol..... 5.631 g
Quantity corresponding to fosfomycin..... 3.000 g
Excipient with known effect: sucrose, sulfites.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

UROFAST 3 g ADULTS, granules for oral solution in sachet is indicated for the treatment of acute uncomplicated cystitis in women and adolescents (see section 5.1).
Official recommendations regarding the appropriate use of antibacterial agents should be taken into account.

4.2. Posology and method of administration

Posology
Uncomplicated acute cystitis in adult and adolescent women (> 12 years) : single administration of 3 g of fosfomycin.
Kidney failure:
The use of UROFAST 3 g ADULTS, granules for oral solution in sachet is not recommended in patients with renal impairment (creatinine clearance < 10 ml/min, see section 5.2).
Pediatric population
The safety and efficacy of UROFAST 3 g ADULTS, granules for oral solution in sachets in children under 12 years of age have not been established.

Method of administration
Oral route.
In the indication of acute uncomplicated cystitis in adult and adolescent women, the drug should be taken on an empty stomach (approximately 2 to 3 hours before or after a meal), preferably before bedtime and after emptying the bladder.
The dose should be dissolved in a glass of water and taken immediately after preparation.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Hypersensitivity reactions
Severe and sometimes fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during treatment with fosfomycin (see sections 4.3 and 4.8).
If such reactions occur, treatment with fosfomycin must be stopped immediately and appropriate emergency measures must be initiated.
Diarrhea associated with *Clostridioides difficile*
Cases of *Clostridioides difficile -associated colitis* and pseudomembranous colitis have been reported with fosfomycin, ranging in severity from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who develop diarrhea during or after fosfomycin administration. Discontinuation of fosfomycin and administration of specific treatment for *Clostridioides difficile should be considered* . Drugs that inhibit peristalsis should not be administered.
Pediatric population
The efficacy and safety of UROFAST 3g ADULTS, granules for oral solution in sachets, have not been established in children under 12 years of age. Therefore, this medicine should not be used in this age group (see section 4.2).

Persistent infections and male patients
In cases of persistent infections, a thorough examination and reassessment 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 should be considered complicated urinary tract infections for which this medicinal product is not indicated (see section 4.1).
Excipients
This medicine contains 2.213 g of sucrose per sachet. Patients with fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase- isomaltase deficiency (rare hereditary disorders) should not take this medicine.
This medicine contains less than 1 mmol (23 mg) of sodium (present in the orange and mandarin flavors) per sachet, that is to say it is essentially 'sodium free'.
This medicine contains sulfites (present in the orange and mandarin flavorings). In rare cases, it may cause severe hypersensitivity reactions and bronchospasms.

4.5. Interactions with other medicinal products and other forms of interaction

Metoclopramide :
It has been shown that concomitant administration of metoclopramide decreases serum and urinary concentrations of fosfomycin and should be avoided.
Other drugs that increase gastrointestinal motility may produce similar effects.
Effect of food :
Food can delay the absorption of fosfomycin, resulting in a slight decrease in peak plasma and urinary concentrations. Therefore, it is best to take the medication on an empty stomach or approximately 2 to 3 hours after meals.
Specific problems related to INR modification:
Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic treatment. Risk factors include severe infection or inflammation, age, and poor general health. In these circumstances, it is difficult to determine whether the change in INR is due to the infectious disease or its treatment. However, certain classes of antibiotics are more frequently implicated, particularly fluoroquinolones, macrolides, tetracyclines, cotrimoxazole, and some cephalosporins.

Pediatric population
Interaction studies have only been conducted in adults.

4.6. Fertility, pregnancy and breastfeeding

Pregnancy
Limited data are available on the safety of fosfomycin treatment during the first trimester of pregnancy (n = 152). These data have not revealed any safety signals regarding teratogenicity to date. Fosfomycin crosses the placenta.
Animal studies have not shown any direct or indirect harmful effects on reproduction (see section 5.3).
UROFAST 3g ADULTS, granules for oral solution in sachet should only be used during pregnancy if absolutely necessary.

Breastfeeding
Fosfomycin is excreted in small amounts in human breast milk. If absolutely necessary, a single oral dose of fosfomycin can be used during breastfeeding.

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

4.7. Effects on the ability to drive vehicles and use machinery

No specific studies have been carried out, but patients should be advised that cases of dizziness have been reported. These symptoms may affect some patients' ability to drive and operate machinery (see section 4.8).

4.8. Undesirable effects

Security Profile Summary

The most frequent side effects after administration of a single dose of fosfomycin Trometamol affects the gastrointestinal tract and primarily causes diarrhea. These effects are usually short-lived and disappear spontaneously.

Summary table of side effects

The following table presents the adverse effects that have been reported with the use of fosfomycin. trometamol during clinical trials or after marketing.

Adverse effects are listed by organ system and frequency using the following convention:

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

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

Organ system class	**Side effects** **Frequency category**		
	Frequent **(≥ 1/100, < 1/10)**	**Uncommon** **(≥ 1/1000, < 1/100)**	**Frequency not known**
Infections and infestations	Vulvovaginitis		
Immune system disorders			Anaphylactic reactions, including anaphylactic shock and hypersensitivity (see section 4.4)
Disorders of the nervous system	Headaches, dizziness		
Gastrointestinal disorders	Diarrhea, nausea, dyspepsia, abdominal pain	Vomiting	Antibiotic-associated colitis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash, hives, itching	Angioedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals report any suspected adverse reactions via the national reporting system: French National Agency for Medicines and Health Products Safety (ANSM) and the network of Regional Pharmacovigilance Centers - Website: www.signalement-sante.gouv.fr .

4.9. Overdose

Experience with cases of overdose of oral fosfomycin is limited. Cases of hypotonia, drowsiness, electrolyte disturbances, thrombocytopenia, and hypoprothrombinemia have been reported with parenteral fosfomycin.
In case of overdose, the patient should be monitored (particularly plasma/serum electrolyte levels) and receive symptomatic and supportive treatment. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively removed from the body by hemodialysis with a mean elimination half-life of approximately 4 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: 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 step of intracellular bacterial cell wall synthesis by blocking peptidoglycan synthesis.
Fosfomycin is actively transported into the bacterial cell via two different transport systems (the hexose-6 and sn-glycerol-3-phosphate transport systems).

Pharmacokinetic/pharmacodynamic relationships
Limited data indicate that fosfomycin most likely acts in a time-dependent manner.

Resistance mechanism
The main resistance mechanism is a chromosomal mutation leading to an alteration of the bacterial transport systems of fosfomycin. Other resistance mechanisms, which are transmitted by plasmids or transposons, result in the enzymatic

inactivation of fosfomycin via binding of the molecule to glutathione or via cleavage of the carbon-phosphorus bond in the fosfomycin molecule, respectively.

Cross resistance
There is no known cross-resistance between fosfomycin and other classes of antibiotics.

Critical concentrations
The critical sensitivity concentrations established by the European Committee on Antimicrobial Susceptibility The following are the EUCAST critical concentrations table (EUCAST version 10):

Species	sensitive	resistant
Enterobacterales	≤ 32 mg/L	> 32 mg/L

Prevalence of acquired resistance
The prevalence of acquired resistance in individual species can vary geographically and over time. Information on local resistance patterns is therefore necessary, particularly to ensure appropriate treatment of severe infections.
The following table is based on data from monitoring programs and studies. It includes the species relevant to the approved indications:

Commonly susceptible species
Gram-negative aerobic microorganisms
Escherichia coli

Species for which acquired resistance could be a problem
Gram-positive aerobic microorganisms
Enterococcus faecalis
Gram-negative aerobic microorganisms
Klebsiella pneumonia
Proteus mirabilis

Naturally resistant species
Gram-positive aerobic microorganisms
Staphylococcus saprophyticus

5.2. Pharmacokinetic properties

Absorption
After oral administration of a single dose, fosfomycin Trometamol has an absolute bioavailability of approximately 33% to 53%. The rate and extent of absorption are reduced by food intake, but the total amount of active substance excreted in the urine over time remains the same. Mean urinary concentrations of fosfomycin are maintained above the MIC threshold of 128 µg/ml for at least 24 hours after administration of a 3 g oral dose on an empty stomach or after a meal, but the time to reach peak urinary concentrations is delayed by 4 hours . trometamol undergoes enterohepatic circulation .

Distribution
Fosfomycin does not appear to be metabolized. Fosfomycin is distributed to tissues, including the kidneys and bladder wall. Fosfomycin does not bind to plasma proteins and crosses the placental barrier.

Elimination
Fosfomycin is excreted unchanged primarily by the kidneys via glomerular filtration (40% to 50% of the dose is recovered in the urine) with an elimination half-life of approximately 4 hours after oral administration, and to a lesser extent in the feces (18% to 28% of the dose). Even when food delays drug absorption, the total amount of drug excreted in the urine over time remains the same.

Specific populations
In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal impairment. Urinary fosfomycin concentrations in patients with impaired renal function remain effective for 48 hours after a usual dose if creatinine clearance is greater than 10 ml/min.
In elderly people, fosfomycin clearance is reduced due to age-related decline in renal function.

5.3. Preclinical safety data

Non-clinical data from conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, and reproductive function revealed no particular risk for the man.

No carcinogenicity data are available for fosfomycin .

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Orange flavour, mandarin flavour, sodium saccharin, sucrose.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at a temperature below 30°C.

6.5. Nature and contents of container

8g in a sachet (surlyn /Aluminium/PE/paper). Box of 1.

6.6. Special precautions for disposal and handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7. HOLDER AND OPERATOR

Holder and Operator of the Export Marketing Authorization

FRILAB LABORATORIES SA
17, Rue des Pierres du Niton
1207 Geneva
SWISS

Manufacturer

LABIANA PHARMACEUTICALS, SLU
Casanova, 27-31. 08757 Corbera de Llobergat
Barcelona
SPAIN

8. DATE OF REVISION OF THE TEXT

September 6, 2021

9. DOSIMETRY

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I