SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Monurol®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 5.631 g of fosfomycin trometamol equivalent to 3 g fosfomycin.

Excipient(s) with known effect:

One sachet contains 2.213 g of sucrose, see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Monurol is indicated for:

- 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

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

Before administration of **Monurol** to patients with severe renal impairment (creatinine clearance < 30 mL/min) or patients undergoing hemodialysis, the physician **should evaluate if the potential benefits of the drug outweigh the potential risks** to the patient, as **Monurol** is principally excreted by the kidney (see section 5.2).

Paediatric population

The safety and efficacy of **Monurol** 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, after emptying the bladder.

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

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 **Monurol** 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

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per sachet that is to say essentially 'sodium-free'.

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this medicine.

Sulphites

May rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

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 determinate 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

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).

Monurol 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

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

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 (≥ 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 form 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 11):

Species	**susceptible**	**resistant**
Enterobacterales	≤ 8 mg/L	> 8 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

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, mandarin flavour, orange flavour, saccharin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Sachets are a four-layer laminate: paper, polyethylene, aluminium, polyethylene.

Sachets are supplied in cardboard outer containing 1 sachet.

6.6 Special precautions for disposal and other handling

The dose must be dissolved in a glass of water and administered soon after dissolving.

Any unused product or waste material should be disposed in accordance with local requirements.

7 MANUFACTURER

Zambon Switzerland Ltd., Via Industria 13, CH- 6814 Cadempino, Switzerland.

8 REGISTRATION HOLDER

Rafa Laboratories Ltd., P.O.B. 405, 9100301 Jerusalem, Israel.

Registration number: 107-93-28982

Revised in May 2024.