Doctor leaflet

1. NAME OF THE MEDICINAL PRODUCT

MONUROL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 5.631g fosfomycin trometamol equivalent to 3.0 g fosfomycin.

Excipients:
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 as a single dose treatment for acute, uncomplicated urinary tract infection and as prophylaxis in diagnostic and surgical transurethral procedures.

4.2 Posology and method of administration

The recommended dose for the treatment of acute uncomplicated lower urinary tract infections is a single 3 g sachet in adults.
The recommended regimen for the prophylaxis of urinary tract infections in surgery and diagnostic procedure involving lower urinary tract in adult males and females is one Monurol 3 g sachet 3 hours before surgery and one 3 g sachet 24 hours after surgery.

Children and young people weighing less than 50 kg and/ or below 12 years old (see Special warnings and precautions for use).

Method of administration
Monurol is for oral administration. It should be taken on an empty stomach, about 2-3 hours before or after eating, preferably before bedtime, after emptying the bladder. The dose should be dissolved into a glass of water or any other non-alcoholic beverage and taken immediately after its preparation.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Patients with severe renal failure (creatinine clearance < 10mL/min).
Patients undergoing haemodialysis.

4.4 Special warnings and precautions for use

Antibiotic associated colitis (incl. pseudomembranous colitis) has been reported in association with the use of broad spectrum antibiotics including fosfomycin trometamol; therefore it is

important to consider this diagnosis in patients who develop serious diarrhea during or after the use of fosfomycin trometamol. In this situation adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.
Food may delay the absorption of the active ingredient of Monurol, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicine on an empty stomach, about 2-3 hours before or after meals.

Monurol contains sucrose. Patients with rare heredity problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Special warnings for patients with diabetes: during the treatment patients with diabetes should keep in mind that every sachet contains 2.213 g of sucrose equivalent to 37 kJ or 0.22 bread unit.

Children and young people weighing less than 50 kg and/or below 12 years old

At the moment there is not enough experience in children and since the dosage of 3 g is not suitable to people weighing less than 50 kg and/ or below 12 years old, Monurol 3 g should not be used for these patients.

4.5 Interaction with other medicinal products and other forms of interaction

Fosfomycin/Metoclopramide: when co-administered with fosfomycin, metoclopramide lowers the serum and urine concentrations of fosfomycin.
For this reason a delayed administration (about 2-3 hours) is recommended.
Other drugs that increase gastrointestinal motility may produce similar effects.

Fosfomycin/antacids or calcium salts: Concomitant administration of antacids or calcium salts induces a significant reduction of fosfomycin therapeutically effective plasmatic and urinary concentrations. For this reason a delayed administration (about 2-3 hours) is recommended.
Similar effects can also occur with other medicines which increase gastrointestinal motility.

Fosfomycin/food: Similarly, if fosfomycin trometamol is administered during meals, fosfomycin plasmatic and urinary rates decrease.

4.6 Pregnancy and lactation

Pregnancy:
Data concerning a restricted number of pregnant women indicate neither on pregnancy nor on thehealth of the foetus/newborn undesirable effects.
There is no experience resulting from epidemiologic studies.
Studies involving animal experiments indicate neither direct nor indirect toxical effects on pregnancy, embryonic development, development of the foetus and/or postnatal development.
Pregnant women should use extreme caution if administering Monurol.

Lactation:
Since Monurol passes into the breast milk, extreme moderation is recommended while breastfeeding.

4.7 Effects on ability to drive and use machines

Since Monurol can cause dizziness, it could reduce the ability to drive and use machines.

4.8 Undesirable effects

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.
The following table displays ADRs that have been reported with the use of Monurol from either clinical-trial or post-marketing experiences.

The displayed frequency categories use 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 frequency Category**			
	Common (≥ 1/100 to < 1/10)	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (< 1/1000)**	**Not known**
Infections and infestations	Vulvovaginitis			
Immune system disorders				Anaphylactic shock, Allergic reaction
Nervous system disorders	Headache, Dizziness	Paraesthesia		
Cardiac disorders			Tachycardia	
Respiratory thoracic				Asthma
Gastrointestinal disorders	Diarrhea, Nausea, Dyspepsia	Abdominal pain, Vomiting		Pseudomembranous colitis
Skin and subcutaneous tissue disorders		Rash, Urticaria, Pruritus		Angioedema
General disorders and administration site conditions		Fatigue		
Vascular Disorders				Hypotension

4.9 Overdosage

The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception.

In the event of overdosage, treatment should be symptomatic and supportive. The patient should drink large quantities of water to promote urinary elimination of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use – other antibacterials ATC code: J01XX01
Monurol contains the active substance fosfomycin in the form of trometamol salt. Fosfomycin is an antibiotic (derivative of phosphonic acid) with bactericidal action. It inhibits bacterial cell wall synthesis by impeding one of the first steps of peptidoglycan synthesis.
Fosfomycin shares structural analogies with p-enolpyruvate: in fact it inactivates the phosphoenolpyruvate transferase enzyme and doing so it irreversibly blocks the condensation of uridine diphosphate N-acetylglucosamine with p-enolpyruvate.
The following table illustrates the in vitro activity of fosfomycin trometamol against clinical isolates. The minimum inhibitory concentration (MIC) has been determined by disk diffusions test with agar plates containing 200 µg of fosfomycin trometamol. Germs with an inhibition zone diameter of >16mm (on Muller-Hinton agar) have been classified as sensitive (equivalent to 200 µg/ml).

	MIC90(µg/ml)	Area
Sensitive germs		
E. coli	8	0.25-128
Klebsiella	32	2-128
Citrobacter spp.	2	0.25-2
Enterobacter spp.	16	0.5-64
Proteus mirabilis	128	0.12-256
S. faecalis	64	8-256
Resistant germs (Inhibition zone <16mm)		
Serratia spp.	32	
Enterobacter cloacae	256	
Pseudomonas aeruginosa	256	
Morganella morganii	>256	
Providencia rettgeri	>256	
Providencia stuartii .	>256	
Pseudomonas spp.	>256	

Resistance/ Cross-resistance
Fosfomycin preserved its action unchanged against the most occurring bacteria causing urinary tract infections. Only few bacteria showed resistance. The resistance rate of E. coli, which causes uncomplicated urinary tract infections, is low.
Most of multi-drug resistant E-coli and extended spectrum beta-Iactamase (ESBL)-producing Enterobacteriaceae are sensitive to fosfomycin, as well as most of MRSA (Methicillin-resistant Staphylococcus aureus).
Up to date no cross-resistance to other antibacterial substances is known. Cross-resistance might be excluded since fosfomycin fundamentally differs from all other antibiotics in its chemical structure and since it has a unique mechanism of action.

Clinical effectiveness
The antibacterial spectrum of fosfomycin includes most of gram-positive/negative bacteria which cause urinary tract infections and also most of penicillinase producing strains. In vivo resistance against enterobacter spp., klebsiella ssp., enterococcus,
proteus mirabilis, staph. aureus and staph. saprophyticus has been observed.
Moreover Monurol reduces bacterial adhesion to bladder mucosa, which can be a predisposing factor for recurring infections.

5.2 Pharmacokinetic properties
Absorption

After oral administration, fosfomycin is well absorbed from the gut and has an absolute bioavailability of about 50%. Food delays absorption, not influencing urinary concentrations.

After administration of 50mg/kg of body weight t_{max} is 2-2.5 hours and Cmax is 20-30 µg/ml.
Distribution

The plasma protein binding of fosfomycin is much low (less than 5%). Distribution volume is

1.5-2.4 l/kg of body weight.

Fosfomycin penetrates the placental barrier and passes into the breast milk.

Metabolism

Fosfomycin is not metabolised.

Elimination

Plasma half life is about 4 hours. 2-4 hours after a single administration of 3 g of fosfomycin trometamol urinary concentration of fosfomycin amounts to 1800-3000 µg/ml. Therapeutically effective concentrations (200-300 µg/ml) remain up to 48 hours after administration. 40-50% of a single dose is excreted unchanged with urine in the first 48 hours.
Kinetic relevant patient populations
Renal insufficiency reduces the excretion of the drug in accordance with the level of limited functionality and extends plasma half life ($t_{1/2}$ to 50 hours with creatinine clearance of 10ml/min).
5.3 Preclinical safety data

Fosfomycin has no mutagenic effects. Teratogenic studies (on rats and rabbits) on fertility (rats)and perinatal and postnatal toxicity (rabbits) have not discovered any signs of toxic effects causedby Monurol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mandarin flavor
Orange flavor
Saccharin
Sucrose

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Store below 25ºC
6.4 Nature and contents of container

Monurol is supplied in cardboard outer containing 1 sachet.

7. MARKETING AUTHORIZATION NUMBER

107 93 28982

Registration holder: Rafa Laboratories Ltd. P.O.Box 405, 9100301 Jerusalem
Manufacturer: Zambon Switzerland Ltd., Switzerland.
The format and content of this document have been approved by the Ministry of Health in JUNE 2013.