SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
URIZONE 3 g, granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains 5,631 g fosfomycin trometamol equivalent to 3 g fosfomycin.

Excipient(s) with known effect:
- Contains sugar: 2,213 g sucrose per sachet.
- Contains sweetener: 0,016 g saccharin per sachet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Granules for oral solution.

White granular powder with a characteristic mandarin flavour.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
URIZONE 3 g is indicated:
- as a single dose in the treatment of acute uncomplicated lower urinary tract infections caused by sensitive *E. Coli*, in women and female adolescents over the age of twelve years.
- for prophylaxis in diagnostic and surgical transurethral procedures in adult men.

4.2 Posology and method of administration
Posology
The recommended dose for uncomplicated urinary tract infections in women, including the elderly up to seventy-five years, is a single 3 g dose.

The recommended dose for prophylaxis prior to transurethral surgical and diagnostic procedures in adult men, including the elderly, is two doses of 3 g. The first dose should be taken three hours before surgery. The second dose should be taken twenty-four hours after surgery.

Special populations
Renal impairment
Use of URIZONE 3 g is not recommended in patients with renal impairment (creatinine clearance < 10 mL/min, see sections 4.3 and 5.2).

Paediatric population
The safety and efficacy of URIZONE 3 g in children below 12 years of age have not been established.

Method of administration
For oral administration.

URIZONE 3 g 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 in a glass of water and taken immediately after its preparation (see section 6.6).

4.3 Contraindications
- Known hypersensitivity to fosfomycin trometamol or to any of the excipients listed in section 6.1.
- Severe renal insufficiency (creatinine clearance < 10 mL/min).

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 reaction occurs, treatment with fosfomycin must be discontinued immediately and adequate emergency measures must be initiated.

***Clostridioides difficile*-associated diarrhoea**
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 diarrhoea 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. Medicines that inhibit peristalsis should not be given.

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 medicine is not indicated (see section 4.1).

URIZONE 3 g contains sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take URIZONE 3 g.

Paediatric population
Safety and efficacy in children under the age of twelve years has not yet been established. Therefore, this medicine should not be used in this age group (see section 4.2).

4.5 Interactions with other medicines and other forms of interaction
Metoclopramide
Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations and should be avoided.

Other medicines 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 medicine on an empty stomach or about 2 – 3 hours after meals.

Specific problems concerning the alteration in International Normalized Ratio (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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
Pregnancy
The safety and efficacy of single-dose therapy have not been established for URIZONE 3 g in pregnancy.

There is limited data on the safety of fosfomycin treatment during 1st trimester of pregnancy. Fosfomycin crosses the placenta.

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

Breastfeeding
URIZONE 3 g should not be given to lactating women. Fosfomycin has been shown to cross into breast milk in low quantities.

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.

URIZONE 3 g may cause dizziness which can affect the ability to drive a vehicle and use machines (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

URIZONE 3 g is generally well-tolerated.

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.

b. Tabulated summary of adverse reactions

The following convention is used to define the frequency of side effects: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); Very rare (< 1/10 000); not known (cannot be estimated form the available data).

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Common	Vulvovaginitis
Immune system disorders	Not known	Anaphylactic reactions including anaphylactic shock, hypersensitivity (see section 4.4).
Nervous system disorders	Common	Dizziness, headache.
Respiratory, thoracic and mediastinal disorders	Common	Pharyngitis (sore throat), rhinitis (runny or stuffy nose).
Gastrointestinal disorders	Common	Abdominal pain, dyspepsia (heartburn, indigestion), diarrhoea, nausea.
	Uncommon	Vomiting.
	Not known	Antibiotic-associated colitis (see section 4.4).
Skin and subcutaneous tissue disorders	Uncommon	Skin rash, urticaria, pruritus.
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Common	Back pain.
Reproductive system and breast disorders	Common	Vaginitis, dysmenorrhoea.

General disorders and administration site conditions	Common	Pain (non-localised), asthenia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of URIZONE 3 g is important. It allows continued monitoring of the benefit/risk balance of URIZONE 3 g. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternatively, adverse reactions may also be reported directly to Adcock Ingram Limited via email at Adcock.aereports@adcock.com.

4.9 Overdose
Experience regarding the overdose of oral fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinaemia 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. Urinary elimination of URIZONE 3 g can be accelerated through adequate administration of oral fluids. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A20.1.1 Broad and medium spectrum antibiotics
ATC code: J01XX01

Mechanism of action
Fosfomycin trometamol is a broad-spectrum bactericidal antibiotic, derived from phosphonic acid with activity in the lower urinary tract.

The antibacterial activity of fosfomycin is due to an inhibition of bacterial cell wall synthesis. Its particular mechanism of action is inhibition of enol pyruvyl transferase.

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.

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.

Fosfomycin is active *in vitro* against species of Gram-positive and Gram-negative bacteria most frequently isolated in urinary tract 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

In vitro sensitivity does not necessarily imply *in vivo* efficacy.

5.2 Pharmacokinetic properties
Fosfomycin trometamol is an orally well-absorbed salt of fosfomycin. It usually provides therapeutic concentrations of the active moiety in the urine for periods of 36 hours or more

from a single dose.

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 a Minimum Inhibitory Concentration (MIC) threshold of 128 µg/mL for at least 24 hours 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 hours. 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 eliminated mainly unchanged through the kidneys by glomerular filtration (40-50 % if 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). This results in very high peak urinary concentrations (approximately 3 000 mg/L) within 2 to 4 hours.

Food delays and reduces absorption of fosfomycin trometamol, resulting in reduced blood and urinary concentrations.

Even if food delays medicine absorption, the total amount of medicine 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 the elderly fosfomycin clearance is reduced in line with age related reduction in renal function, but urinary concentration remains therapeutically adequate.

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

Mandarin flavour
Orange flavour
Saccharin
Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.
Store at or below 30 °C.

6.4 Special precautions for storage

Store in the original packaging until required for use.

6.5 Nature and contents of container

Printed carboard carton containing one paper-polyethylene-aluminium-polyethylene laminated sachet.

6.6 Special precautions for disposal

No special requirements.

The dose must be dissolved in a glass containing 90–120 mL of water and administered soon after dissolving.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

28/20.1.1/0480

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 September 1994

10. DATE OF REVISION OF THE TEXT

25 July 2025

Namibia (NS2): 04/20.1.1/1598
Botswana (S2): BOT2404259