SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

UROSEPTIC 3 g granules for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITON

Each sachet contains 5,631 g fosfomycin trometamol equivalent to 3 g fosfomycin base.

Contains sweetener (sucralose, 0,113 g per sachet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sachets containing white to off-white, homogeneous granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

UROSEPTIC is indicated as a single dose in the treatment of acute uncomplicated lower urinary tract infections caused by sensitive *E. Coli*, in women 12 years and older.

UROSEPTIC is indicated 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.

Paediatric population

UROSEPTIC in a dose of 3 g is not suitable for children under the age or 12 years.

Method of administration:

UROSEPTIC is for oral use.

UROSEPTIC is administered orally after reconstitution in water. To be taken at least two hours prior to the next meal.

The contents of the sachet must be dissolved in water and taken immediately.

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

Prescribers are advised to adhere to the principles of antibiotic stewardship.

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 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 UROSEPTIC 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*). In general, urinary tract infections in male patients have to be considered as complicated UTIs for which UROSEPTIC is not indicated (see section 4.1).

Use in Children:

Safety and efficacy in children under the age of 12 years have not yet been established.

4.5 Interaction 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~~ UROSEPTIC 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:

No evidence in animals or humans has been found to indicate adverse effects of UROSEPTIC in pregnancy. However, the safety and efficacy of single dose therapy has not been established for UROSEPTIC in pregnancy.

Breastfeeding:

UROSEPTIC should not be given to lactating women. Fosfomycin has been shown to cross into breast milk.

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 frequent adverse reactions following the single-dose administration of UROSEPTIC involve the gastrointestinal tract, mainly diarrhoea. These events are usually self-limited in duration and resolve spontaneously.

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Vulvovaginitis
Immune system disorders	Frequency unknown	Anaphylactic reactions including anaphylactic shock, hypersensitivity (see section 4.4)
Nervous system disorders	Frequent	Headache, dizziness
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis (sore throat), rhinitis (runny or stuffy nose).
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Diarrhoea, nausea, abdominal pain, dyspepsia (heartburn, indigestion) Vomiting Antibiotic-associated colitis
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Skin rash Urticaria, pruritus Angioedema

Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain
Reproductive system and breast disorders	Frequent	Vaginitis, dysmenorrhoea
General disorders and administrative site conditions	Frequent	Pain (non-localised), asthenia

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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. 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

Pharmacological classification: A.20.1.1 Broad & Medium Spectrum Antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use - other antibacterials

ATC code: J01XX01

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 active in vitro against species of Gram-positive and Gram-negative bacteria most frequently isolated in urinary tract infections (*E. Coli, Proteus, Klebsiella, Enterobacter, Staphylococcus, Streptococcus*). *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

5.2 Pharmacokinetic Properties

Absorption:

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 thirty-six hours or more from a single dose.

Biotransformation and Elimination:

Fosfomycin is eliminated mainly unchanged through the kidneys and this results in very high peak urinary concentrations (approx. 3000 mg/L) within two to four hours. Therapeutic concentrations in urine are usually maintained for at least thirty-six hours.

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

Special patient groups:

In patients with moderately reduced renal function (creatinine clearance

> 80 mL/min). including the physiological reduction in the elderly, the half-life of fosfomycin is prolonged but urinary concentration remains therapeutically adequate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aerosil 380

Glycine

Lemon flavour

Povidone

Sucralose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened sachets:

36 months.

After dissolution:

After its dissolution, the granulated must be administered to the patient immediately.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Aluminium foil, externally covered by paper featured as a dull, smooth surface, and internally seen as a brilliant surface. Sachets are packed into cardboard boxes with the leaflet.

Pack size: 1, 2 or 10 sachets per carton.

Not all pack sizes may be marketed.

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. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBERS

53/20.1.1/0246

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 23 January 2024