

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE
UTIMICYN (Granules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:
Contains sugar: 2,153 g sucrose per sachet (see section 4.4).
Contains sweetener (16,0 mg saccharin sodium) per sachet (see section 4.4).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral solution.
Sachets containing almost white granules with citrus flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Method of administration

Oral route after reconstitution in water.
To be taken at least two hours prior to the next meal.
The contents of a sachet should be dissolved in water and taken immediately after its preparation.

4.3 Contraindications

UTIMICYN is contraindicated in:
• Patients with hypersensitivity to fosfomycin or to any of the excipients (see section 6.1);
• Severe renal insufficiency (creatinine clearance < 10 ml/min.);

4.4 Special warnings and precautions for use

Prescribers must abide by the principles of proper antibiotic stewardship.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment (see section 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). It is important to consider this diagnosis in patients who present with diarrhoea during or after treatment with fosfomycin. Therapy with fosfomycin should be discontinued and treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Paediatric population

Safety and efficacy of UTIMICYN in paediatric populations have not been established.

Persistent infections and male patients

A full examination and re-evaluation of the diagnosis is recommended in case of persistent infections as this is often due to the prevalence of resistant pathogens (e.g. *Staphylococcus saprophyticus*) or complicated urinary tract infections. In general, urinary tract infections in male patients must be considered as complicated UTIs for which this medicinal product is not indicated (see section 4.1).

Excipients

UTIMICYN contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take UTIMICYN.
Sulphites
May rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicines and other forms of interaction

Metoclopramide

Concomitant use with metoclopramide may lead to lower urinary and serum concentrations and should be avoided.

Effect of food

Food may delay the absorption of the active ingredient of UTIMICYN, with consequent slight decrease in urinary concentrations and peak plasma levels. It is therefore preferable to take UTIMICYN on an empty stomach or about 2 to 3 hours after meals.

Specific problems concerning the alteration in International Normalised Ratio (INR)

Several cases of increased oral anticoagulant activity in patients receiving antibiotic therapy have been reported. Risk factors include severe infection or inflammation, age and poor general health. Under these circumstances, it is challenging to determine whether the change in INR is due to the infectious disease or its treatment. However, certain classes of antibiotics (in particular fluoroquinolones, macrolides, cyclins, co-trimoxazole and certain cephalosporins) are more often involved.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety and efficacy of single dose therapy with UTIMICYN has not been established in pregnancy. Only limited data on the safety of Fosfomycin treatment during 1st trimester of pregnancy (n=152) are available. This data does not raise any safety signal for teratogenicity so far. Fosfomycin crosses the placenta.

Breastfeeding:

UTIMICYN 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 details are available regarding the influence of fosfomycin on the ability to drive and use machines. However, the possibility of undesirable effects, such as dizziness should be considered.

4.8 Substances of abuse and safety profile

The most frequent 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

System Organ Class	Frequency	Undesirable effect
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 system disorders	Frequent	Diarrhoea, nausea, abdominal pain, dyspepsia (heartburn, indigestion), vomiting.
	Frequency unknown	Antibiotic-associated colitis (see section 4.4).
Skin and subcutaneous tissue disorders	Frequent	Skin rash, urticaria, pruritus.
	Frequency unknown	Angioedema
Musculoskeletal and connective tissue disorders	Frequent	Back pain.
Reproductive system and breast disorders	Frequent	Vaginitis, dysmenorrhoea.
General disorders and administrative site conditions	Frequent	Pain (non-localised), asthenia.

c. Reporting of suspected adverse reactions

Reporting 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

Treatment

In the event of overdose, urinary elimination of the medicine can be accelerated through adequate administration of oral fluids. Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.1 Broad & Medium Spectrum Antibiotics

ATC code: J01XX01

Fosfomycin trometamol is a broad-spectrum bactericidal antibiotic, derived from phosphonic acid for the treatment of lower urinary tract infections.

The antibacterial activity of fosfomycin is due to an inhibition of bacterial cell wall synthesis. Its mechanism of action is inhibition of enol pyruvyl transferase thus irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in the synthesis of the bacterial cell wall.

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.

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.

Species in which acquired resistance may be a problem

Aerobic Gram-positive microorganisms

Enterococcus faecialis

Aerobic Gram-negative microorganisms

Klebsiella pneumonia

Proteus mirabilis

Inherently resistant species

Aerobic Gram-positive microorganisms

Staphylococcus saprophyticus

5.2 Pharmacokinetic properties

Absorption

Following oral administration, fosfomycin trometamol is easily absorbed from the gastrointestinal tract and has absolute bioavailability of about 33-53 %. Food reduces and delays absorption of fosfomycin trometamol, resulting in reduced blood and urinary concentrations.

Mean urinary fosfomycin concentrations are maintained for at least 24 hours post 3 g oral dose above the minimum inhibitory concentrations (MIC) threshold of 128 µg/ml in either the fed or fasting state. The time to reach maximal concentrations in urine however are delayed by 4 hours. Fosfomycin trometamol undergoes enterohepatic recirculation.

Distribution

Fosfomycin trometamol is distributed to tissues including the kidneys and bladder wall. Fosfomycin has been shown to cross the placental barrier, it is not bound to plasma proteins.

Elimination

Fosfomycin is eliminated mainly unchanged through the kidneys by glomerular filtration (40-50 % of the dose is found in the urine and to a lesser extent in faeces (18-28 %). This results in very high peak urinary concentrations (approx. 3000 mg/l) within two to four hours after oral use. Therapeutic concentrations in urine are usually maintained for at least thirty-six hours. 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 moderately reduced renal function (creatinine clearance > 80 ml/min), including the physiological reduction in the elderly, the half-life of fosfomycin trometamol is prolonged but urinary concentration remains therapeutically adequate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose.
Saccharin sodium E954.
Natural orange flavouring 87D645 (contains maltodextrin, arabic gum (E 414), citric acid (E 330), sodium citrate (E 331), butylated hydroxyanisole (E 320)).
Natural mandarin flavouring WONF 87D646 (contains maltodextrin, arabic gum (E 414), citric acid (E 330), sodium citrate (E 331)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Paper/ Alu/Polyethylene sachets. 1 or 2 sachets in a carton box.
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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

56/20.1.1/0646

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

21 August 2024

10 DATE OF REVISION OF THE TEXT

NA