NEW ZEALAND DATA SHEET

1 PRODUCT NAME

UroFos 3 g granules for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 3 g of fosfomycin (as fosfomycin trometamol)

Excipient(s) with known effect: each sachet contains 2.216 g of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral solution.

White or almost white granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of uncomplicated acute cystitis caused by pathogens susceptible to fosfomycin in adult women and adolescents aged over 12.

Prophylaxis of urinary tract infections during surgery and trans-urethral diagnostic maneuvers.

4.2 Dose and method of administration

- Treatment of uncomplicated acute cystitis in adult women and adolescents (aged over 12): 1 sachet of 3 g (single dose).
- Prophylaxis of urinary tract infections during surgery and trans-urethral diagnostic maneuvers: 1 sachet of 3 g administered 3 hours before surgery and a second sachet administered 24 hours after the surgery.

Renal impairment

This medicine is not to be used in patients with severe renal failure, nor haemodialyzed patients (see section 4.3.).

For patients with mild to moderate renal impairment, dose adjustments within recommended dose range are not needed, as its therapeutic concentration in urine remains unchanged (see section 5.2.).

Paediatric population

Uncomplicated acute cystitis:

This medicine should not be used in children under the age of 12 (see section 4.3.).

Prophylaxis of urinary tract infections:

Not recommended in this population.

Method of administration:

Route of administration: oral use

The contents of each sachet should be dissolved and in half a glass of water and taken immediately after (see section 6.6.). The reconstituted solution is a uniform opalescent solution. It is recommended to administer this medicine on an empty stomach, preferably before the night resting, and after voiding the bladder.

4.3 Contraindications

This medicine should not be administered in the following cases:

- Patients with known hypersensitivity to the active substance or to any of the excipients listed in the section 6.1.
- Patients with severe renal failure (creatinine clearance (Clcr) <10 mL/min)
- Patients undergone haemodialysis
- Children younger than 12 years old

4.4 Special warnings and precautions for use

Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment and may be life-threatening (see section 4.8). If such reaction occurs, fosfomycin should be interrupted and an adequate medical treatment is required.

In patients with renal impairment, the concentrations of fosfomycin in urine maintain their efficacy after 48 hours after a usual dose, as long as the levels of creatinine clearance are higher than 10 ml/min.

The occurrence of diarrhoea associated with antibiotics has been reported with most antibacterial agents, including fosfomycin trometamol, whose severity may vary from mild diarrhoea to fatal colitis. The occurrence of diarrhoea, especially if it is severe, persistent and / or bloody, during or after treatment with this medication (even after several weeks after treatment), may be a symptom of Clostridium difficile-associated diarrhoea (DACD). Therefore, it is important to consider this diagnosis in patients who develop severe diarrhoea during or after treatment with UroFos. If DACD is suspected or confirmed, the appropriate treatment should be instituted immediately (see section 4.8). In this clinical situation antiperistaltic medicines are contraindicated.

Clinical symptoms generally disappear in 2 or 3 days after treatment. The occasional persistence of some symptoms does not mean a therapeutic failure, it could probably be a consequence of the inflammation process.

Warning on excipients:

This medicine contains 2.216 g of sucrose in each sachet. Patients with hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

The concomitant administration of metoclopramide reduces the concentrations of fosfomycin in serum and urine.

Other medicines that increase the movement of the stomach or intestines (like bethanechol, cisapride, domperidone and laxatives) may also produce similar effects.

The ingestion of food may delay the absorption of the active substance of this medicine, resulting in a slight decrease in plasma peaks and urinary concentrations, respectively. It is therefore preferable to take the medication on an empty stomach or 2 to 3 hours after meals.

Specific problems of INR alteration:

Several cases of increased vitamin K antagonist activity have been reported in patients treated with antibiotics. Risk factors include severe infection or inflammation, age and poor health status. In these circumstances, it is difficult to determine if the INR alteration is due to the infectious disease or its treatment. However, it is observed that certain classes of antibiotics are more frequently

involved, especially: fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

Paediatric population:
Interaction studies have been conducted only in adults.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy
Currently, the treatment of uncomplicated acute cystitis in pregnant women in single dose regime is not considered appropriate.

Studies in animals have not shown toxicity for reproduction. Although a large amount of safety data regarding the efficacy of fosfomycin during pregnancy is available, the amount of data available is moderate and not indicative of foetal or neonatal toxicity.

Use in Lactation
Fosfomycin is excreted in breast milk in a reduced amount after the administration of a single injection. Accordingly, fosfomycin trometamol can be used in a single oral dose, during breastfeeding.

Fertility
No data are available in humans. No effect on fertility has been described in animals studies.

4.7 Effects on ability to drive and use machines

No specific studies have been performed. However, patients should be informed that dizziness has been described. This may have an influence on 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 fosfomycin from either clinical-trial or post-marketing experiences.

The following CIOMS frequency rating is used:

very common ≥ 1/10 (≥ 10%)
common ≥ 1/100 and < 1/10 (≥ 1% and < 10%)
uncommon ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1.0%)
rare ≥ 1/10,000 and < 1/1000 (≥ 0.01% and < 0.1%)
very rare < 1/10,000 (< 0.01%)
not known (cannot be estimated from the available data)

Adverse reactions are presented in decreasing order within each frequency interval.

MedDRA System Organ Class	**Common (1/100 to < 1/10)**	**Uncommon (≥1/1000 to < 1/100)**	**Rare (≥1/10000 to < 1/1000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Vulvovaginitis		Superinfections from resistant bacteria.	

Blood and lymphatic system disorders			Aplastic anaemia	Eosinophils increase, petechiae.
Immune system disorders				Anaphylactic reactions, including anaphylactic shock, hypersensitivity
Metabolism and nutrition disorders				Decrease appetite
Nervous system disorders	Cephalea, Dizziness	Paraesthesia		
Eye disorders				Visual disturbances
Respiratory, thoracic and mediastinal disorders				Dyspnea, Bronchospasm
Gastrointestinal disorders	diarrhoea, nausea,	vomiting, abdominal pain		Colitis associated to antibiotics (see section 4.4.)
Hepatobiliary disorders				Transient increase of alkaline phosphatase
Skin and subcutaneous tissue disorder		Skin rash, Urticaria, Pruritus		Angioedema
General disorders and administration site conditions				Phlebitis in administration site

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

4.9 Overdose

There is limited experience with oral fosfomycin overdose. In patients who have taken an overdose of this drug, the following adverse effects have been observed: vestibular loss, hearing difficulty, metallic taste and generalized decrease in taste perception.

With the parenteral use of fosfomycin, cases of hypotonia, somnolence, electrolyte disturbance, thrombocytopenia and hypoprothrombinemia have been reported.

In case of overdose, the treatment will be symptomatic and supportive. Rehydration is recommended to favour the elimination of the drug in urine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other antibacterials; ATC Code: J01XX01.

Mechanism of action

This medicine contains fosfomycin [mono (2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis) -(3-methyloxyranyl) phosphonate], antibiotic with a broad spectrum of activity, derivate from phosphonic acid.

Fosfomycin acts on the first stage of the synthesis of the bacterial wall. As an analogue of phosphoenolpyruvate, it inhibits the enzyme phosphoenolpyruvate transferase and, thereby, irreversibly blocks the binding of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first phases in the synthesis of the bacterial wall.

Its mechanism of action explains the absence of cross resistances with other antibiotics and the synergistic action with other classes of antibiotics, such as beta-lactams.

Mechanisms of resistance

The occurrence of *in vitro* resistances occurs through a chromosomal mutation of the genes GlpT and UhpT that control the transport of L-alpha-glycerophosphate and hexose phosphate, respectively.

Limit values

The limit values of the minimum inhibitory concentrations (MIC) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to isolate susceptible from resistant germs were the following (v 5.0 2015-01-01):

Bacterial agent	**Limit value (mg/l)**	
	Susceptible	Resistant
Enterobacteriaceae	≤ 32 mg/l	> 32 mg/l

The MIC cut-off point for other microorganisms is not defined.

The prevalence of resistance for specific species can vary geographically and over time, and local information on resistance is preferable, particularly in the treatment of serious infections. If necessary, an expert's opinion should be sought when the local prevalence of resistance is such that the utility of an agent in some types of infection is questionable.

Frequently susceptible organism
Aerobic Gram-positives *Enterococcus faecalis*
Aerobic Gram-negatives *Escherichia coli*
Species for which the acquired resistance can be a problem
Aerobic Gram-negatives *Klebsiella pneumoniae Proteus mirabilis*
Intrinsically resistant organism
Aerobic Gram-positives *Staphylococcus saprophyticus*

5.2 Pharmacokinetic properties

Absorption

After oral administration, fosfomycin (as trometamol) is well absorbed from the intestine and shows an absolute bioavailability below 40%. The food intake delays the absorption without influencing in the concentrations in urine.

Distribution

Fosfomycin (as trometamol) is distributed to the kidneys, bladder wall, prostate and seminal vesicles. 24-48 hours after oral administration of fosfomycin concentrations in urine are kept above the minimum inhibitory concentrations (MIC) steadily. Fosfomycin does not bind to plasma proteins and crosses the placental barrier.

Elimination

Fosfomycin (as trometamol) is excreted unchanged mainly though the kidney by glomerulqar filtration (30-60% of the dose is recovered in urine) and in a smaller proportion is excreted in the faeces. It has an elimination half-life that varies between 4 and 8 hours. The appearance of a second serum peak after 6 and 10 hours of drug administration suggests that it is subject to enterohepatic recirculation.

The drug is accumulated in patients with chronic renal failure, the elimination half-life increases significantly (up to 50 hours) and is associated with a lower recovery of fosfomycin in urine. It has been established a linear relationship between the pharmacokinetic parameters of fosfomycin and glomerular filtration rate data.

5.3 Preclinical safety data

In acute toxicity studies, a single oral dose of 5.000 mg / kg of fosfomycin (as trometamol) was well tolerated both in mice and rats. After a single dose of 2.000 mg / kg of fosfomycin (as trometamol) in dogs, anorexia was observed on the same day of administration and diarrhoea 2-3 days after administration.

In oral repeated dose toxicity studies, after 4 and 13 weeks of treatment in dogs and rats, respectively, the main effects were observed in the gastrointestinal tract (emesis and unformed stools) as well as body weight loss.

Genotoxicity studies have shown that fosfomycin trometamol lacks mutagenic potential.

Carcinogenicity studies with fosfomycin (as trometamol) have not been conducted.

Studies of reproductive toxicity and development with fosfomycin (as trometamol) have not revealed any teratogenic effects, signs of perinatal and postnatal toxicity or adverse effects on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Sodium saccharin, Orange flavour (containing corn starch), Mandarin flavour (containing corn starch and sucrose)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at our below 25°C.

6.5 Nature and contents of container

Single dose sachets (surlyn/polyethylene/aluminium/paper).
Boxes containing 1 or 2 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

This medicine should be administered immediately after being dissolved.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Te Arai BioFarma Ltd
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Herne Bay
Auckland 1147

0800 TEARAI (832 724)

9 DATE OF FIRST APPROVAL

18 June 2020

10 DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES