SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

1. Name of the medicinal product:

MONODOSE (FOSFOMYCIN GRANULES FOR ORAL SOLUTION)

2. Qualitative and quantitative composition

Each sachet contains:

Fosfomycin Trometamol BP

Eq. to Fosfomycin ..... 3 gm

Excipients ..... Q.S.

3. Pharmaceutical form

Granules for oral solution
A light orange colored granules.

4. Clinical Particulars

4.1 Therapeutic indications

Fosfomycin is indicated for the treatment of acute uncomplicated lower urinary tract infections in adults, caused by pathogens sensitive to fosfomycin.
Fosfomycin is indicated for periprocedural prophylaxis in diagnostic and surgical transurethral procedures.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Adults
Uncomplicated lower urinary tract infections: one sachet (3g)
Perioperative prophylaxis of urinary tract infections: one 3g sachet 3 hours before the procedure
Paediatric population
Fosfomycin trometamol in a dose of 3g is not suitable for children under the age of 12 years.

Perioperative antibiotic prophylaxis for transrectal prostate biopsy:
Adults: One fosfomycin 3 g sachet 3 hours before the procedure and a second dose of 3 g 24 hours after the procedure.

Method of administration
Fosfomycin is for oral administration and should be taken on an empty stomach, either 1 hour before or at least 2 hours after meals and preferably before bedtime after emptying the bladder. The contents of a sachet should be dissolved in a glass of water and taken immediately after its preparation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Fosfomycin is contraindicated in:
• patients with severe renal insufficiency (CLcr<10ml/min)
• patients undergoing haemodialysis

4.4 Special warnings and precautions for use

Older people and Patients with Renal Impairment
Fosfomycin trometamol is principally excreted by the kidney. Caution should be exercised in administering this antibiotic to patients with impaired renal function.
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 diarrhoea 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.
This medicine contains 1,923 g of sucrose per sachet. Patients with rare hereditary problems of fructose intolerance, glucose - galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations and should be avoided.
Paediatric population
Interaction studies have only been performed in adults.
Food Effect
Food may delay the absorption of the active ingredient, 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 INR

Numerous cases of increased oral anticoagulant activity 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.

4.6 Pregnancy and Lactation

Pregnancy

There are limited data from the use of fosfomycin in pregnant women. Animal studies with fosfomycin trometamol (the form used in Fosfomycin) have shown no hazard to the fetus.
Previous studies in the rat showed fetal toxicity following administration of the calcium and sodium salts of fosfomycin at the maximum doses tested (approximately 25 times the therapeutic dose). However, toxicity to the foetus was not observed at lower doses in the rat or at any of the doses tested in the rabbit. Fosfomycin should only be used in pregnancy when the expected benefits outweigh the risk.

Breast-feeding

Fosfomycin is excreted in breast milk. A decision must be made whether to discontinue breast- feeding or to discontinue/abstain from Fosfomycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available; hence the potential risk for humans is unknown.

4.7. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.
However, there are some side effects such as dizziness and fatigue associated with this product that may affect some patients' ability to drive or use machinery.

4.8. Undesirable effects

Adverse reactions are listed below by System Organ Class and Frequency according to the MedDRA frequency convention and System Organ Classification:

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 from the available data)

Immune system disorders	
Not known	Not known anaphylactic shock allergic reaction
Nervous System Disorder	
Common	Headache, diziness
Uncommon	Paraesthesia
Cardiac disorders	
Rare	tachycardia
Vascular disorders	
Not known	hypotension
Respiratory, thoracic and mediastinal disorders	
Not known	Asthma
Gastrointestinal Disorders	
Common	dyspepsia
Uncommon	Diarrhoea, nausea, vomiting, abdominal pain
Not known	Pseudomembranous colitis
Skin and subcutaneous tissue disorders	
Uncommon	Ras, urticaria, pruritus
Rare	itching
Not Known	angioedema
Reproductive system and breast disorders	
Common	Vulvovaginitis
General disorders and administration site conditions	
Uncommon	Fatigue

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting Systems (PVERS) https://pv.pharmacboardkena.org.

4.9. Overdose

The following events have been observed who have taken fosfomycin in overdose: vestibular loss, impaired hearing, metallic taste and general decline in taste perception.
In the event of an overdose, treatment should be symptomatic and supportive. Urinary elimination of the drug should be promoted through adequate administration of oral fluids.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials. ATC code: J01XX01

Fosfomycin trometamol is an orally applicable salt of the agent fosfomycin, a fosfonic acid epoxy.

Mechanism of action

Fosfomycin trometamol is a broad spectrum antibiotic, derived from phosphonic acid.

It inhibits the enzyme phosphoenolpyruvate transferase, which catalyses the formation of n- acetylmuramic acid from n-acetyl aminoglucose and phosphoenolpyruvate. N-acetylmuramic acid is required for the build-up of peptidoglycan, an essential component of the bacterial cell wall. Fosfomycin has a mainly bactericidal action.

PK/PD relationship

Limited data indicate that fosfomycin most likely acts in a time dependent.

Mechanisms of resistance

A resistance to fosfomycin can be based on the following mechanisms:

• Fosfomycin is admitted into the bacterial cell actively via two different transport systems (glycerin-3-phosphate and hexose-6 transport system). In Enterobacteriaceae the glycerin-3- phosphate transport system can be changed in such a way that fosfomycin is no longer transported into the cell.

• Another plasmid-encoded mechanism occurring in Enterobacteriaceae, Pseudomonas spp. and Acinetobacter spp. is based on the presence of a specific protein, under the effect of which fosfomycin metabolises and is bound to glutathione (GSH).

In staphylococci a plasmid-encoded fosfomycin resistance also occurs. The exact mechanism of the resistance has not yet been determined.

A cross-resistance of fosfomycin with other antibiotics classes is not known.

Break points

EUCAST clinical MIC breakpoints for oral fosfomycin to separate susceptible (S) pathogens from resistant (R) pathogens are:

• Enterobacteriaceae S≤32mcg/ml, R>32mcg/ml

Susceptibility

The prevalence of the acquired resistance of individual species can vary locally and in the course of time. Local information on the resistance situation is therefore required – particularly for the adequate treatment of severe infections. If the effectiveness of fosfomycin is doubtful due to the local resistance situation, a therapy consultation by experts is recommended. Particularly in the case of serious infection or therapy failure, a microbiological diagnosis indicating the pathogen and its sensitivity to fosfomycin is recommended.

The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to fosfomycine or not.

Common susceptible species
Gram-positive aerobes
Staphylococcus saprophyticus*
Gram-negative aerobes:

Escherichia coli
Species for which acquired resistance may be a problem:
Gram-positive aerobes
Enterococcus faecalis
Gram-negative aerobes
Proteus mirabilis

*No current data was available when the tables were published. Primary literature, standard works and therapy recommendations assume sensitivity.

5.2 Pharmacokinetic properties

Fosfomycin contains fosfomycin trometamol which is an orally well absorbed salt of fosfomycin. It provides therapeutic concentrations of the active moiety in the urine for periods of 36 hours or more from a single dose.
Fosfomycin is orally administered after reconstitution in water, in which the formulation is completely soluble. A dose of 2g and 3g in terms of fosfomycin, respectively in children and adults, including elderly, is rapidly absorbed from the gastrointestinal tract. These doses give peak plasma concentrations after 2 hours of 20-30 mcg/ml, serum half life is largely independent of dose.
Fosfomycin is eliminated mainly unchanged through the kidneys and this results in very high urinary concentrations (approx. 3000mg.A) within 2-4 hours. Therapeutic concentrations in urine are usually maintained for at least 36 hours.
Food delays and reduces absorption of fosfomycin trometamol, resulting in reduced blood and urinary concentrations. However, it is unlikely that the efficacy in urinary tract infection would be seriously affected.
In patients with moderately reduced renal function (Creatinine clearance - CrCl ≤80 ml/min), including the physiological reduction in the elderly, the half-life of fosfomycin is slightly prolonged but urinary concentration remains therapeutically adequate.

5.3. Preclinical safety data

There are no non clinical data of relevance to the prescriber which are additional to that already included in other sections of this SmPC

6. Pharmaceutical particulars

6.1 List of excipients

As per dossier

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10 gm/sachet

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.
The content of one sachet should be poured into a glass and 50-75 ml of water or other aqueous drink should be added to obtain a uniform opalescent solution. If necessary, the solution may be stirred. The solution should be taken immediately after being prepared.

7. Marketing Authorisation holder

AVETINA LIFESCIENCES LTD

8. Marketing Authorisation Number

CTD10706

9. Date of First Authorisation/ renewal of the authorisation

25/10/2023

10. Date of Revision of the text

11/05/2025