Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Monuril 3 g granules for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose sachet contains 5.631 g fosfomycin – trometamol (1:1) equivalent to 3 g fosfomycin.

Excipients: Each single-dose sachet contains 2.213 g of sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral solution.

White granular powder with a characteristic odour of mandarin flavour.

4.1 Therapeutic Indications

Treatment of acute uncomplicated urinary tract infections due to sensitive organisms in adults.

4.2 Posology and method of administration

Posology

Adults only:

A single dose of 3 g taken on an empty stomach, preferably before bedtime, after bladder emptying.

The contents of the sachet should be dissolved in water and the solution swallowed immediately.

Elderly patients:

Not recommended due to diminished urinary excretion.

Paediatric population:

There is insufficient clinical use in children to make a recommendation for use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with severe renal failure (creatinine clearance < 10 ml/min).

Patients undergoing haemodialysis.

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 never be re-administered and an adequate medical treatment is required. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C.difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

Antibiotic associated diarrhoea has been reported with use of nearly all antibacterial agents, including fosfomycin trometamol, and may range in severity from mild diarrhoea to fatal colitis. Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Monuril (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (CDAD). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with Monuril. If CDAD is suspected or confirmed, appropriate treatment should be initiated without delay (see section 4.8). Anti-peristaltic medicinal products are contra-indicated in this clinical situation. Do not use more than one single dose of Monuril to treat a single episode of acute cystitis. Prolonged use of an anti-infective may result in the development of superinfection due to organisms resistant to that anti-infective.

Renal insufficiency: urinary concentrations of fosfomycin remain effective for 48 hours after a usual dose if creatinine clearance is above 10 ml/min.

Monuril contains sucrose. Its use is not recommended in patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency.

Paediatric population:

There is insufficient clinical use in children to make a recommendation for use.

4.5 Interaction with other medicinal products and other forms of interactions

When co-administered with fosfomycin, metoclopramide lowers the serum and urine concentrations of fosfomycin. Other drugs that increase gastrointestinal motility may produce similar effects.

Food may delay the absorption of the active ingredient of Monuril 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 antivitamin K antagonists activity have been reported in patients receiving antibiotics. Risk factors include severe infection or inflammation, age and poor general health. Under these circumstances, it is difficult to determine 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

At the present time, single-dose antibacterial treatments are not suitable to treat urinary tract infections in pregnant women.

Animal studies do not indicate reproductive toxicity. A large amount of data concerning effectiveness of fosfomycin during pregnancy is available. However, only moderate amount of safety data on pregnant women is available and does not indicate any malformative or feto/neonatal toxicity of fosfomycin.

Lactation

Fosfomycin is excreted into human milk at low level after a single injection. Therefore Fosfomycin can be used during breastfeeding, after a single oral dose.

Fertility

No effect on fertility has been reported in animal studies. No data are available in human.

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.

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 Monuril from either clinical-trial or post-marketing experiences.

The displayed frequency categories use the following convention:

Very common (2 1/10); common (2 1/100 to < 1/10); uncommon (2 1/1,000 to < 1/100); rare (2 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated form the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reactions**			
	Common	**Uncommon**	**Rare**	**Not Known**
Infections and infestations	Vulvovaginitis			
Immune system disorders				anaphylactic reactions including anaphylactic shock, hypersensitivity
Nervous system disorders	Headache, Dizziness	Paraesthesia		
Cardiac disorders			Tachycardia	
Respiratory, thoracic and mediastinal disorders				Asthma
Gastrointestinal disorders	Diarrhoea, Nausea, Dyspepsia	Vomiting, Abdominal pain		Antibiotic-associated colitis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash, Urticaria, Pruritus		Angioedema

General disorders and administration site conditions		Fatigue		
Vascular Disorders				Hypotension

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website:www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms

Experience regarding the overdose of oral fosfomycin is limited. The following events have been observed in patients who have taken Monuril 3 g granules for oral solution in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception.

Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin.

Treatment in the event of overdose

In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use – other antibacterials ATC code: J01XX01

Monuril 3 g granules for oral solution contains fosfomycin [mono(2-ammonium-2-hydroxymethyl-1,3-propandiol)(2R-cis)-(3-methyloxyranil)phosphonate], a broad spectrum antibiotic, derived from phosphonic acid, for the treatment of urinary tract infections. It acts on at the first stage of bacterial wall synthesis. Being an analogue of phosphoenolpyruvate, it inhibits the phosphoenolpyruvate transferase enzyme, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. It can also reduce bacterial adhesion to bladder mucosa, which can be a predisposing factor for recurring infections. Its mechanism of action explains the lack of cross-resistance with other antibiotics and the synergism with other classes of antibiotics, such as beta-lactam antibiotics.

Fosfomycin-trometamol acts against a broad range of Gram-positive and Gram-negative microorganisms commonly isolated in urinary tract infections, such as E.coli, Citrobacter spp., Klebsiella spp., Proteus spp., Serratia spp., P. aeruginosa and Enterococcus faecalis.

The emergence of in vitro resistance occurs as a mutation of the chromosomal genes glpT and uhp, which control the transport of L-alpha-glycerophosphate and hexose phosphate, respectively.

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

• For other species MIC breakpoint not defined.

5.2 Pharmacokinetic properties

Absorption

After oral administration, fosfomycin is well absorbed from the gut and has an absolute bioavailability of about 50%. Food delays absorption, not influencing urinary concentrations.

Distribution

Fosfomycin is distributed to the kidneys, bladder wall, prostate and seminal vesicles. Sustained concentrations of fosfomycin higher than the minimum inhibitory concentrations (MIC) are obtained in urine for 24-48 hours after oral administration.

Fosfomycin is not bound to plasma proteins and crosses the placental barrier.

Elimination

Fosfomycin is excreted unchanged mainly via the kidneys by glomerular filtration (40-50% of the dose is found in the urine) with an elimination half-life of about 4 hours and to a lesser extent in feces (18-28% of the dose). The appearance of a second serum peak 6 and 10 hours after drug intake suggests that the drug is subject to enterohepatic recirculation.

The pharmacokinetic features of fosfomycin are not modified by age or pregnancy. The drug accumulates in patients with renal failure; linear relationships have been established between fosfomycin pharmacokinetic parameters and glomerular filtration rate data.

5.3 Preclinical safety data

In acute toxicity studies a single oral dose of 5000 mg/kg was well tolerated both in mice and rats and a single dose of 2000 mg/kg did not produce changes in rabbits and dogs.

Repeated dose studies by oral route showed that the no-effect dose was between 100 and 200 mg/kg after 4 weeks of treatment in dogs and rats, respectively.

Genotoxicity studies have shown that fosfomycin is devoid of mutagenic potential.

Reproductive and development toxicity studies have not disclosed any teratogenic effects, any signs of peri- and postnatal toxicity or any untoward effects on fertility.

6.1 List of excipients

Mandarin flavour

Orange flavour

Saccharin

Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Sachets are a four layer laminate: paper, polyethylene, aluminium, polyethylene.

Sachets are supplied in cardboard outer containing either 1 sachet or 2 sachets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The dose must be dissolved in a glass of water and administered soon after dissolving.

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

7 MARKETING AUTHORISATION HOLDER

Zambon S.p.A.

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20091-Bresso

Milan

Italy

8 MARKETING AUTHORISATION NUMBER

PA1441/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13 November 2010

10 DATE OF REVISION OF THE TEXT

January 2019