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 CLINICAL PARTICULARS

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.
Monuril should not be used in patients with impaired renal function (creatine-clearance <80ml/min).

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. Antibiotic associated diarrhoea has been reported with use of nearly all antibacterial agents, including fosfomycin trometamol, and may range in severity from mild diarrhea to fatal colitis.

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

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 interaction

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 (≥ 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 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			
Cardiac disorders				
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		Asthenia		
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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic anti-infections, antibiotics, other antibacterial products. ATC code: J01X X01

Fosfomycin trometamol [mono (2-ammonium-2-hydroxymethil-1,3-propandiol) (2R-cis) (3- methiloxyranil) phosphonate] is a broad spectrum antibiotic, derived from phosphonic acid, for the treatment of urinary tract infections. The antibacterial activity of fosfomycin is due to an inhibition of bacterial cell wall synthesis. Its particular mechanism of action, specific inhibition of enol pyruviltransferase, results in lack of cross resistance with other classes of antibiotic, and the possibility of synergism with other antibiotics (in vitro synergic effect with amoxicillin, cephalexin, pipedimic acid and aztrenam).
In vitro antibacterial spectrum of fosfomycin trometamol includes the most common gram- negative and gram-positive bacteria isolated in urinary tract infections. They include E.coli, Klebsiella spp., Proteus spp., Staphylococcus spp., Str. Faecalis, P. Aeruginosa, and Serratia spp.
Proteus indole-positive is only slightly sensitive or resistant.
Cross-resistance with other antibiotic is not reported.
Fosfomycin trometamol inhibits in vitro the adhesion of bacteria to the urinary epithelium.
The emergence of in vitro resistance occurs as a mutation of the chromosomal genes glpT and uhp controlling the transport of L-alpha-glycerophosphate and hexose phosphate, respectively. The frequency of resistant mutations in Klebsiella pneumonie is about 10-9 and between 10-4 and 10-6 in the other species mentioned. The incidence of resistance decreases with the increasing of the acidity of the milieu.

5.2 Pharmacokinetic properties

MONURIL 3 g granules for oral solution contains fosfomycin trometamol which is an orally well absorbed salt of fosfomycin. MONURIL 3 g granules for oral solution is orally administered after reconstitution in water, in which the formulation is completely soluble. Bioavailability after fasting oral administration is of 30-55% . Food taking concomitantly diminishes adsorption and urinary excretion. A 50mg/kg dose, gives peak plasma concentration after 2 hours from the administration. Serum half-life is independent of dosage. Food delays and reduces the absorption of fosfomycin trometamol, resulting in reduced blood and urinary concentrations. Fosfomycin, unbound to the plasma-proteins, is eliminated mainly unchanged through the kidneys and these results in very high urinary concentrations (about 3000mcg/ml) within 24 hours. Therapeutic concentrations of the active moiety in the urine are usually maintained for at least 36-48 hours. In patients with moderately reduced renal function (including elderly patients) the serum half-life of fosfomycin is slightly prolonged but urinary concentration remains therapeutically adequate.

5.3 Preclinical safety data

The oral LD50 in rats and mice exceeds 10,000 mg/kg.
Oral doses up to 1000 mg/kg induced no relevant toxic effects affecting functions and structures of the various organs and systems during subacute toxicity tests in rats and chronic toxicity tests in dogs.
Fosfomycin has no mutagenic action. Teratogenicity (rats, rabbits), fertility (rats) and peri- and postnatal (rats) toxicity studies did not evidence signs of possible fosfomycin-related toxic effects.

6 PHARMACEUTICAL PARTICULARS

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.
via Lillo del duca,10
20091-Bresso
Milano
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

November 2014