Monuril 3g granules for oral solution

Summary of Product Characteristics Updated 30-Jul-2016 | Profile Pharma Limited

1. Name of the medicinal product

Monuril 3 g granules for oral solution

2. Qualitative and quantitative composition

One sachet contains 5.631 g of fosfomycin trometamol equivalent to 3.0 g fosfomycin

Excipient(s) with known effect:

One sachet contains 2.213 g of sucrose, see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Granules for oral solution.

4. Clinical particulars

4.1 Therapeutic indications

Monuril is indicated in the treatment of acute lower uncomplicated urinary tract infections, caused by pathogens sensitive to fosfomycin in adult and adolescent females.

Monuril is also indicated for 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

Acute lower uncomplicated urinary tract infections:

Adults: and adolescent females (>12 years of age): 1 sachet (3 g) once

Prophylaxis of urinary tract infections for surgery and diagnostic procedure involving the lower urinary tract:

Adults: One Monuril 3 g sachet 3 hours before surgery. A second dose of 3 g may be given 24 hours after surgery.

Paediatric population

The safety and efficacy of Monuril 3 g in children below 12 years of age have not been established.

Method of administration

Monuril is for oral administration. It should be taken on an empty stomach (about 2-3 hours before or 2-3 hours after a meal), preferably before bedtime and after emptying the bladder.

The dose should be dissolved into a glass of water and taken immediately after its preparation.

4.3 Contraindications

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

Patients with severe renal insufficiency (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-administrated and an adequate medical treatment is required.

Antibiotic-associated diarrhoea has been reported with use of nearly all antibacterial agents, including fosfomycin 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.

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 sucrase-isomaltase insufficiency.

Paediatric population

Experience in children with Monuril 3 g is limited. The product is not recommended for children below the age of 12.

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 of fosfomycin and should be avoided.

Other drugs that increase gastrointestinal motility may produce similar effects.

Paediatric population

Interaction studies have only been performed in adults.

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 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 Fertility, pregnancy and lactation

Pregnancy

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

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

The use of Monuril may be considered during pregnancy, if necessary.

Breast-feeding

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			
Gastrointestinal disorders	Diarrhoea, nausea	Vomiting, abdominal pain		Antibiotic-associated colitis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritus		Angioedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Experience regarding the overdose of oral fosfomycin is limited. However cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin.

In the event of overdose, 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: Antibacterials for systemic use – other antibacterials.

ATC code: J01XX01

Mode of action:

Fosfomycin acts on at the first stage of bacterial wall synthesis. It inhibits the phosphoenolpyruvate transferase enzyme, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate. Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems). 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.

Commonly susceptible species:

Citrobacter spp

Escherichia coli

Klebsiella oxytoca

Proteus mirabilis

Staphylococcus aureus

Species in which acquired resistance may be a problem:

Enterococcus faecalis

Enterobacter cloacae

Pseudomonas aeruginosa

Serratia marcescens

Inherently resistant species:

Bacteroides spp.

Resistance:

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems.

Susceptibility testing Break points Version 4.0, valid from 2014-01-01

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

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

• For other species MIC breakpoint not defined.

Clinical efficacy against specific pathogens:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable.

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship:

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

5.2 Pharmacokinetic properties

Absorption

After single-dose oral administration, fosfomycin trometamol has an absolute bioavailability of about 34-41%. Rate and extent of absorption are reduced by food.

Distribution

Fosfomycin is distributed to tissues including the kidneys and bladder wall. Fosfomycin is not bound to plasma proteins and crosses the placental barrier.

Biotransformation and Elimination

Fosfomycin does not appear to be metabolised and is excreted unchanged mainly via the kidneys by glomerular filtration with an elimination half-life of about 4 hours after oral administration.

Special populations

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency.

In older people fosfomycin clearance is reduced in line with the age related reduction in renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for fosfomycin trometamol.

6. Pharmaceutical particulars

6.1 List of excipients

Mandarin flavour

Orange flavour

Saccharin

Sucrose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

After reconstitution in water, the solution is stable at room temperature for 24 hours.

6.4 Special precautions for storage

Store away from direct sunlight.

6.5 Nature and contents of container

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

Sachets are supplied in cardboard outer containing 1 sachet, 2 sachets or 5 sachets.

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

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 31654/0006

9. Date of first authorisation/renewal of the authorisation

18/03/1994 / 19/09/2008

10. Date of revision of the text

20/01/2016

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