## 1. NAME OF THE MEDICINAL PRODUCT

MONURAL 3 g granules for oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*MONURAL 3 g granules for oral solution*
Each sachet contains:
Active substance: fosfomycin 3.0 g (as fosfomycin trometamol 5.631 g)

Excipients: mandarine flavoring 0.07 g, orange flavoring 0.07 g, saccharin 0.016 g, sucrose 2.213 g (corresponding to 37 kJ or 0,088 carbohydrate exchange).
Composition of orange flavouring: Flavouring 8%, maize maltodextrin 72%, modified waxy maize starch E1450 10%
Composition of mandarin flavouring: Flavouring 7,4%, sugar 70%, arabic gum E414 22%, calcium phosphate E341 0.6%, butylated hydroxyanisole (BHA) E320 <0,01%

## 3. PHARMACEUTICAL FORM

Granules for oral solution.
White to off-white granules.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Monural is indicated for the treatment of the following infections, caused by fosfomycin-sensitive pathogens:

- acute, uncomplicated urinary tract infections
- asymptomatic bacteriuria
- prophylaxis in surgical or diagnostic procedures involving lower urinary tract (e.g. TUR)

Should take into account the recommendations given to official guidance on the appropriate use of antibiotics; in particular in order to avoid the increase in antibiotic resistance.

### 4.2 Posology and method of administration

**Usual dose**

Adults: 1 sachet of Monural 3 g as single dose.
Prophylaxis: 1 sachet of Monural 3 g approximately 3 hours before and 24 hours after surgery.
Children and adolescents below 50 kg body weight: As the experience in children is limited and Monural 3 g, due to its dosage strength, is not suitable for children and adolescents under 50 kg body weight, Monural should not be used in this age group.

**Correct method of administration**

Monural should be taken on an empty stomach, i.e. 2-3 hours before or after meals, preferably in the evening before bedtime, after emptying the bladder.
Monural should be dissolved in a glass of water or in another non-alcoholic drink and taken immediately after its preparation.

### 4.3 Contraindications

- Hypersensitivity to the active substance fosfomycin or to any of the excipients.
- Renal failure with creatinine clearance< 10 ml/min.
- Patients undergoing haemodialysis

### 4.4 Special warnings and precautions for use

Before initiating MONURAL treatment, it is appropriate to collect pertinent data about the patient's clinical history in terms of a possible hypersensitivity to fosfomycin (see section 4.8).
Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during treatment with fosfomycin, which can be life-threatening (see section 4.8). If such reactions occur, fosfomycin should not be readministered and an appropriate medical treatment is required.
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. Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Monural (even in the weeks following the treatment administration), 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 Monural. If CDAD infection is suspected or confirmed, an appropriate treatment should be initiated immediately (see section 4.8). Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Renal insufficiency: fosfomycin urinary concentrations are effective for 48 hours after a usual dose provided that creatinine clearance exceeds 10 ml/min.

Important information about some of the ingredients:
Monural contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this medicine. Caution should be exercised in case of diabetic patients or patients on a low-calorie diet.
Monural contains saccharin.

**4.5 Interaction with other medicinal products and other forms of interaction**
When co-administered with fosfomycin, metoclopramide lowers the oral absorption of fosfomycin. Other drugs that increase gastrointestinal motility may produce similar effects
The concomitant administration of antacids or calcium salts induces a reduction in serum levels and urinary concentrations of fosfomycin.
Food may delay the absorption of the active ingredient of Monural, with a consequent mild decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicinal product on an empty stomach or about 2-3 hours after meals.

- Specific problems associated with INR changes
Several cases of increased vitamin K-antagonist activity have been reported in patients treated with antibiotics. Possible risk factors include severe infection or inflammation, age and poor general health status. Under these circumstances, it is difficult to determine if INR changes are due to the infective disease or to its treatment. However, some classes of antibiotics are more often involved, in particular: fluoroquinolones, macrolides, cyclins, cotrimoxazole and some cephalosporins.

**4.6 Fertility, pregnancy and lactation**
Fertility
In animal studies no effects on fertility have been reported. No data on human fertility are available.

Pregnancy
To date, single-dose treatments are not suitable for the treatment of urinary tract infections in pregnant women.
Animal studies do not indicate reproductive toxicity.
A large amount of safety data relative to fosfomycin efficacy during pregnancy is available. However, only a moderate amount of data on pregnant women is available, and indicates no malformative nor feto/neonatal toxicity of fosfomycin trometamol. This medicinal product should be administered in pregnant women only in case of real clinical need and always under strict medical surveillance.

Lactation
Fosfomycin is excreted in low concentrations in human milk after a single injection. Consequently, fosfomycin can be used during breastfeeding after administration of a single oral dose. However, during breastfeeding this medicinal product should be administered only in case of real clinical need and always under direct medical surveillance.

**4.7 Effects on ability to drive and use machines**
No specific studies have been performed, but patients should be informed that cases of vertigo have been reported. This may affect the ability to drive and use machines in some patients.

**4.8 Undesirable effects**
The most common undesirable effects following the single-dose administration of fosfomycin trometamol involve the gastrointestinal tract; diarrhoea appears to be the most frequently reported adverse event. These events are usually self-limited in duration and resolve spontaneously.
The following table displays adverse reactions that have been reported with the use of MONURIL, from either clinical trials and post-marketing experience, classified according to MedDRA system organ class. The frequency of the undesirable effects described here below is defined according to 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 (the frequency cannot be estimated from the available data).

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

| System organ class | Undesirable effects | | | |
|---|---|---|---|---|
| | **Common** | **Uncommon** | **Rare** | **Not known** |
| Infections and infestations | vulvovaginitis | | superinfections caused by resistant bacteria | |
| Immune system disorders | | | | anaphylactic reactions, including anaphylactic shock and hypersensitivity |
| Nervous system disorders | headache, vertigo | paraesthesia | | |
| Cardiac disorders | | | tachycardia | |
| Respiratory, thoracic and mediastinal disorders | | | | asthma, bronchospasm, dyspnoea |
| Gastrointestinal disorders | diarrhoea, nausea, dyspepsia | vomiting, abdominal pain | | antibiotic-associated colitis (see section 4.4) inappetence |
| Hepatobiliary disorders | | | | transient increase in alkaline phosphatase and aminotransferase plasmatic levels |
| Skin and subcutaneous tissue disorders | | rash, urticaria, itching | | angioedema |
| General disorders and | | fatigue | | |
| administration site conditions | | | | |
| Blood and lymphatic system disorders | | | aplastic anaemia | slight increase in eosinophil and platelet counts, with formation of petechiae |
| Eye disorders | | | | visual disturbances |
| Vascular disorders | | | | hypotension phlebitis |

**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 at the following address: www.agenziafarmaco.gov.it/it/responsabili.

**4.9 Overdose**
*Symptoms*
The experience relative to oral fosfomycin overdose is limited.
However, cases of hypotonia, somnolence, electrolyte disturbances, thrombocytopenia and hypoprothrombinaemia have been reported with fosfomycin use by parenteral route.
Following the intake of excessive doses of fosfomycin trometamol the following symptoms may occur: vestibular disturbances, impaired hearing, metallic taste and general decline in taste perception.
*Treatment*
In the event of accidental overdose (5-10 sachets), treatment should be symptomatic and supportive. Rehydration is recommended to promote the urinary elimination of the drug.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary tract antibacterial – ATC code: J01XX01

Fosfomycin trometamol, [mono (2-ammonium-2-hydroxymethyl-1,3-propandiol) (2R-cis) (methyloxyranyl) phosphonate] is a broad-spectrum antibiotic, derived from phosphonic acid, for the treatment of lower urinary tract infections.

Fosfomycin trometamol is active against Gram-positive and Gram-negative bacteria, including penicillinase-producing strains and the pathogens most frequently isolated in urinary tract infections (Escherichia Coli, Proteus, Klebsiella, Enterobacter, Staphylococcus, Streptococcus and other resistant strains).

Mechanism of action

Fosfomycin trometamol is a structural analogous of phosphoenolpyruvate and inhibits the phosphoenolpyruvatetransferase enzyme, which catalyzes the formation of N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate. N-acetylmuramic acid is required for the build-up of peptidoglycan, an essential component of the bacterial cell wall. Therefore, fosfomycin has a mainly bactericidal action.

Pharmacokinetic/pharmacodynamic relationship

Fosfomycin therapeutic effectiveness essentially depends on the period of time during which the active substance level is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanism 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 systems). In Enterobacteriacee the glycerin-3-phosphate transport system may be changed in such a way that fosfomycin is no longer transported into the cell.
- Another plasmid-encoded mechanism of resistance occurring in Enterobacteriaceae, Pseudomonas spp. and Acinetobacter spp., is based on the presence of a specific protein, under the effect of which fosfomycin is metabolized and bound to glutathione (GSH).
- Staphylococcus shows a plasmid-encoded fosfomycin resistance, whose mechanism has not yet been determined.

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

Breakpoints

Testing of fosfomycin is done with the aid of the usual dilution series. The evaluation of the results is done on the basis of the limit values for fosfomycin. The following table displays the minimum inhibitory concentrations established for sensitive and resistant strains.

**EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints**

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacteriaceae | ≤ 32 mg/l | >32 mg/l |

Prevalence of acquired resistance

The prevalence of acquired resistance may vary geographically and with time for selected species. Therefore, local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that fosfomycin efficacy is questionable: particularly in the event of severe infections or in case of a treatment failure, a microbiological diagnosis with identification of the causative pathogen and its susceptibility to fosfomycin should be sought.

### 5.2 Pharmacokinetic properties

Fosfomycin trometamol is completely absorbed in the gastrointestinal tract after oral administration, reaching effective urinary concentrations which are maintained up to 36 hours after administration of a single dose.

Food may delay the absorption of the medicinal product, resulting in a slight reduction in peak plasma levels and urinary concentrations, however not so important as to compromise in any way the antibacterial activity of the drug.

By administration of 2 or 3 g fosfomycin, plasma concentrations equal to 20-30 mcg/ml are reached. Fosfomycin half-life is about 3 hours and is independent of dosage.

In elderly subjects with impaired renal function, serum half-life appears slightly prolonged; anyway, urinary concentrations undergo only negligible changes with respect to normal adults, and therefore no dose adjustments are recommended.

Fosfomycin is not bound to plasma proteins and is excreted unchanged mainly in urine.

High urinary concentrations (about 3000 mcg/ml) are rapidly attained within 2-4 hours and are maintained for at least 36-48 hours.

**5.3 Preclinical safety data**

Subacute toxicity tests in rats and chronic toxicity tests in dogs (doses up to 1000 mg/kg) evidenced no toxic effects on organs and systems.

Fosfomycin has no mutagenic action. Although fosfomycin crosses the placental barrier, teratogenicity (rats, rabbits), fertility (rats) and peri- and postnatal toxicity (rats) studies did not disclose any signs of possible drug-related toxic effects.

Fetotoxicity was observed in female rabbits treated with maternal toxic fosfomycin doses (with effects on the intestinal microflora).

## 6. PHARMACEUTICAL PARTICULARS

**6.1 Incompatibilities**

*Monural 3 g granules for oral solution*

None known.

**6.2 Shelf life**

3 years.

Do not use after the expiration date printed on the package. After reconstitution of solution, the medicinal product should be taken immediately.

**6.3 Special precautions for storage**

At temperature below 30 ºC.

**6.4 Nature and contents of container**

Granules for preparation of oral solution. The drug is placed in bags of 4-layer laminated foil (paperpolyethylene-aluminum-polyethylene). 1 or 2 bags are placed in a cardboard box along with instructions for use.

**6.5 Special precautions for disposal and other handling**

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

## 7. MARKETING AUTHORIZATION HOLDER

ZAMBON S.p.A. - Via Lillo del Duca, 10 - 20091 Bresso (MI)

## 8. MARKETING AUTHORIZATION NUMBER(S)

MONURAL 3 g granules for oral solution - 2 sachets MA n° 025680024

MONURAL 3 g granules for oral solution - 1 sachets MA n° 025680036

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

MONURAL 3 g granules for oral solution - 2 sachets

First authorization: July 12th 1986

Renewal: June 1st 2010

MONURAL 3 g granules for oral solution - 1 sachet

First authorization: July 17th 2009

Renewal: June 1st 2010

## 10. DATE OF REVISION OF THE TEXT

June 21, 2016