

FOSWOMYN 3G GRANULES FOR ORAL SOLUTION

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

In each sachet;

5.631 g fosfomycin trometamol (equivalent to 3 g fosfomycin)

PHARMACEUTICAL FORM

Granules for Oral solution

Before reconstitution: White or almost white granulate without lumps or particulates

After reconstitution: The reconstituted solution is a slightly whitish turbid solution with fruit odour (orange-mandarin).

PHARMACOLOGICAL PROPERTIES

ATC code: J01XX01

Mechanism of action

FOSWOMYN contains the active substance fosfomycin [mono (2-ammonium-2- hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxyranil)-phosphonate] in the form of trometamol salt.

Fosfomycin is an antibiotic (derived from phosphonic acid) with a bactericidal effect. This is based on inhibition of bacterial cell wall synthesis, blocking one of the first steps of peptidoglycan synthesis.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3- phosphate and hexose-6 transport systems).

Pharmacodynamics

The structure of Fosfomycin is analogous to that of p-enolpyruvate. This is why it inactivates the enzyme enolpyruvyl transferase and thus the condensation of uridine diphosphate-Nacetylglucosamine with p-enolpyruvate is irreversibly blocked, one of the first steps in the synthesis of the bacterial cell wall. Fosfomycin may also reduce bacterial adhesion to the bladder mucosa, which may be a predisposing factor for recurrent urinary tract infections.

The susceptibility breakpoints established by the European Committee on Antimicrobial Susceptibility Testing are as follows (EUCAST breakpoint table version 11, 01.01.2021):

Species	Susceptible	Resistant
Enterobacterales	≤ 8mg/l	> 8mg/l

Prevalence of acquired resistance

The prevalence of acquired resistance of individual species may vary geographically and over time. Local information about the resistance situation is therefore necessary, particularly in order to ensure appropriate treatment of severe infections.

The following table is based on data from surveillance programs and studies. It comprises relevant for the approved indications:

Commonly susceptible species
- Aerobic Gram-negative microorganisms
- Escherichia coli
Species in which acquired resistance may be a problem
- Aerobic Gram-positive microorganisms
- Enterococcus faecalis
- Aerobic Gram-negative microorganisms

- Klebsiella pneumonia
 - Proteus mirabilis
- Inherently resistant species
- Aerobic Gram-positive microorganisms
 - Staphylococcus saprophyticus

Mechanism of resistance

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial Fosfomycin transport systems. Further resistance mechanisms, which are plasmid or transposon-borne, cause enzymatic inactivation of fosfomycin by binding the molecule to glutathione or by cleavage of the carbon-phosphorus bond in the fosfomycin molecule, respectively.

The activity of fosfomycin against the most common germs in case of urinary tract infections remained unchanged. Only a few bacteria can develop resistance. The resistance rate of E. coli, which causes uncomplicated urinary tract infection, is low.

Most resistant «Multidrug» E. coli and other Enterobacteriaceae, producing Extended Spectrum Beta-Lactamase (ESBL), are susceptible to fosfomycin.

Most MRSA (Methicillin-resistant Staph aureus) are also susceptible to fosfomycin.

Cross-resistance

Cross-resistance between fosfomycin and other antibiotic classes is not known. Cross-resistance should not be expected because the chemical structure of Fosfomycin is fundamentally different from that of all other antibiotics and fosfomycin has a unique mechanism of action.

Clinical efficacy

Fosfomycin has a broad antibacterial spectrum, which includes most of the gram-positive and gram-negative bacteria associated with urinary tract infections, as well as penicillinase producing strains.

In vivo, resistance has been observed in Enterobacter ssp., Klebsiella ssp., Enterococci, Proteus mirabilis, Staph. aureus and Staph. saprophyticus.

In addition, FOSWOMYN prevents the adhesion of bacteria to the bladder mucosa, which is a predisposing factor for recurrent urinary tract infections.

Pharmacokinetic

Absorption:

After a single-dose administration, fosfomycin trometamol has an absolute bioavailability of about 33-53%. Rate and extent of absorption are reduced by food, but the total amount of active substance excreted in the urine over the time is the same. Mean urinary Fosfomycin concentrations are maintained above an MIC threshold of 128 µg/ml for at least 24 h post 3 g oral dose in either the fasting or fed state, but the time to reach maximal concentrations in urine are delayed by 4 h. Fosfomycin trometamol undergoes enterohepatic recirculation.

After a single-dose administration of 3 g, t_{max} is 2-2.5 hours and C_{max} is 22-32 µg/ml.

Distribution:

Fosfomycin is distributed to tissues including the kidneys and bladder wall. Fosfomycin is not bound to plasma proteins. The volume of distribution is 136.1 L.

Fosfomycin crosses the placental barrier and is excreted in human breast milk.

Metabolism

Fosfomycin does not appear to be metabolised.

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 after oral use and to a lesser extent in faeces (18-28 % of the dose). Even if food delays the drug absorption the total amount of the drug excreted in the urine over time is the same. After a single dose of 3 g Fosfomycin trometamol, a urine concentration of fosfomycin of 1053- 4415 µg/ml is reached after 2-4 hours. Therapeutically effective concentrations (> 100 µg/ml) are still present up to 48 hours after administration

Pharmacokinetics in special populations

In patients with impaired renal function, the elimination half-life is increased proportionally to the degree of renal insufficiency. Urinary concentrations of fosfomycin in patients with impaired renal function remain effective for 48 hours after a usual dose if creatinine clearance is above 10 ml/min.

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

CLINICAL PARTICULARS**Therapeutic indications**

FOSWOMYN is indicated for

- the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in females of 18 years of age and older caused by the following susceptible pathogens: Escherichia coli and Enterococcus faecalis
- Perioperative antibiotic prophylaxis for transrectal prostate biopsy in adult man.

Consideration should be given to official guidance on the appropriate use of antibacterial agents, especially to avoid increasing antibiotic resistance.

Posology and method of administration***Acute uncomplicated lower urinary tract infections (acute cystitis) in females of 18 years of age and older:***

One Sachet (3g of active substance), single dose regimen.

Clinical symptoms usually disappear 2-3 days after beginning of treatment

- In acute infections of the lower urinary tract (cystitis, non-gonococcal urethritis) caused by microorganisms susceptible to FOSWOMYN, a single dose (3 g of active substance in adults) is sufficient for recovery. The persistence of local symptoms, if any, after treatment, is not necessarily a sign of therapeutic failure, but usually the consequence of the past inflammation.
- In more clinically problematic cases (elderly, bedridden patients, recurrent infections) or in infections due to microorganisms usually susceptible to the highest antibiotic doses (Pseudomonas, Enterobacter, Indolke - Proteus) two FOSWOMYN doses can be administered at a 24-hr interval.

Perioperative antibiotic prophylaxis for transrectal prostate biopsy:

1 sachet of FOSWOMYN 3g approx. 3 hours before, and 24 hours after the procedure.

Method of administration

For oral use.

For the indication of acute uncomplicated lower urinary tract infections (acute cystitis), FOSWOMYN 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 (50 - 75ml) and taken immediately after its preparation

Contraindications

Hypersensitivity to the active substance fosfomycin or to any of the excipients listed in the composition.

Special warnings and precautions for use

The use of FOSWOMYN is not recommended in patients with renal impairment (creatinine clearance < 10 ml/min).

Since there is insufficient data for children under 12 years of age, FOSWOMYN should not be given to them.

Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during Fosfomycin treatment and may be life-threatening.

If such reactions occur, fosfomycin should never be re-administered to these patients. An adequate medical treatment is required.

Antibiotic-associated diarrhoea has been reported with the use of nearly all antibacterial agents, including fosfomycin trometamol and may range in severity from mild diarrhoea to fatal colitis. Diarrhoea, particularly if severe and persistent, during or after treatment, may be symptomatic of Clostridium difficile-associated diarrhoea (CDAD). It is therefore important to consider the diagnosis of CDAD in patients who develop serious diarrhoea during or after treatment with FOSWOMYN. If CDAD is suspected or confirmed, appropriate treatment should be initiated without delay.

Anti-peristaltic medicinal products are contraindicated in this situation.

In case of persistent infections, a thorough examination and a re-evaluation of the diagnosis is recommended as this is often due to complicated urinary tract infections or the prevalence of resistant pathogens (e.g., Staphylococcus saprophyticus). In general, urinary tract infections in male patients have to be considered as complicated urinary tract infections, for which this medicinal product is not indicated.

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

Interaction with other medicinal products and other forms of interaction

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

If fosfomycin trometamol is taken with food, the plasma, and urinary levels of fosfomycin decrease. For this reason, it is recommended to take this medicine on an empty stomach or 2 to 3 hours after a meal or after taking other medications.

Specific problems concerning INR (International Normalized Ratio) alteration: numerous cases of increased anti-vitamin K antagonist activity have been reported in patients taking antibiotics. Risk factors include serious infections or inflammations, old age, and poor general health. Under these circumstances, it is difficult to determine whether the change in the INR is due to infectious disease or is caused by the treatment. However, there are certain classes of antibiotics which are more frequently involved, in particular: fluoroquinolones, macrolides, cyclines, co-trimoxazole and certain cephalosporins.

Interaction studies have only been carried out in adults.

Pregnancy and lactation

Pregnancy

Only limited data on the safety of fosfomycin trometamol treatment during 1st trimester of pregnancy (n=152) are available. These data do not raise any safety signal for teratogenicity so far. Fosfomycin crosses the placenta.

Animal studies have not indicated any direct or indirect toxicity with any effect on pregnancy, embryonic development, development of the foetus and/or postnatal development.

FOSWOMYN should only be used during pregnancy, if clearly necessary.

Lactation

Since FOSWOMYN passes into breast milk even after taking just a single dose, women who are breast-feeding should not be treated with FOSWOMYN unless strictly necessary.

Fertility

No data in humans are available. In male and female rats, oral administration of fosfomycin up to 1000 mg/kg/d did not impair fertility.

Effects on ability to drive and use machines

No corresponding studies have been performed. Since FOSWOMYN can cause dizziness, this could affect the ability to drive vehicles or use machines.

Undesirable effects

After administration of a single dose of fosfomycin trometamol, the most common adverse effects are those which affect the gastrointestinal tract, primarily diarrhoea.

The following frequency criteria are used as the basis for evaluating undesirable effects: 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).

Infections and infestations

Common: Vulvovaginitis

Immune System Disorders

Not known: Anaphylactic reactions including anaphylactic shock, hypersensitivity

Nervous system diseases

Common: Headache, dizziness

Gastrointestinal disorders

Common: Diarrhoea, nausea, dyspepsia, abdominal pain

Uncommon: Vomiting

Not known: Antibiotic-associated colitis

Skin and subcutaneous tissue disorders

Uncommon: Rash, urticaria, pruritus

Not known: Angioedema

Overdose and treatment

There are limited data on the overdose with oral fosfomycin.

Signs and symptoms

Cases of hypotonia, somnolence, electrolyte disturbances, thrombocytopenia, and hypoprothrombinaemia have been reported after parenteral administration of fosfomycin.

Treatment

In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive.

Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.

PHARMACEUTICAL PARTICULARS**Special precautions for storage**

Store in its original package. Do not use if the package is open or torn. Store below 30°C.

To use immediately after dilution, discard any unused portion.

Nature and contents of container

Fosfomycin trometamol are packed in a four layered sachet which are made by surlyn/aluminium/low-density polyethylene/paper.

One sachet per box.

MANUFACTURER

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