Uroday 3g Granules for Oral Solution

Fosfomycin Trometamol

Product Name

URODAY 3 g Granules for Oral Solution

Product Description

Appearance: White powder in sachet.

Odor: Orange, tangerine scented.

Appearance of solution: It should be homogenous and opaque with an orange, tangerine.

Composition

Each sachet contains 5.631 g fosfomycin trometamol equivalent to 3 g fosfomycin as active substance.

Pharmacodynamics

The structure of fosfomycin is analogous to that of p-enolpyruvate. This is why it inactivates the enzyme enolpyruvyl tranferase and thus the condensation of uridine diphosphate-Nacetylglucosamine with p-enolpyruvate is irreversible 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	≤ 8 mg/l	> 8 mg/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 id 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 my 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 plasmidor 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 infection 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 (Methicillinresistant 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 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, Uroday prevents the adhesion of bacteria to the bladder mucosa, which is predisposing factor for recurrent urinary tract infections.

Pharmacokinetics

General properties

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, tmax is 2-2,5 hours and Cmax 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.

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 population

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.

Metabolism

Fosfomycin does not appear to be metabolized.

Indication

URODAY 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.

Recommended Dosage

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 URODAY, 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 URODAY doses can be administered at a 24 hr interval.

Perioperative antibiotic prophylaxis for transrectal prostate biopsy:
- 1 sachet of URODAY 3g approx. 3 hours before, and 24 hours after the procedure.

Contraindications

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

Warnings and Precautions

The use of URODAY is not recommended in patients with renal impairment (creatinine clearance < 10 ml/min, see section «Pharmacokinetics»).

Since there is insufficient data for children under 12 years of age, URODAY should not be given to them. Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during Fosfomycin treatment and may be life-threatening (see section «Adverse Reactions»).

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 URODAY. If CDAD is suspected or confirmed, appropriate treatment should be initiated without delay (see section «Adverse Reactions»). Antiperistaltic 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 (see section «Indications»).

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

Interactions with Other Medicaments

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 hours after 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 infections 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 fetus and/or postnatal development.

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

Lactation

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

Reproduction/Fertility

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

Side Effects

After administration of a single dose of Fosfomycin trometamol, the most common side effect are those which effect 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 (>1/1000 to 1/100); rare (>1/10,000 to 1/1000); very rare (<1/10,000); not common: (cannot be estimated from the available data).
Infections and infestations
Common: Vulvovaginitis
Immune disorders
Not known: Anaphylactic reactions including anaphylactic shock, hypersensitivity (see section *Warning and Precautions*).
Nervous system disorders
Common: headache, dizziness.
Gastrointestinal disorders
Common: Diarrhroea, nausea, dyspepsia, abdominal pain.
Uncommon: vomiting.

Not known: Antibiotic-associated colitis (see section *Warning and precautions*)

Skin and subcutaneous tissue disorders

Uncommon: Rash, urticaria, pruritus.

Not known: Angioedema.

Symptoms and Treatment of Overdose

There are limited data on the overdose with oral fosfomycin.

Signs and symptoms

Cases of hypotonia, somnolence, electrolyte disturbances, thrombocytopaenia, 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.

Effects and Ability to Drive and Use Machine

No specific studies have been performed, but patients should be informed that dizziness reports have been received. This may affect the ability of some patients to drive and use the machine.

Instruction for Use

For oral use.

For the indication of acute uncomplicated lower urinary tract infections (acute cystitis), URODAY 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.

Storage Condition

Store below 30°C. Use immediately after opening/ dilute with water. For single use. Discard any unused portion.

Pack size

1 sachet / box

Shelf-Life

The sachet can be used within 24 months from the date of manufactured if kept as recommended.

Registration number

Uroday 3g Sachet – MALXXXXXXXXXX

Manufactured by

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1. Yol No: 3 ve 2. Yol No:2
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Date of revision of package insert

3rd January 2024

*Font size – 10 (Times New Roman)