Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

UROCARE Sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Each single-dose sachet;

5.631 g fosfomycin tromethamine (equivalent to 3g fosfomycin.)

Excipients:

Sucrose 2.107 g

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granule for oral solution

White, granular, characteristic tangerine odor powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

UROCARE is indicated in the treatment of acute uncomplicated urinary tract infections, caused by pathogens sensitive to fosfomycin.

It is used in the prophylaxis of diagnostic and surgical interventions of urinary tract infections, including lower urinary tract infections in adult males and females.

4.2 Posology and method of administration

Posology/frequency of administration and duration:

UROCARE is used in the acute uncomplicated urinary tract infections as a single dose (3 g).

The recommended dose of prophylaxis is two sachets (2 times 3 g) prior to transurethral surgical or diagnostic purposes. The first dose should be taken 3 hours before surgery, second dose should be taken 24 hours after the surgery.

Method of administration:

The contents of a sachet should be dissolved in a glass of water and taken immediately after its preparation completely. UROCARE aqueous solution is homogenous and dull colored (opalescent).

UROCARE should be taken on an empty stomach (2-3 hours after meals). It is recommended to use before bedtime and after emptying the bladder.

Additional information on special populations:

Renal impairment:

It should not be used in patients with severe renal impairment (creatinine clearance<10ml/min).

Hepatic impairment:

There is no dosage adjustment for patients with hepatic impairment.

Pediatric population:

It is not recommended to use in children under the age of 12 because there is no adequate and well-controlled clinical studies with fosfomycin about the efficacy and safety.

Geriatric population:

It is the same as recommended in adults.

4.3 Contraindications

UROCARE is contraindicated in:

• Hypersensitivity to the fosfomycin or any ingredients in product

• In patients with creatinine clearance less than 10 mL / min, undergoing severe renal insufficiency and hemodialysis

• Patients with hereditary fructose intolerance, glucose-galactose malabsorption or sucrosezomaltose insufficiency should not use this drug.

4.4 Special warnings and precautions for use

During fosfomycin therapy, hypersensitivity reactions including anaphylaxis and anaphylactic shock may occur and may be life-threatening (see section 4.8 Undesirable effects). If these

reactions occur, fosfomycin should not be reapplied and appropriate medical treatment is required.

Antibiotic-induced diarrhea has been reported in the use of almost all antibacterial agents, including fosfomycin trometamol, and it can vary from mild diarrhea to fatal quality.

Diarrhea during or after treatment with UROCARE (including after weeks of treatment), especially if serious, persistent and / or bloody, it can be a sign of clostridium difficile-associated diarrhea (CDAD). It is therefore important to consider this diagnosis in patients with severe diarrhea during or after UROCARE treatment. If CDAD is suspected or the diagnosis of CDAD is confirmed, appropriate treatment should be started without delay (see section 4.8 Undesirable effects). Anti-peristaltic drugs are contraindicated in this clinical setting.

Renal insufficiency: If the clearance of creatinine is above 10 ml / min, the urine concentration of fosfomycin remains effective for 48 hours after the usual dose.

- It should be noted that in diabetics or dieters, 2.107 g of sugar is contained in each UROCARE sachet.
- It is not recommended for use in upper urinary tract infections such as nephritis and pyelonephritis.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant metoclopramide should not be used together as it may reduce serum and urine concentrations. Administration with drugs that increase gastrointestinal motility may cause increased efficacy.

Taking with food may delay the absorption of UROCARE's active substance, causing peak plasma levels and a slight drop in urine concentrations. For this reason, it is preferable to take the medicine on an empty stomach or 2-3 hours after the meal.

Specific problems have been reported in INR changes in patients receiving antibiotics, and increased activity of antivitamin K antagonists in innumerable cases. Risk factors include severe infection or 4/10 inflammation, age and general health condition impairment. Under these conditions it is difficult to determine whether the change in INR is due to infectious disease or its treatment. However, some antibiotic classes show this effect more frequently, and in particular these are: fluoroquinolones, macrolides, cyclins, cotrimoxazole and some cephalosporins.

Additional information on special populations:

Interaction studies have not been reported on specific populations.

Pediatric population:

Interaction studies have not been reported on pediatric populations.

4.6 Pregnancy and lactation

General advice:

Pregnancy category B.

Women with childbearing potential / birth control (contraception)

There is no known effect on birth control methods of fosfomycin.

Pregnancy period:

For fosfomycin, there is no clinical data on exposure in pregnancies.

Studies on animals show no direct or indirect harmful effects on pregnancy / embryonal / fetal development / birth or postnatal development.

Currently, single dose antibacterial treatments are not suitable for urinary tract infections in pregnant women.

But for fosfomycin trometamol, animal studies have not shown reproductive toxicity. There is a lot of data on the efficacy of fosfomycin in pregnancy. There is moderate data on safety data for pregnant women and does not indicate any sign of malformative or feto / neonatal toxicity of fosfomycin. If UROCARE is deemed necessary, use during pregnancy can be evaluated.

Data on exposure to limited numbers of pregnancies do not indicate that fosfomycin has adverse effects on pregnancy or the health of the fetus / newborn child. No significant epidemiological data have been obtained until today. Studies on animals do not show that they are directly or indirectly harmful in relation to pregnancy / embryonal / fetal development / birth or postnatal development (see section 5.3 Preclinical safety data). Caution should be exercised when prescribing to pregnant women.

Lactation period:

After a single injection, fosfomycin passes to the mother in low levels. But after a single oral dose, fosfomycin can be used during the lactation period.

Reproductive ability / Fertility:

No effect on fertility has been reported in animal studies.
There is no data available on the effect in humans.

4.7 Effects on ability to drive and use machines

No specific study of the effect of UROCARE on vehicle and machine use has been made, but patients should be informed that dizziness has been reported. This may affect the ability of some patients to drive and use the machine.

4.8 Undesirable effects

Following the administration of trometamol in a single dose of fosfomycin, the most common adverse events are in the gastrointestinal tract, primarily in diarrhea.
These are usually self-limiting and spontaneous conditions.

Frequencies are defined as: very common (1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000 , <1/1000), very rare (<1/10000) and not known (cannot be estimated from the available data).

Infections and infestations:

Common: Vaginitis

Immune system disorders:

Unknown:
Anaphylactic reactions included anaphylactic shock, hypersensitivity

Nervous system disorders:

Common:
Headache, dizziness
Unusual:
Paresthesia

Cardiac diseases

Rare:
tachycardia

Vascular diseases

Unknown:

Hypotension

Respiratory, thoracic disorders and mediastinal disorders

Unknown:

Asthma

Gastrointestinal disorders:

Common:

Diarrhea, nausea, dyspepsia

Unusual:

Vomiting, abdominal pain

Unknown:

Antibiotic-associated diarrhea (see section 4.4 Special warnings and precautions for use)

Skin and subcutaneous disorders:

Unusual:

Rash, urticaria, itching

Unknown:

Angioedema

General disorders and administration site conditions:

Unusual:

Tiredness

4.9 Overdose and Treatment

Experience with overdose of oral fosfomycin is limited. Patients receiving overdose UROCARE have been shown to have balance and hearing loss, metallic taste, loss of taste.

Hypotonia, somnolence, electrolyte disturbances, thrombocytopenia and hypoprotrombinemia cases have been reported with parenteral use of fosfomycin.

UROCARE is packaged as disposable sachets. This is why the overdose risk has been removed. However, symptomatic and supportive treatment should be given when overdose occurs. Rehydration is recommended to promote elimination of urine by the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic anti-infections, antibiotics (Other antibacterial products)

ATC Code: J01XX01

UROCARE contains fosfomycin [mono (2-ammonium-2-hydroxymethyl-1,3 propanediol) (2R-cis) - (3-methyloxiranyl) -phosphonate], a phosphonate derivative, a broad spectrum antibiotic used for the treatment of urinary tract infections.

Fosfomycin activity is shown in the first phase of bacterial cell wall synthesis. As a phosphoenolpyruvate analgesic, it inhibits the enzyme phosphoenolpyruvate transferase; thus irreversibly blocking condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps of bacterial cell wall synthesis. It may also reduce bacterial adhesion to the bladder mucosa, a factor predisposing to recurrent infections. The mechanism of action is not cross-resistance to other antibiotics and synergism with other antibiotic classes such as beta-lactam antibiotics.

Fosfomycin is an effective against many gram-negative and gram-positive bacteria such as *E.coli, Citrobacter spp., Klebsiella spp., Proteus spp., Serratia spp., P. aeruginosa* and *Enterococcus faecalis* which are frequently isolated in urinary tract infections.

The emergence of *in vitro* resistance occurs in the form of mutations in the chromatin genes glpT and uHP, respectively, which control the transfer of L-alpha-glycerophosphate and hexose phosphate.

5.2 Pharmacokinetic properties

General Properties

Absorption:

Following oral administration, fosfomycin is well absorbed from the intestines and the absolute bioavailability is approximately 50%. Food delays absorption, but does not affect urine concentrations.

Distribution:

Fosfomycin is distributed in the kidneys, bladder wall, prostate and seminal vesicles. Following oral administration, continued concentrations of fosfomycin higher than the minimum inhibitor concentrations (MIC) were obtained for 24-48 hours.

Fosfomycin does not bind to plasma proteins and passes through the placental barrier.

Metabolism:

There is not enough data.

Elimination:

Fosfomycin is excreted by the glomerular filtration unchanged mainly in the kidneys (dose 40-50%) and fewer (dose 18-28%) fecal, with a half-life of about 4 hours. The appearance of a second serum peak after 6 and 10 hours of ingestion suggests that the drug has been exposed to enterohepatic circulation.

The pharmacokinetic properties of fosfomycin do not change with age or pregnancy. The drug accumulates in patients with renal insufficiency; a linear relationship between the pharmacokinetic parameters of fosfomycin and glomerular filtration rate was demonstrated.

Linearity/non-linearity:

Fosfomycin pharmacokinetics in the 2-4 g dose ranges are independent dose.

5.3 Preclinical safety data

In acute toxicity studies, a single oral dose of 5000 mg / kg was well tolerated in both mice and rats and a single dose of 2000 mg / kg did not cause any change in rabbits and dogs.

Oral repeated dose studies have shown that doses that are inactive after 4 weeks of treatment in cats and rats are between 100 and 200 mg / kg, respectively.

Genotoxicity studies have shown that fosfomycin is not of mutagenic potential.

Reproductive and developmental toxicity studies have not produced any teratogenic effect, peri- and post-natal toxicity or an unexpected effect on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Orange flavor

Mandarin flavor

Saccharin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

1 sachet of 8 grams is presented in cardboard box together with usage instructions in three layers pet-aluminum-polyethylene package.

6.6 Special precautions for disposal and other handling

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.

Oğuzlar Mah. 1370. sok. 7/3

Balgat - Ankara

TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

220/93 (in Turkey)

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06/05/2015