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Technical Document

On

FOSFOMAX

(Fosfomycin 3g sachet containing granules)

Annexure IV

For Kenya

This document is the property of
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FOSFOMYCIN 3 g Sachet Containing Granules

Fosfomax

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

5.631 g fosfomycin trometamol equivalent to 3 g fosfomycin

Excipients:

Sugar	2.205 g
Sodium Saccharine	0.116 g

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Sachet

White powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Fosfomycin is indicated for the treatment of uncomplicated lower urinary tract infections caused by fosfomycin sensitive pathogens.

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

4.2. Posology and method of administration

Posology/ frequency and duration of administration:

FOSFOMYCIN is used as a single dose (3 g) in uncomplicated urinary system infections.

FOSFOMYCIN 's recommended prophylactic dose is 2 sachets (2 times 3 g) before the diagnostic and surgical interventions of urinary tract infections, including lower urinary tract infections in adult males and females. The first dose should be taken 3 hours before surgery and the second dose should be taken 24 hours after surgery.

Method of administration:

The FOSFOMYCIN content is dissolved by mixing in a glass of water at room temperature and drink it straight away.

FOSFOMYCIN should be taken on an empty stomach (2-3 hours after meals). Preferably, it is recommended to use the night before bedtime and after the bladder has been emptied.

Additional information on special populations:

Renal impairment:

It should not be used in patients with severe renal insufficiency (creatinine clearance <10 mL / min) (see Section 4.3).

Hepatic impairment:
There is no specific dose adjustment for patients with hepatic insufficiency.

Pediatric population:
The use of FOSFOMYCIN is not recommended because there is no clinical study on the efficacy and safety of FOSFOMYCIN in children under 12 years of age.

Geriatric population:
Treatment in the geriatric population is the same as recommended in adults.

4.3. Contraindications
The use of FOSFOMYCIN is contraindicated in the following situations:

- If you are hypersensitive to FOSFOMYCIN or to any of the excipients in FOSFOMYCIN
- Creatinine clearance below 10 ml / min, patients with severe renal insufficiency and hemodialysis
- Patients with hereditary fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase 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). If these reactions occur, FOSFOMYCIN should not be reapplied and appropriate medical treatment is required.

Antibiotic-induced diarrhea has been reported with the use of almost all antibacterial agents, including FOSFOMYCIN trometamol, and its severity may vary from mild diarrhea to as much as fatal colitis. Diarrhea occurring during or after treatment with FOSFOMYCIN (including after treatment weeks) may be indicative of *Clostridium difficile*-induced diarrhea (CDID), particularly if severe, persistent, and / or bloody. It is therefore important to consider this diagnosis in patients with severe diarrhea during or after FOSFOMYCIN treatment. If CDID is suspected or the diagnosis of CDID is confirmed, appropriate treatment should be started without delay (see Section 4.8). Anti-peristaltic drugs are contraindicated in this clinical situation.

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 taken into account that diabetics or dieters have 2.205 g of sugar per FOSFOMYCIN sachet.
- It is not recommended for use in upper urinary tract infections such as nephritis, pyelonephritis.

Sugar warning:
Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this drug.

Sodium warning:
This medicinal product contains less than 1 mmol (23 mg) of sodium per dose; no side effects due to sodium are expected at this dose.

4.5. Interaction with other medicinal products and other forms of interaction
Concomitant metoclopramide should not be used concomitantly as it may reduce serum and urine concentrations. Administration with drugs that increase gastrointestinal motility may lead to increased efficacy.

Taking with food may delay the absorption of FOSFOMYCIN '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, increased activity of antivitamin K antagonists in numerous cases. Severe infection or inflammation, age and general health condition impairment are within the scope of risk factors. 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:
The interaction study for the specific population has not been reported.

Pediatric population
Interaction studies of the pediatric population have not been reported.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: B

Women of childbearing potential/Birth control (contraception)
FOSFOMYCIN has no known effect on contraceptive methods.

Pregnancy
Clinical data for exposure to pregnancy is not available for FOSFOMYCIN.
Studies on animals do not show any direct or indirect harmful effects on pregnancy / embryonal / fetal development / birth or postnatal development.

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

But for FOSFOMYCIN trometamol, animal studies have not shown reproductive toxicity. There is a large amount 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 FOSFOMYCIN is considered necessary, use during pregnancy can be evaluated.

Data on exposure to limited numbers of pregnancies do not indicate that phosphomycin has adverse effects on pregnancy or on the health of the fetus / newborn child. No significant epidemiological data have been obtained to date. Studies on animals do not indicate that they are directly or indirectly harmful in relation to pregnancy / embryonal / fetal development / birth or postnatal development (see section 5.3).

It should be cautious when given to pregnant women.

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

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

4.7. Effects on ability to drive and use machines
No specific work has been done on the effect of FOSFOMYCIN on vehicle and machine use. However, patients should be informed that dizziness is reported. This may affect the ability of some patients to drive and use the machine.

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

FOSFOMYCIN is usually well tolerated. According to the results obtained from clinical trials and postmarketing surveillance studies, the undesirable effects are presented in tables according to the following systems and their frequency.

Frequencies are defined as: Very common (≥1 / 10); Common (≥1 / 100, <1/10); Uncommon (≥1 / 1.000, <1/100); Rare (≥1 / 10.000, <1 / 1.000); Very uncommon (<1 / 10.000), unknown (cannot be estimated from the given data).

Infections and infestations
Common: Vulvovaginitis

Immune system diseases
Unknown: Anaphylactic reactions include anaphylactic reactions, hypersensitivity

Nervous system diseases
Common: Headache, dizziness
Uncommon: Paresthesia

Cardiac diseases
Rare: Tachycardia

Vascular diseases
Unknown: Hypotension

Respiratory, thoracic disorders and mediastinal disorders
Unknown: Asthma

Gastrointestinal diseases
Common: Diarrhea, nausea, dyspepsia
Uncommon: Vomiting, abdominal pain
Not known: Antibiotic-induced diarrhea (See Section 4.4).

Skin and subcutaneous tissue diseases
Uncommon: Rash, urticaria, itching
Unknown: Angioedema

General disorders and application zone diseases
Uncommon: Fatigue

4.9. Overdose
Experience with overdose of oral FOSFOMYCIN is limited. Patients receiving excessive doses of FOSFOMYCIN have been shown to have balance and hearing loss, metallic taste, loss of taste.
Hypotony, somnolence, electrolyte disturbances, thrombocytopenia and hypoprotrombinemia cases have been reported with parenteral use of FOSFOMYCIN.
FOSFOMYCIN is packed as single sachet. For this reason, the overdose risk has been removed. Nevertheless, symptomatic and supportive treatment should be given when overdose occurs. Rehydration is recommended to promote elimination of the drug by the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antibacterials (Other Antibacterials)
ATC Code: J01XX01
FOSFOMYCIN contains FOSFOMYCIN [mono (2-ammonium-2-hydroxymethyl-1,3-propanediol) (2R-cis)-(3-methyloxiranyl)-phosphonate], a phosphonic acid derivative, a broad spectrum antibiotic used for the treatment of urinary tract infections.

It demonstrates the activity of FOSFOMYCIN 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 trometamol is 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 system 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.
Phosphomycin does not bind to plasma proteins and passes through the placental barrier.

Biotransformation:
Sufficient data are not available.

Elimination:
FOSFOMYCIN is excreted with glomerular filtration unchanged mainly in the kidneys (40-50% of dose was found in urine) and fewer (18-28% of dose) fecal excretion half-life about 4

hours. The appearance of a second serum peak after 6 and 10 hours of drug intake suggests that the drug has been subjected to enterohepatic circulation.

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

Linearity / non-linearity:
Pharmacokinetics of FOSFOMYCIN at doses of 2-4 grams are dose-independent.

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 changes in rabbits and dogs.
Oral repeated dose studies have shown that doses that are not active 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
Sugar
Sodium Saccharine
Aerosil 200
Orange Flavor
Mandarin Flavor

6.2. Incompatibilities
Not valid.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 30 °C.

6.5. Nature and contents of container
Packaged in PE / Aluminum / Coated Paper in 1 and 2 sachet cardboard boxes together with instruction leaflet.

6.6. Special precautions for disposal and other handling
Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulations".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation:
Renewal of the Authorisation:
Prescription only Medicine

10. DATE OF REVISION OF THE TEXT

September 2020