

FOSIROL Powder (Fosfomycin trometamol)

Composition

Each sachet contains:

Fosfomycin trometamol BP equivalent to Fosfomycin3.0 gm

Excipientsq.s.

Dosage Form

Powder

Pharmacology

Pharmacodynamics

Mechanism of Action

Fosfomycin trometamol is a synthetic, broad-spectrum, bactericidal antibiotic for oral administration. Fosfomycin (the active component of fosfomycin trometamol) has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic microorganisms which are associated with uncomplicated urinary tract infections. Fosfomycin is bactericidal in urine at therapeutic doses. The bactericidal action of fosfomycin is due to its inactivation of the enzyme enolpyruvyl transferase, thereby irreversibly blocking the condensation of uridine diphosphate-N acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. It also reduces adherence of bacteria to uroepithelial cells.

There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents such as beta-lactams and aminoglycosides.

Microbiology

Fosfomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

Aerobic Gram-positive Microorganisms

Enterococcus faecalis

Aerobic Gram-negative Microorganisms

Escherichia coli

The following *in vitro* data are available, but their clinical significance is unknown.

Fosfomycin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 64 µg/mL or less against

most ($\geq 90\%$) strains of the following microorganisms; however, the safety and effectiveness of fosfomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic Gram-positive Microorganisms

Enterococcus faecium

Aerobic Gram-negative Microorganisms

Citrobacter diversus

Citrobacter freundii

Enterobacter aerogenes

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris

Serratia marcescens

Susceptibility Testing

Dilution Techniques

Quantitative methods are used to determine MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized agar dilution method or equivalent with standardized inoculum concentrations and standardized concentrations of fosfomycin trometamol (in terms of fosfomycin base content) powder supplemented with 25 $\mu\text{g/mL}$ of glucose-6-phosphate. **Broth dilution methods should not be used to test susceptibility to fosfomycin.** The MIC values obtained should be interpreted according to the following criteria:

MIC ($\mu\text{g/mL}$)	Interpretation
≤ 64	Susceptible (S)
128	Intermediate (I)
≥ 256	Resistant (R)

A report of 'susceptible' indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the urine. A report of 'intermediate' indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of ''resistant' indicates that usually achievable concentrations of the antimicrobial compound in the urine are unlikely to be inhibitory and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard fosfomycin trometamol powder should provide the following MIC values for agar dilution testing in media containing 25 µg/mL of glucose-6-phosphate. **[Broth dilution testing should not be performed].**

Microorganism	MIC (µg/mL)
<i>Enterococcus faecalis</i> ATCC 29212	32-128
<i>Escherichia coli</i> ATCC 25922	0.5-2
<i>Pseudomonas aeruginosa</i> ATCC 27853	2-8
<i>Staphylococcus aureus</i> ATCC 29213	0.5-4

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 200 µg fosfomycin and 50 µg of glucose-6-phosphate to test the susceptibility of microorganisms to fosfomycin.

Reports from the laboratory providing results of the standard single-disk susceptibility tests with disks containing 200 µg of fosfomycin and 50 µg of glucose-6-phosphate should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

Interpretation should be stated as above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for fosfomycin.

As with standardized dilution techniques, diffusion methods require use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 200 µg fosfomycin disk with the 50 µg of glucose-6-phosphate should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter (mm)
<i>Escherichia coli</i> ATCC 25922	22-30
<i>Staphylococcus aureus</i> ATCC 25923	25-33

Pharmacokinetics

Absorption: Fosfomycin trometamol is rapidly absorbed following oral administration and converted to the free acid, fosfomycin. Absolute oral bioavailability under fasting conditions is 37%. After a single 3 gm dose of fosfomycin trometamol, the mean (\pm 1 SD) maximum serum concentration (C_{max}) achieved was 26.1 (\pm 9.1) µg/mL within 2 hours. The oral bioavailability of fosfomycin is reduced to 30% under fed conditions. Following a single 3 gm oral dose of fosfomycin trometamol with a high-fat meal, the mean C_{max} achieved was 17.6 (\pm 4.4) µg/mL within 4 hours.

Cimetidine does not affect the pharmacokinetics of fosfomycin when co-administered with fosfomycin trometamol. Metoclopramide lowers the serum concentrations and urinary excretion of fosfomycin when co-administered with fosfomycin.

Distribution: The mean apparent steady-state volume of distribution (V_{ss}) is 136.1 (± 44.1) L following oral administration of fosfomycin trometamol. Fosfomycin is not bound to plasma proteins.

Fosfomycin is distributed to the kidneys, bladder wall, prostate, and seminal vesicles. Following a 50 mg/Kg dose of fosfomycin to patients undergoing urological surgery for bladder carcinoma, the mean concentration of fosfomycin in the bladder, taken at a distance from the neoplastic site, was 18.0 μg per gram of tissue at 3 hours after dosing. Fosfomycin has been shown to cross the placental barrier in animals and man.

Excretion: Fosfomycin is excreted unchanged in both urine and feces. Following oral administration of fosfomycin trometamol, the mean total body clearance (CL_{TB}) and mean renal clearance (CL_R) of fosfomycin were 16.9 (± 3.5) L/hr and 6.3 (± 1.7) L/hr, respectively. Approximately 38% of a 3 gm dose of fosfomycin trometamol is recovered from urine, and 18% is recovered from feces. Following intravenous administration, the mean CL_{TB} and mean CL_R of fosfomycin were 6.1 (± 1.0) L/hr and 5.5 (± 1.2) L/hr, respectively.

A mean urine fosfomycin concentration of 706 (± 466) $\mu\text{g}/\text{mL}$ was attained within 2-4 hours after a single oral 3 gm dose of fosfomycin trometamol under fasting conditions. The mean urinary concentration of fosfomycin was 10 $\mu\text{g}/\text{mL}$ in samples collected at 72-84 hours following a single oral dose of fosfomycin trometamol.

Following a 3-gm dose of fosfomycin trometamol administered with a high fat meal, a mean urine fosfomycin concentration of 537 (± 252) $\mu\text{g}/\text{mL}$ was attained within 6-8 hours. Although the rate of urinary excretion of fosfomycin was reduced under fed conditions, the cumulative amount of fosfomycin excreted in the urine was the same, i.e 1,118 (± 201) mg (fed) vs. 1,140 mg (± 238) (fasting). Further, urinary concentrations equal to or greater than 100 $\mu\text{g}/\text{mL}$ were maintained for the same duration (26 hours), indicating that fosfomycin trometamol can be taken without regard to food.

Following oral administration of fosfomycin trometamol, the mean half-life for elimination ($t_{1/2}$) is 5.7 (± 2.8) hours.

Pharmacokinetics in Special Populations

Geriatric: Based on limited data regarding 24-hour urinary drug concentrations, no differences in urinary excretion of fosfomycin have been observed in elderly subjects. No dosage adjustment is necessary in the elderly.

Gender: There are no gender differences in the pharmacokinetics of fosfomycin.

Renal Impairment: In five anuric patients undergoing hemodialysis, the $t_{1/2}$ of fosfomycin during hemodialysis was 40 hours. In patients with varying degrees of renal impairment (creatinine clearances varying from 54 mL/min to 7 mL/min), the $t_{1/2}$ of fosfomycin increased from 11 hours to 50 hours. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin.

Indications

FOSIROL is indicated only for the treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.

FOSIROL is not indicated for the treatment of pyelonephritis or perinephric abscess.

If bacteriuria persists or reappears after treatment with **FOSIROL**, other therapeutic agents should be selected.

Dosage and Administration

The recommended dosage for women, 18 years of age and older, for uncomplicated urinary tract infection (acute cystitis) is one sachet of **FOSIROL**.

FOSIROL may be taken with or without food.

FOSIROL should not be taken in its dry form. Always mix **FOSIROL** with water before ingesting.

Method of Preparation

FOSIROL should be taken orally. Pour the entire contents of a single-dose sachet of **FOSIROL** into a glass of water (90-120 ml) and stir to dissolve. Do not use hot water. **FOSIROL** should be taken immediately after dissolving in water.

Contraindications

FOSIROL is contraindicated in patients with known hypersensitivity to the drug.

Warnings and Precautions

General

Do not use more than one single dose of **FOSIROL** to treat a single episode of acute cystitis. Repeated daily doses of fosfomycin trometamol did not improve the clinical success or microbiological eradication rates compared to single dose therapy, but did increase the incidence of adverse events. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy.

Clostridium difficile-associated diarrhoea (CDAD) 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. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *Clostridium difficile*.

Clostridium difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require a colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically

indicated.

Drug Interactions

Metoclopramide: When co-administered with fosfomycin trometamol, metoclopramide, a drug which increases gastrointestinal motility, lowers the serum concentration and urinary excretion of fosfomycin. Other drugs that increase gastrointestinal motility may produce similar effects.

Cimetidine: Cimetidine does not affect the pharmacokinetics of fosfomycin when co-administered with fosfomycin trometamol.

Information for Patients

Patients should be informed:

- That FOSIROL can be taken with or without food.
- That their symptoms should improve in 2-3 days after taking FOSIROL; if not improved, the patient should contact her health care provider.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Renal Impairment

Dosage adjustment is not necessary.

Hepatic Impairment

No specific dosage recommendations can be made.

Pregnancy

Pregnancy Category B

When administered intramuscularly as the sodium salt at a dose of 1 gm to pregnant women, fosfomycin crosses the placental barrier. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

It is not known whether fosfomycin trometamol is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fosfomycin trometamol, a decision should be made whether to discontinue nursing or to not administer the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children age 12 years and under have not been established in adequate and well-controlled studies.

Geriatric Use

Clinical studies of fosfomycin trometamol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Undesirable Effects

Clinical Trials

In clinical studies, drug related adverse events which were reported in greater than 1% of the fosfomycin trometamol treated study population are listed below:

Drug-Related Adverse Events (%) in Fosfomycin Trometamol and Comparator Populations

Adverse Events	Fosfomycin Trometamol N=1233	Nitrofurantoin N=374	Trimethoprim/ Sulfamethoxazole N=428	Ciprofloxacin N=455
Diarrhoea	9.0	6.4	2.3	3.1
Vaginitis	5.5	5.3	4.7	6.3
Nausea	4.1	7.2	8.6	3.4
Headache	3.9	5.9	5.4	3.4
Dizziness	1.3	1.9	2.3	2.2
Asthenia	1.1	0.3	0.5	0.0
Dyspepsia	1.1	2.1	0.7	1.1

In clinical trials, the most frequently reported adverse events occurring in >1% of the study population regardless of drug relationship were as follows: diarrhoea (10.4%), headache (10.3%), vaginitis (7.6%), nausea (5.2%), rhinitis (4.5%), back pain (3.0%), dysmenorrhoea (2.6%), pharyngitis (2.5%), dizziness (2.3%), abdominal pain (2.2%), pain (2.2%), dyspepsia (1.8%), asthenia (1.7%), and rash (1.4%).

The following adverse events occurred in clinical trials at a rate of less than 1%, regardless of drug relationship: abnormal stools, anorexia, constipation, dry mouth, dysuria, ear disorder, fever, flatulence, flu syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, SGPT increased, skin disorder, somnolence, and vomiting.

One patient developed unilateral optic neuritis, an event considered possibly related to fosfomycin trometamol therapy.

Postmarketing Experience

Serious adverse events from the marketing experience with fosfomycin trometamol outside of the United States have been rarely reported and include the following: angio-oedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, hepatic necrosis, and toxic megacolon.

Although causality has not been established, during post marketing surveillance, the following events have occurred in patients prescribed fosfomycin trometamol: anaphylaxis and hearing loss.

Laboratory Changes

Significant laboratory changes reported in U.S. clinical trials of fosfomycin trometamol without regard to drug relationship include: increased eosinophil count, increased or decreased WBC count, increased bilirubin, increased SGPT, increased SGOT, increased alkaline phosphatase, decreased hematocrit, decreased hemoglobin, increased and decreased platelet count. The changes were generally transient and were not clinically significant.

Overdosage

The following events have been observed in patients who have taken fosfomycin trometamol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive.

Storage and Handling Instruction

Store below 25°C.

Packaging Information

FOSIROL..... Sachet of 3 gm each

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