Rev. 6/02 RMC 237

MONUROL®

[mon' ur ol]

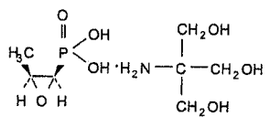
(fosfomycin tromethamine)

SACHET

Rx only

DESCRIPTION

MONUROL (fosfomycin tromethamine) sachet contains fosfomycin tromethamine, a synthetic, broad-spectrum, bactericidal antibiotic for oral administration. It is available as a single-dose sachet which contains white granules consisting of 5.631 grams of fosfomycin tromethamine (equivalent to 3 grams of fosfomycin), and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose. The contents of the sachet must be dissolved in water. Fosfomycin tromethamine, a phosphonic acid derivative, is available as (1*R*,2*S*)-(1,2-epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). It is a white granular compound with a molecular weight of 259.2. Its empirical formula is $C_3H_7O_4P \cdot C_4H_{11}NO_3$, and its chemical structure is as follows:



CLINICAL PHARMACOLOGY

Absorption: Fosfomycin tromethamine 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 MONUROL, the mean (± 1 SD) maximum serum concentration (C_{max}) achieved was 26.1 (± 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 MONUROL with a high-fat meal, the mean C_{max} achieved was 17.6 (± 4.4) µg/mL within 4 hours.

Cimetidine does not affect the pharmacokinetics of fosfomycin when coadministered with MONUROL. Metoclopramide lowers the serum concentrations and urinary excretion of fosfomycin when coadministered with MONUROL. (See **PRECAUTIONS, Drug Interactions**.)

Distribution: The mean apparent steady-state volume of distribution (V_{SS}) is 136.1 (±44.1) L following oral administration of MONUROL. 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 MONUROL, 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 MONUROL 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) µg/mL was attained within 2-4 hours after a single oral 3-gm dose of MONUROL under fasting conditions. The mean urinary concentration of fosfomycin was 10 µg/mL in samples collected 72-84 hours following a single oral dose of MONUROL.

Following a 3-gm dose of MONUROL administered with a high fat meal, a mean urine fosfomycin concentration of 537 (± 252) µg/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, 1118 (± 201) mg (fed) vs. 1140 mg (±238) (fasting). Further, urinary concentrations equal to or greater than 100 µg/mL were maintained for the same duration, 26 hours, indicating that MONUROL can be taken without regard to food.

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

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 Insufficiency: In 5 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.

Microbiology

Fosfomycin (the active component of fosfomycin tromethamine) 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.

Fosfomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

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 (MIC's) of 64 µg/mL or less against most (≥ 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 minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized agar dilution method[1] or equivalent with standardized inoculum concentrations and standardized concentrations of fosfomycin tromethamine (in terms of fosfomycin base content) powder supplemented with 25 µg/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 (µg/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 tromethamine 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)
Enterococcus faecalis ATCC 29212	32-128
Escherichia coli ATCC 25922	0.5-2
Pseudomonas aeruginosa ATCC 27853	2-8
Staphylococcus aureus 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[2] 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 test 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)
Escherichia coli ATCC 25922	22-30
Staphylococcus aureus ATCC 25923	25-33

INDICATIONS AND USAGE

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

If persistence or reappearance of bacteriuria occurs after treatment with MONUROL, other therapeutic agents should be selected. (See **PRECAUTIONS** and **CLINICAL STUDIES** section.)

CONTRAINDICATIONS

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

PRECAUTIONS

General

Do not use more than one single dose of MONUROL to treat a single episode of acute cystitis. Repeated

daily doses of MONUROL 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.

Information for Patients
Patients should be informed:
- That MONUROL (fosfomycin tromethamine) can be taken with or without food.
- That their symptoms should improve in two to three days after taking MONUROL; if not improved, the patient should contact her health care provider.

Drug Interactions
Metoclopramide: When coadministered with MONUROL, 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 coadministered with MONUROL.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term carcinogenicity studies in rodents have not been conducted because MONUROL is intended for single dose treatment in humans. MONUROL was not mutagenic or genotoxic in the *in vitro* Ames' bacterial reversion test, in cultured human lymphocytes, in Chinese hamster V79 cells, and the *in vivo* mouse micronucleus assay. MONUROL did not affect fertility or reproductive performance in male and female rats.

Pregnancy: Teratogenic Effects
Pregnancy Category B
When administered intramuscularly as the sodium salt at a dose of 1 gm to pregnant women, fosfomycin crosses the placental barrier. MONUROL crosses the placental barrier of rats; it does not produce teratogenic effects in pregnant rats at dosages as high as 1000 mg/kg/day (approximately 9 and 1.4 times the human dose based on body weight and mg/m^2, respectively). When administered to pregnant female rabbits at dosages as high as 1000 mg/kg/day (approximately 9 and 2.7 times the human dose based on body weight and mg/m^2, respectively), fetotoxicities were observed. However, these toxicities were seen at maternally toxic doses and were considered to be due to the sensitivity of the rabbit to changes in the intestinal microflora resulting from the antibiotic administration. 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.

Nursing Mothers
It is not known whether fosfomycin tromethamine 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 MONUROL, 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 Monurol 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.

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

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

Adverse Events	Fosfomycin N=1233	Nitrofurantoin N=374	Trimethoprim / sulfamethoxazole N=428	Ciprofloxacin N=445
Diarrhea	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:
diarrhea 10.4%, headache 10.3%, vaginitis 7.6%, nausea 5.2%, rhinitis 4.5%, back pain 3.0%, dysmenorrhea 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 MONUROL therapy.

Post-marketing Experience:
Serious adverse events from the marketing experience with MONUROL outside of the United States have been rarely reported and include:
angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, hepatic necrosis, and toxic megacolon.

Laboratory Changes:
Significant laboratory changes reported in U.S. clinical trials of MONUROL 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
In acute toxicology studies, oral administration of high doses of MONUROL up to 5 gm/kg were well-tolerated in mice and rats, produced transient and minor incidences of watery stool in rabbits, and produced diarrhea with anorexia in dogs occurring 2-3 days after single dose administration. These doses represent 50-125 times the human therapeutic dose.

There have been no reported cases of overdosage. In the event of overdosage, treatment should be symptomatic and supportive.

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 MONUROL. MONUROL may be taken with or without food.

MONUROL should not be taken in its dry form. Always mix MONUROL with water before ingesting. (See PREPARATION section.)

PREPARATION
MONUROL should be taken orally. Pour the entire contents of a single-dose sachet of MONUROL into 3 to 4 ounces of water (1/2 cup) and stir to dissolve. Do not use hot water. MONUROL should be taken immediately after dissolving in water.

HOW SUPPLIED
MONUROL is available as a single-dose sachet containing the equivalent of 3 grams of fosfomycin.

NDC # 0456-4300-08

Store at controlled room temperature
15° to 30° C (59° to 86°F).

Keep this and all drugs out of the reach of children.

Manufactured by:
Inpharzam S.A.
Division of Zambon Group, SpA
Via Industria
6814 Cadempino, Switzerland

Made in Switzerland

Distributed by:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045

REFERENCES
1. National Committee for Clinical Laboratory Standards, Methods for Dilution. Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition; Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards, Performance Standard for Antimicrobial Disk Susceptibility Tests - Fifth Edition; Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24 NCCLS, Villanova, PA, December,1993.

CLINICAL STUDIES
In controlled, double-blind studies of acute cystitis performed in the United States, a single-dose of MONUROL was compared to three other oral antibiotics (See table below). The study population consisted of patients with symptoms and signs of acute cystitis of less than 4 days duration, no manifestations of upper tract infection (e.g., flank pain, chills, fever), no history of recurrent urinary tract infections (20% of patients in the clinical studies had a prior episode of acute cystitis within the preceding year), no known structural abnormalities, and no clinical or laboratory evidence of hepatic dysfunction, and no known or suspected CNS disorders, such as epilepsy, or other factors which would predispose to seizures. In these studies, the following clinical success (resolution of symptoms) and microbiologic eradication rates were obtained:

Treatment Arm	Treatment Duration (days)	Microbiologic Eradication Rate		Clinical Success Rate	Outcome (based on difference in microbiologic eradication rates at 5-11 days post therapy)
		5-11 days post therapy	Study day 12-21		
Fosfomycin	1	630/771 (82%)	591/771 (77%)	542/771 (70%)	
Ciprofloxacin	7	219/222 (98%)	219/222 (98%)	213/222 (96%)	Fosfomycin inferior to ciprofloxacin
Trimethoprim/ sulfamethoxazole	10	194/197 (98%)	194/197 (98%)	186/197 (94%)	Fosfomycin inferior to trimethoprim/ sulfamethoxazole
Nitrofurantoin	7	180/238 (76%)	180/238 (76%)	183/238 (77%)	Fosfomycin equivalent to nitrofurantoin

Pathogen	Fosfomycin 3 gm single dose	Ciprofloxacin 250 mg bid x 7d	Trimethoprim/sulfamethoxazole 160 mg/ 800 mg bid x 10 d	Nitrofurantoin 100mg bid x 7d
E. coli	509/644 (79%)	184/187 (98%)	171/174 (98%)	146/187 (78%)
E.faecalis	10/10 (100%)	0/0	4/4 (100%)	1/2 (50%)