

PRODUCT MONOGRAPH

PrMONUROL®

(Fosfomycin Tromethamine)
3 g Sachet

Therapeutic Classification
Antibiotic

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(fosfomycin tromethamine)

3 g Sachet

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

MONUROL (fosfomycin tromethamine), a phosphoric acid derivative is the mono-acid salt of fosfomycin with tromethamine.

Fosfomycin is bactericidal in urine at therapeutic doses. Its bactericidal action is due to inactivation of the enzyme enolpyruvyl transferase, thereby blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell synthesis. It also reduces adherence of bacteria to uroepithelial cells.

Following oral administration, fosfomycin tromethamine is converted to the free acid, fosfomycin, which is rapidly absorbed. After a single dose of **MONUROL** (equivalent to 3 g fosfomycin), the mean maximum serum concentration (C_{max}) achieved within 2 hours is 26.1 µg/mL in fasted subjects. Absolute oral bioavailability of fosfomycin under fasting conditions is 37% and 30% under fed conditions. When **MONUROL** is given with a high fat meal, the mean C_{max} achieved is 17.6 µg/mL within 4 hours. The mean half-life for elimination ($t_{1/2}$) in serum is 5.7 hours without food and 5.8 hours with food.

Fosfomycin is widely distributed in body tissues and is not bound to plasma proteins. Following a 50 mg/kg dose of fosfomycin, a concentration of 18 µg/gram in bladder tissue is achieved at 3 hours after dosing. Fosfomycin has been shown to cross the human placental barrier.

Fosfomycin tromethamine is not metabolized and is excreted unchanged in urine and feces. Following oral administration of **MONUROL** to fasted patients, the total body clearance (CL_{BT}) and mean renal clearance (CL_R) of fosfomycin are 16.9 L/hr and 6.3 L/hr respectively. Approximately 38% of a **MONUROL** dose (equivalent to 3 g of fosfomycin) is recovered from urine and 18% is recovered from feces.

A mean maximum urine fosfomycin concentration of 706 µg/mL is attained within 2-4 hours after a single oral dose of **MONUROL** (equivalent to 3 g of fosfomycin) under fasting conditions.

Following a high fat meal, a mean maximum urine fosfomycin concentration of 537 µg/mL is attained within 6-8 hours. The cumulative amount of fosfomycin excreted in the urine is approximately the same under fed and fasting conditions and urinary concentrations greater than 10 µg/mL are maintained for 72-84 hours.

In patients with varying degrees of renal impairment (creatinine clearance ranging from 54.2 mL/min to 7.3 mL/min), the $t_{1/2}$ of fosfomycin has been shown to increase from 11 hours to 50 hours. The percentage of fosfomycin recovered in urine decreases to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin. However, urinary concentrations of fosfomycin remain greater than 100 µg/mL for at least 48 hours even in the group with the lowest level of renal function. In contrast, with normal subjects, the urinary concentration at 36-48 hours is 54 µg/mL.

INDICATIONS AND CLINICAL USE

MONUROL (fosfomycin tromethamine) is indicated in the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in women of 18 years of age and older caused by the following susceptible pathogens: *Escherichia coli*, *Enterococcus faecalis*.

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

CONTRAINDICATIONS

MONUROL (fosfomycin tromethamine) is contraindicated in patients with a known hypersensitivity to the drug.

PRECAUTIONS

General:

A single dose only of **MONUROL** (fosfomycin tromethamine) should be used to treat an 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.

***Clostridium difficile*-associated disease**

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including fosfomycin tromethamine. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and many permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an

antibacterial agent clinically effective against *C. difficile*. Drugs that inhibit peristalsis may delay clearance of *C. difficile* and its toxins, and therefore should not be used in the treatment of CDAD. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases (see ADVERSE REACTIONS).

Pediatric Use:

Safety and effectiveness have not been established in children under 18 years of age.

Use in Pregnancy and Nursing Mothers:

Fosfomycin crosses the placental barrier and its safety in the treatment of infections during pregnancy has not been established. **MONUROL** should not be used during pregnancy unless clearly needed and after taking into account the benefits to the mother and potential risks to the fetus.

It is not known whether fosfomycin tromethamine is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to not administer **MONUROL**, taking into account the benefits to the mother and potential risks to the neonate.

Drug Interactions:

Metoclopramide: When co-administered 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.

Probenecid should not be co-prescribed with **MONUROL**, as it has been shown to significantly decrease renal clearance and excretion of fosfomycin.

Probenecid when administered to healthy volunteers given an infusion of disodium fosfomycin significantly decreased renal clearance, probably by inhibiting tubular secretion, leading to lower urinary concentrations.

No therapeutic assessments of the effect of either metoclopramide or probenecid on urinary levels of fosfomycin have been carried out following their administration with **MONUROL** to women with acute urinary tract infection. Based on the information from healthy volunteers, urinary levels of fosfomycin may not exceed bactericidal levels for long enough to result in microbiological cure. Neither of these drugs should be co-prescribed with **MONUROL**.

Cimetidine: Cimetidine does not affect the pharmacokinetics or the urinary concentrations of fosfomycin when co-administered with **MONUROL**.

ADVERSE REACTIONS

In three US trials, 1233 patients were treated with **MONUROL** (fosfomycin tromethamine). 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%).

In addition, adverse events occurring in clinical trials at a rate of less than 1%, regardless of drug relationship were: abnormal stools, anorexia, constipation, dry mouth, dysuria, ear disorder, fever, flatulence, flu syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paraesthesia, pruritus, skin disorder and vomiting.

In the US study population, statistically significant laboratory changes reported without regard to causal relationship included: 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, not clinically significant and occurred in less than 1% patients.

In the same study population, adverse events which were considered to be drug related by the investigators and reported in greater than 1% of the fosfomycin-treated patients were diarrhea

(9.0%), vaginitis (5.5%), nausea (4.1 %), headache (3.9%), dizziness (1.3%), asthenia (1.1 %) and dyspepsia (1.1 %). The most frequently observed symptom, diarrhea, was considered mild and self-limiting.

A single case of unilateral optic neuritis was reported and considered possibly related to **MONUROL** therapy. Post marketing experience with **MONUROL** outside of Canada has resulted in reports of single cases of angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, and hepatic necrosis. A single case of toxic megacolon was reported and found to be not related to **MONUROL**.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

WARNING

For management of suspected drug overdose, contact your Regional Poison Control Centre.

No cases of overdosage have been reported. However, in the event of overdosage, urinary elimination of fosfomycin should be encouraged by adequate administration of oral fluids.

DOSAGE AND ADMINISTRATION

The recommended dosage for women over 18 years with acute uncomplicated urinary tract infections (acute cystitis) is one sachet containing the equivalent of 3 grams of fosfomycin. The contents of the single dose sachet should be added to about 125 mL (½ cup) of cold water, stirred to dissolve and immediately taken orally. **MONUROL** (fosfomycin tromethamine) may be taken with or without food. As for other medications, **MONUROL** should not be co-administered, if possible, with other drugs.

PHARMACEUTICAL INFORMATION**Drug Substance:**

Fosfomycin tromethamine is the mono-acid salt of fosfomycin with tromethamine.

1. NAMES

Established Name: Fosfomycin trometamol (international non-proprietary name [INN])

USAN: Fosfomycin tromethamine

Chemical Name: 1. Mono(2-ammonium-2-hydroxymethyl-1,3-propanediol)(2R- cis)-
3(methyloxiranyl) phosphonate

Proprietary Name: **MONUROL**

Therapeutic Class: Antibiotic

Pharmacological
Class: Antibacterial

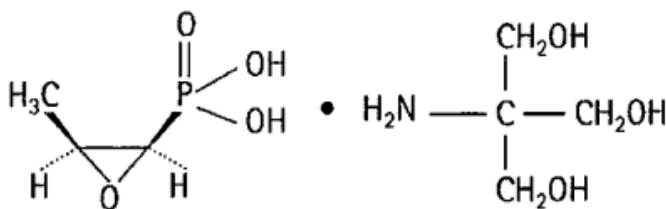
2. PHYSICAL AND CHEMICAL CHARACTERISTICS

Appearance: White to near white crystalline powder.

Solubility: Very soluble in water.
Slightly soluble in 95% methanol and ethanol.
Insoluble in acetone, ether and chlorinated solvents

Melting point: 116-122°C

Structural formula:



Molecular weight: 259.2 [Acid: 138.0]

Product Monograph

MONUROL®

Molecular formula $C_7H_{18}NO_7P$

pH: 4.0 to 5.0 (5% w/v aqueous solution)

Composition: Each sachet of **MONUROL** contains: 5.631 g of fosfomycin tromethamine (equivalent to 3 g of fosfomycin) plus mandarin and orange flavouring, saccharin and sucrose.

Storage Conditions: Store at controlled room temperature 15° to 30°C (59° to 86°F)

AVAILABILITY OF DOSAGE FORMS

MONUROL (fosfomycin tromethamine) is available as a single-dose sachet containing the equivalent of 3 grams of fosfomycin.

INFORMATION FOR THE PATIENT

The following leaflet provides information on **MONUROL**, the medication your doctor has prescribed for your urinary bladder infection (cystitis), as well as background on the infection itself. It is important to know that your therapy is completed when you take the single dose of **MONUROL** and you should expect your symptoms to improve by the second or third day. Ask your doctor if you have any questions about your infection.

What is MONUROL for?

Your doctor has diagnosed you as having a urinary bladder infection and inflammation called cystitis. **MONUROL** is an antibiotic prescribed to kill the bacteria causing your infection. Although you only take **MONUROL** once, it is eliminated via the urine after being absorbed into the body where it comes into contact with the bacteria in the bladder. **MONUROL** is eliminated in the urine over about three days and continues to kill the bacteria during this period. As the bacteria die, your bladder begins to heal and symptoms begin to disappear.

How does MONUROL work?

MONUROL starts working to kill bacteria within hours after taking it. The bladder irritation caused by the bacteria and the resulting symptoms that you may be experiencing can persist for a short time even after the bacteria have been killed. You should see complete relief or improvement in your symptoms within 2 to 3 days. If your symptoms do not improve by the fourth day, you should contact your healthcare professional.

What is in the sachet (packet)?

The sachet (packet) contains white granules of **MONUROL**, an antibiotic, along with a small amount of sweetener (saccharin and sucrose) plus mandarin and orange flavouring.

Can I take MONUROL if I am pregnant or breast-feeding?

MONUROL can reach the fetus and may enter breast milk. If you know you are pregnant, or are breast-feeding, please inform your doctor who will decide if you should take MONUROL.

How do I take MONUROL?

1. Empty entire contents of **MONUROL** sachet into about 125 mL (½ cup) of cold water and stir to dissolve.
2. Take immediately after dissolving in water, making sure to drink the complete contents of the glass. One sachet of **MONUROL** is a complete therapy for treating your bladder infection. Since **MONUROL** is eliminated in urine over a period of three days, the bacteria in the bladder are killed by **MONUROL** during this period of time.

Will I experience side effects?

Some patients taking **MONUROL** may experience diarrhea, which is the most common side effect. Headache and vaginal irritation are also side effects that may be experienced less frequently by some patients.

If you develop persistent or severe diarrhea (bloody or watery) with or without fever and abdominal pain, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, contact your doctor immediately.

What if I am allergic to antibiotics?

Allergic reactions to **MONUROL** are rare. **MONUROL** is not related to penicillin or other antibiotics that commonly cause allergic reactions. If you have a history of allergy to antibiotics, inform your doctor before taking **MONUROL**. Do not take **MONUROL** if you have previously had an allergic reaction to it.

What about taking MONUROL with other drugs?

MONUROL has very few known interactions with other drugs. If you are currently taking a gastrointestinal drug with the chemical name metoclopramide hydrochloride, you should not take **MONUROL** unless you have discussed this with your doctor.

WARNING

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional poison control centre, even if there are no symptoms.

Some other precautions:

Do not take this or any other medication if it was prescribed for someone else. **MONUROL** is indicated for use in women over the age of 18 years of age. Keep **MONUROL** out of the reach of children. Do not use after the expiration date printed on the box.

What is cystitis?

Cystitis is a urinary bladder inflammation associated with a bacterial infection. Bacteria have entered your bladder (which is normally bacteria free) and are causing irritation to your bladder lining. This irritation may trigger burning or pain when you urinate, make you feel like you have to urinate frequently, or cause pain above your pubic bone.

What causes cystitis?

Cystitis is usually caused by bacteria that enter the bladder. Bacteria sometimes can travel from the anal area to collect in the vagina and then enter the urethra to finally reach the bladder.

What are the usual symptoms?

Typical symptoms include frequent urination, painful urination and a bladder that never feels totally empty. Other symptoms include pain or tenderness above the pubic area.

Is cystitis dangerous?

Normally it is not, unless the bacteria in the urine causing the cystitis have traveled upward to infect the kidneys. Your doctor has prescribed **MONUROL** to prevent this from occurring.

How is cystitis diagnosed and treated?

Cystitis is diagnosed on the basis of your symptoms and/or a urine culture to identify the responsible bacteria. It is most often treated with antibiotics.

What can I do to help prevent cystitis?

Following these simple guidelines will help prevent cystitis:

- drink plenty of fluids every day
- urinate frequently and try to empty the bladder completely each time
- wipe front to back after urinating and moving your bowels to help prevent bacteria from entering the urethra
- avoid tight clothing in the genital area and wear cotton undergarments
- empty your bladder before and after sexual intercourse
- change sanitary napkins frequently during your period

MICROBIOLOGY

Fosfomycin is bactericidal by inhibiting the cytoplasmic enzyme, enolpyruvyl transferase, which serves as a catalyst to create the basic monomer (uridine diphosphate-N-acetylmuramic acid) needed for the first step of the bacterial cell wall (peptidoglycan) synthesis.

Fosfomycin (the active component of fosfomycin tromethamine) has *in-vitro* activity against a range of gram-positive and gram-negative aerobic microorganisms, some of which are associated with uncomplicated urinary tract infections. The antibacterial activity of fosfomycin, using agar dilution test, is shown in Table 1.

TABLE 1: ANTIBACTERIAL ACTIVITY OF FOSFOMYCIN *IN VITRO* (AGAR DILUTION TEST)

Microorganism (No. Tested)	Minimal Inhibitory Concentration (µg/mL) Agar Dilution		
	50%	90%	Range
<i>Escherichia coli</i> (51)	1.0	4.0	≤0.5 – 32
<i>Citobacter species</i> (30)	2.0	4.0	2.0 – 8.0
<i>Klebsiella species</i> (30)	16	32	2.0 – 128
<i>Enterobacter species</i> (45)	16	32	1.0 – >256
<i>Serratia marcescens</i> (20)	8.0	16	4.0 – 32
<i>Morganella morganii</i> (10)	128	>256	32 – >256
<i>Providencia species</i> (25)	16	128	2.0 – 256
<i>Pseudomonas species</i> (35)	128	256	≤ 0.5 – 512
<i>Acinetobacter calcoaceticus</i> <i>subsp. anitratus</i> (10)	128	128	64 – 128
<i>Enterococcus species</i> (41)	32	64	16 – >256
<i>Staphylococcus saprophyticus</i> (30)	128	512	64 – >256

(Reference: 21)

The *in vitro* activity of fosfomycin against urinary tract pathogens, isolated from 1233 patients in US clinical studies is presented in the following Table 2, which shows MIC (µg/mL) distribution among the six most common uropathogens:

TABLE 2: DISTRIBUTION OF FOSFOMYCIN MICs AGAINST UROPATHOGENS IN US CLINICAL TRIALS

Microorganism	Number of Isolates with MIC 90(µg/mL) of							
	≤2	4	8	16	32	64	128	≥256
<i>Escherichia coli</i>	566	10	5	3	1	2	0	0
<i>Enterobacter aerogenes</i>	0	0	3	3	0	0	0	0
<i>Klebsiella pneumoniae</i>	1	5	11	6	2	1	3	0
<i>Proteus mirabilis</i>	20	4	1	1	0	0	1	1
<i>Enterococcus faecalis</i>	0	0	0	1	5	4	0	0
<i>Staphylococcus saprophyticus</i>	2	0	0	0	1	9	1	8
All	589	19	20	14	9	16	5	9

(Reference 28, 29 and 30)

Resistance to fosfomycin can develop either through chromosomal or plasmid mediated mechanisms. Chromosomally mediated mutations result in reduced uptake of fosfomycin by the L-α-glycerophosphate (primary) or the hexose phosphate (alternative) transport system. Catalytic conjugation between glutathione and fosfomycin which gives an inactive entity is the mechanism for plasmid mediated resistance. Surveys of developing resistance patterns in Europe have not revealed either any major development of chromosomal mutants or plasmid mediated resistance with fosfomycin. Also, there appears to be little cross-resistance between fosfomycin and other antibacterial agents, likely due to the fact that its chemical structure and mode of action differ from those of other agents.

In healthy volunteers, a single dose of **MONUROL** (equivalent to 3 g fosfomycin) decreased the coliform count in six of eight volunteers, the count returning to normal by Day 7 in seven of eight of the volunteers. While there was an increase in fosfomycin-resistant coliforms isolated on Days 2 to 3 in three volunteers, these had disappeared by Day 7 to 14. The total number of fecal anaerobes was often slightly increased, largely due to an elevation of *Bacteroides* species. There was no rise in the proportion of fosfomycin resistant anaerobes.

Neither *C. difficile* nor its toxin were detected in any sample nor was there colonization with pseudomonas or yeasts.

IN VITRO SUSCEPTIBILITY TESTING

SUSCEPTIBILITY TESTS

Dilution Techniques:

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized agar dilution method (Reference 23) 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 METHOD SHOULD NOT BE USED TO TEST**

SUSCEPTIBILITY OF FOSFOMYCIN. The MIC values obtained should be interpreted according to the following criteria:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤64	Susceptible (S)
128	Intermediate (I)
≥256	Resistant (R)

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable concentrations of the antimicrobial compound in urine. A report of "Intermediate" indicates that the results 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 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):**

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<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:

Qualitative methods that require measurement of zone diameters also provide reproducible estimate of the susceptibility of bacteria to antimicrobial agents. One such standardized procedure (Reference 24) 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 microorganism to fosfomycin.

Laboratory results utilizing the standard single-disk susceptibility test should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥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 standard dilution techniques, diffusion methods require the 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 50 µg/mL of glucose-6-phosphate should provide the following zone diameters in these laboratory quality control strains:

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

PHARMACOLOGY

Animal:

Five studies in two species of rodent and dog demonstrated that fosfomycin tromethamine is well absorbed, distributed to highly perfused organs and predominantly excreted as unchanged drug in the urine. The results are shown in Table 3.

TABLE 3: PLASMA AND URINE CONCENTRATIONS OF FOSFOMYCIN IN ANIMALS

Species	Route	Dose mg/kg	Plasma		Urine recovery%		
			Cmax (µg/mL)	Tmax (mins.)	6-8 hrs.	24 hrs.	48 hrs.
Mouse	Oral	30	8.65	15	27.8	55.8	-
Rat	Oral	50	16.6	60	36.5	49.2	-
Rat	Oral	50	14.3	-	-	-	88.5
Dog	Oral	50	39.6	120	52.2	62.0	-
Dog	Oral	500	91.3	120	22.9	41.6	-

In rats administered 50 mg/kg fosfomycin tromethamine (mean oral dose 11.3 ± 0.6 mg) mean recovery (% of total dose) over 48 hours was $8.7 \pm 6.9\%$ in feces, $88.5 \pm 3.9\%$ in urine and $97.3 \pm 5.1\%$ in urine and feces combined. Peak plasma concentrations of 14.3 ± 3.5 µg/mL occurred 1 hour after drug intake. Peak concentrations in all organs examined, also occurred at 1 hour and levels in the kidney exceeded those in plasma by approximately 5 fold (mean 74.9 ± 23.3 µg/g)

Human:

Healthy Volunteers

Pharmacokinetic parameters following administration of a single dose of **MONUROL** (equivalent to 3 g of fosfomycin) to young healthy volunteers, with and without a high fat meal, were compared to those following a 3 g iv dose of fosfomycin (disodium fosfomycin) in the same subjects. The results covering an 84 hour period are shown in Table

4. Corresponding urine concentrations measured at time intervals up to 84 hours are shown in Table 5.

TABLE 4: SUMMARY OF PHARMACOKINETIC DATA (±SD)

Route and Dose	# of Subjects	Cmax (µg/mL)	Tmax (hr.)	AUC (µg-hr/mL)	t _½ (hr.)	Urinary Excretion (% dose)	Feces Excretion (% dose)
oral MONUROL (equivalent to 3 g fosfomycin) without food	24 12F,12M	26.1(±9.1)	2.1(±0.42)	184.0(±33.6)	5.7(±2.8)	38.0 (±7.9)	18.0(±1 0.6)
oral MONUROL (equivalent to 3 g fosfomycin) with food	24 12F,12M	17.6(±4.4)	4.0(±0.55)	154.0(±34.2)	5.8(±1.9)	37.3(±6.7)	19.0(±13.0)
intravenous disodium fosfomycin (equivalent to 3 g fosfomycin) Without food	24 12F,12M	-	-	504.0(±87.6)	2.7(±0.6)	89.6(±13.5)	-

(Reference: 2)

**TABLE 5: MEAN (\pm SD) FOSFOMYCIN URINE CONCENTRATIONS (μ g/mL) FOLLOWING A
SINGLE 3G DOSE**

Time Interval (hours)	Oral (fasted)	Oral (fed)	Intravenous (fasted)
0.0 - 2.0	649.2 (\pm 442.1)	209.6 (\pm 127.2)	6353.2 (\pm 3653.4)
2.0 - 4.0	706.5 (\pm 466.4)	428.1 (\pm 153.5)	1810.5 (\pm 1608.5)
4.0 - 6.0	594.2 (\pm 267.5)	531.5 (\pm 187.2)	829.9 (\pm 362.4)
6.0 - 8.0	549.9 (\pm 302.4)	537.7 (\pm 251.8)	954.7 (\pm 603.8)
8.0 - 10.0	478.5 (\pm 176.2)	404.4 (\pm 221.3)	498.0 (\pm 221.1)
10.0 - 12.0	492.9 (\pm 212.2)	351.8 (\pm 179.4)	403.5 (\pm 269.1)
12.0 - 16.0	265.0 (\pm 143.3)	250.0 (\pm 123.9)	195.2 (\pm 141.9)
16.0 - 24.0	168.1 (\pm 108.9)	163.5 (\pm 99.3)	82.3 (\pm 64.2)
24.0 - 36.0	62.2 (\pm 29.8)	62.8 (\pm 30.2)	14.4 (\pm 16.1)
36.0 - 48.0	54.2 (\pm 45.5)	54.1 (\pm 30.7)	3.3 (\pm 2.8)
48.0 - 60.0	30.6 (\pm 21.2)	29.3 (\pm 23.3)	-
60.0 - 72.0	21.6 (\pm 17.7)	17.4 (\pm 17.2)	-
72.0 - 84.0	10.8 (\pm 11.4)	10.6 (\pm 10.7)	-

(Reference: 2)

Other Pharmacokinetics Considerations:

Food: While food produces some decrease in the rate and extent of absorption of fosfomycin following oral administration of **MONUROL** (fosfomycin tromethamine), urine concentrations remain above the MICs for most uropathogens for a similar time, whether administered with food or fasting. **MONUROL** may therefore be administered without regard to food.

Administration with calcium-containing products: In comparative studies of the bioavailability of fosfomycin tromethamine and fosfomycin calcium, the rate and extent of absorption of fosfomycin from fosfomycin tromethamine were approximately 6 times greater than from fosfomycin calcium during the first two hours post dose and approximately 3-4 times greater during the 12 hour post dose period. *In vitro* studies indicate that addition of a solution of antacid tablet (containing 750 mg calcium) to a solution of fosfomycin tromethamine in simulated gastric fluid does not result in complexation of calcium with fosfomycin. There is, therefore, no need to avoid **MONUROL** intake with antacids or calcium.

Elderly population: In seven (7) elderly women of average age 77 yrs and mean serum creatinine of 121 $\mu\text{mol/L}$ and mean estimated creatine clearance of 40 mL/min., mean urinary concentrations over 84 hours following a single oral dose of **MONUROL** (equivalent to 3 g fosfomycin) are shown in Table 6.

TABLE 6: URINARY CONCENTRATIONS OF FOSFOMYCIN IN ELDERLY WOMEN

Sample	Mean Urinary Concentration µg/mL; (±SD)
0 - 12 hr	1,383 (±1,354)
12 - 24 hr	508 (±487)
24 - 36 hr	510 (±794)
36 - 48 hr	165 (±116)
48 - 60 hr	222 (±386)
60 - 72 hr	78 (±63)
72 - 84 hr	143 (±239)

(Reference: 12)

The total percentage of the administered dose recovered at 84 hours in the urine was $37 \pm 15\%$, which was comparable to that reported in young healthy volunteers. In the U.S. trials, there was no difference in drug efficacy or tolerance for patients older than 65 years compared with patients younger than 65 years. There is, therefore, no need to adjust the dose in the elderly with age-dependent renal impairment.

Renal Impairment:

In another trial, the pharmacokinetic parameters and urinary excretion were compared in healthy subjects and patients with varying degrees of renal impairment. The results are shown in Table 7.

TABLE 7: FOSFOMYCIN PHARMACOKINETIC PARAMETERS (±SD) IN HEALTHY SUBJECTS AND IN PATIENTS WITH VARYING DEGREES OF RENAL IMPAIRMENT

Parameters	Healthy Subjects (n=5)	Group I (n=7) mild	Group II (n=6) moderate	Group III (n=5) severe	Group IV (n=5) anuric
Creatinine clearance (mL/min)	127.0	54.2	16.4	7.3	0
Dose (25mg/kg; total mg)	2032 (±444)	1792 (±410)	1667 (±368)	1811 (±58)	1836 (±240)
C _{max} (µg/mL)	15.5 (±10.2)	26.0 (±10.00)	35.7 (±10.4)	27.4 (±8.4)	37.9 (±7.9)
T _{max} (hr)	1.6 (±0.2)	2.4 (±1.4)	4.6 (±1.2)	5.1 (±1.3)	7.92 (±3.5)
AUC (µg-hr/mL)	102.8 (±42.1)	388.5 (±184.7)	1266.8 (±457.4)	2108.6 (±824.0)	2367.0 (±855.8)
t _½ serum (hr)	5.37 (±2.6)	10.76 (±4.5)	24.5 (±11.7)	50.3 (±12.9)	39.6 (±19.6)
Urinary elimination 24 hr (% of dose)	57.7 (±30.2)	31.6 (±10.5)	24.0 (±17.3)	11.0 (±4.6)	-
Age (yr)	29.0 (±2.7)	43.7 (±22.9)	56.8 (±11.9)	55.8 (±5.0)	56.4 (±6.0)

(Reference: 11)

Although renal excretion of fosfomycin decreased in association with the impairment in renal function, the urinary concentration of fosfomycin remained greater than 100µg/mL at 48 hours post-dose even in the group with the lowest creatinine clearance. In contrast, in normal subjects, the urinary concentration at 36 - 48 hours was 54 µg/mL. While renal impairment significantly prolongs the elimination of fosfomycin, and since **MONUROL** is intended to be administered as a single dose therapy only, continued drug accumulation is not expected. Even

though renal impairment significantly decreases the excretion of fosfomycin, dosage adjustment is not required.

No clinical trials in renally impaired patients were conducted to clearly determine the efficacy and safety of fosfomycin tromethamine.

TOXICOLOGY

Acute Toxicity

The acute toxicity of fosfomycin tromethamine was established in mice, rats, rabbits and dogs at doses 100 fold higher than human doses. The LD₅₀ values are shown in Table 8.

TABLE 8: LD₅₀ VALUES

Animal	Route	LD50 (mg/kg) Male	LD50 (mg/kg) Female
Mouse	po	>5000	>5000
	ip	4441	4344
Rat	po	>5000	>5000
	ip	4539	4342
Rabbit	po	>2000	>2000
Dog	po	>2000	>2000

No deaths occurred in the acute oral studies listed above. The only unusual findings noted were anorexia and diarrhea in the dog. In the intraperitoneal studies, the observations noted one hour after dosing were piloerection, blepharoptosis and diarrhea. These symptoms are mainly attributable to the peritoneal inflammation due to the hypertonicity of the injected solution. No changes were noted in behaviour, body weight or food consumption during the 14 day observation period, in any species.

By the intraperitoneal route, deaths occurred at doses above 4000 mg/kg, in rodents. These were mainly on the first day of treatment and no animal died after day 4.

Sub-acute Toxicity

4- Week Rat Study:

Fosfomycin tromethamine was administered once daily by oral gavage to 3 groups of Sprague Dawley rats (15 male, 15 female per group) at doses of 200, 800 and 3200 mg/kg/day for 4 weeks. An additional group acted as control.

Physical examinations, body weights, food consumption, ophthalmoscopic examinations, hematology values, urinalysis values, and gross or histopathological observations did not reveal any drug-related effects.

A dose-related increase in cholesterol was noted in the treated animals; differences from control values were most significant in the high-dose group. Statistically significant increases in serum glutamic pyruvic transaminase and slight increases in serum glutamic oxaloacetic transaminase values were also noted in the 3200 mg/kg/day group.

These changes were suggestive of an effect on liver function. Statistically significant increases in absolute and relative liver weights were noted in the high-dose animals; absolute kidney weights were also slightly increased in the high-dose males.

Based on the increased cholesterol in the 800 and 3200 mg/kg/day groups and on the increased liver weights in the high-dose animals, the no-effect level in this study was determined to be 200 mg/kg/day of fosfomycin tromethamine.

12-Week Rat Study:

In another rat study, fosfomycin tromethamine was given daily by oral gavage for 12 weeks, with 4 weeks recovery. Male and female rats, eighteen per dosing group, respectively received

doses 250, 1000 and 4000 mg/kg. The no-effect level was seen at the 1000 mg/kg dose level. The males and females in the 4000 mg/kg group had areas of mucosal inflammation in the terminal ileum and colon. Also, liver weight and kidney weight increases were evident at the high doses for the male and female rats. In the females, kidney weight increases were also noted at 250 and 1000 mg/kg respectively. There was no drug-related mortality. Treatment effects did not persist during the 4 week recovery period.

4-Week Dog Study:

In another study, fosfomycin tromethamine was administered once daily by oral gavage to three groups of Beagle dogs for 4 weeks at doses of 100, 300 and 1000 mg/kg/day. Each group consisted of 4 male and 4 female dogs and an additional group acted as control.

Survival, physical and ophthalmoscopic examinations, hematology values, urinalysis data, and gross or histopathological evaluations did not reveal any drug-related effects.

The body weights of the high-dose males were about 10% lower than control males during the first three weeks and 8% lower than at study termination. The body weights in the 300 mg/kg/day females were 8 to 10% lower than controls and in the 1000 mg/kg/day females 11 to 14% lower. The body weight effects were generally more pronounced during the early part of the study and appeared to become less marked over time.

A statistically significant increase in aspartate aminotransferase as compared to control values was observed in the high-dose males at study termination.

The absolute and relative testes weights of the high-dose males were slightly or statistically significantly lower than controls, respectively. Based on the body weight effects seen in females given 300 mg/kg/day, the no adverse effect level for this study was determined to be 100 mg/kg/day of fosfomycin tromethamine.

Chronic Toxicity

26-Week Dog Study:

Fosfomycin tromethamine was administered daily, by oral gavage, to dogs at doses of 100, 300 and 1000 mg/kg for 26 weeks, with a 6 week recovery period.

Diarrhea was observed in the animals in the high-dose group during the first four weeks of treatment, but this returned to normal as the study progressed. There were no deaths.

At all dose levels, the external appearance of the animals, food consumption, hematology, blood chemistry, urinalysis, and ECG results revealed no changes attributable to either of the drugs tested. Gross autopsy and histopathological examinations did not reveal any differences between the control and treatment groups.

Reproduction

Fertility Study:

In a fertility study, Sprague Dawley rats received fosfomycin tromethamine by oral gavage at doses of 0, 250, 500 and 1000 mg/kg/day. Treatment groups consisted of 24 males per dose and 24 females per dose. Dosing in males was once daily beginning at puberty for 63 days before mating and throughout cohabitation. The females were dosed daily for at least 14 days before mating, throughout 14 days of cohabitation and until day 7 post-coitum.

The only side effects observed were diarrhea in the males during the first four weeks of treatment and a reduction in food intake in the males given 500 and 1000 mg/kg/day during the first four days of treatment. Treatment did not adversely affect spermatogenesis or the reproductive capacity of the male rats nor adversely affect oogenesis, the regularity of the estrus cycle, or fertility and gestation in the female rats.

Teratology Studies

Rat Study:

In a teratogenicity study, fosfomycin tromethamine was administered by oral gavage to 4 groups of female Sprague Dawley rats at doses of 0, 250, 500 and 1000 mg/kg/day. The dosing was done from gestation day 6 through gestation day 15. Litter viability, sizes, and weights in the treated groups were comparable with those in the control group, except for one litter in the 250 mg/kg/day group in which scarcely viable and underweight fetuses were observed.

At high doses of 1000 mg/kg/day, comparable to approximately 20 times the normal human dose, treatments did not produce teratogenic effects and the litters of dams left to deliver at term developed normally during the period of lactation. The maternal and the fetal no adverse effect level was 1000 mg/kg/day.

Rabbit Study:

In the rabbit teratogenicity study, fosfomycin tromethamine was administered by oral gavage to four groups at doses of 100, 200 and 400 mg/kg/day. These rabbits were divided after mating into four groups of 14-15 rabbits who were dosed from gestation days 6 to 16 and sacrificed on gestation day 28. Six female rabbits died in the course of gestation: two (1 at 100 mg/kg, 1 at 400 mg/kg) as a result of faulty gavage procedure, and four (1 control, 1 at 100 mg/kg and 2 at 400 mg/kg) died after a few days of anorexia; the cause of death was not evident during necropsy. Diarrhea was observed in all groups and melena occurred in one animal and mucoid stools in another in the 400 mg/kg/day group.

Treatment did not adversely affect the normal course of gestation except in one 100 mg/kg/day female that aborted on gestation day 28 and expelled dead fetuses in various stages of resorption. Treatment did not adversely affect the development of the viable fetuses and the external, visceral and skeletal examinations of the fetuses did not reveal any drug-related major malformations or minor anomalies. There was a possible increase in resorptions at the mid

and high doses. These toxicities were considered to be due to the well recognized sensitivity of the rabbit to changes in the intestinal microflora resulting from antibiotic administration.

Peri-postnatal Study

Fosfomycin tromethamine was administered by oral gavage once daily to groups of 20 pregnant dams at doses of 250, 500 and 1000 mg/kg/day, respectively. The dosing was on day 6 of gestation through day 21 of lactation. Observation of the F1 generation showed normal morphological and psychomotor development in all groups. The fertility gestation and parturition in the F1 generation were also normal in all groups. The survival rate and postnatal body growth in all groups of the F2 generation were normal for the colony of rats used in this study. The maternal and fetal no adverse effect level was 1000 mg/kg/day.

Placenta Transfer Study

In a placenta transfer study, rats (dams) were dosed by oral gavage 50 mg/kg/day on either gestation day (GD) 14 or 19. Samples collected at 2, 4, 6 and 24 hours included liver, kidney, plasma and placenta for the dams, embryonic tissue, pooled embryos and amniotic fluid for the fetuses. Study results showed fosfomycin concentration in maternal plasma and tissue below limits of quantification on GD 14 at 24 hours. Detectable levels were observed in plasma, the kidney and placenta in dams dosed on GD 19. For the fetuses, maximum accumulation of fosfomycin in amniotic fluid occurs between 4 to 6 hours post dose and at GD 19 fosfomycin was detected only in the amniotic fluid. Conclusive results demonstrated fosfomycin readily crosses the placenta and that the fetal kidney was the major site of fosfomycin accumulation. The fetal-maternal ratio is 0.65.

Mutagenicity

A standard Ames *in vitro* test was conducted using fosfomycin tromethamine in a *Salmonella typhimurium* system (strains TA-98, TA-100, TA-1535, TA-1537 and TA-1538). The results showed fosfomycin tromethamine did not cause an increase in the number of reversions in the *Salmonella* strains.

Also, in the *in vitro* bacterial reversion test, fosfomycin tromethamine was not mutagenic. No genotoxicity was demonstrated in the *in vitro* tests using cultured human lymphocytes, the Chinese hamster V79 cells or with *in vivo* mouse micronucleus assay.

Carcinogenicity

Long term carcinogenicity studies in rodents have not been conducted because **MONUROL** is to be administered as a single dose treatment in humans.

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