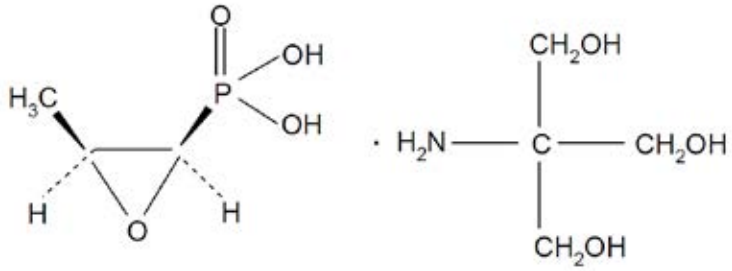
MONUROL®

granules for oral solution

NAME OF THE MEDICINE

Fosfomycin trometamol

Chemically, fosfomycin trometamol is 2-hydroxy-1,1-bis(hydroxymethyl) ethylammonium (2R,3S)-(3-methyloxiran-2-yl) phosphonate and has the following chemical structure:



Molecular formula: $C_7H_{18}NO_7P$

Relative molecular mass: 259.2

CAS Registry No.: 78964-85-9

DESCRIPTION

One sachet of MONUROL granules for oral solution contains 5.631 g of fosfomycin trometamol equivalent to 3.0 g fosfomycin. One sachet also contains the following excipients: Tangerine flavour PHP-139220, Orange Juice flavour PHS-192439, saccharin and 2.213 g of sucrose.

Fosfomycin trometamol is a white or nearly white crystalline powder. It is very soluble in water, slightly soluble in 95% methanol and ethanol, almost insoluble in anhydrous acetone, in ether and in chlorinated solvents.

PHARMACOLOGY

Mechanism of Action

Fosfomycin inhibits the first stage of bacterial wall synthesis. It inhibits the phosphoenolpyruvate transferase enzyme, thereby irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate.

Fosfomycin is actively transported into the bacterial cell via two different transport systems (the sn-glycerol-3-phosphate and hexose-6 transport systems). Fosfomycin has a mainly bactericidal

action. It can also reduce bacterial adhesion to bladder mucosa, which can be a predisposing factor for recurring infections. As this mechanism of action is unique to fosfomycin cross-resistance is not expected with other antibiotics.

Microbiology

There has been very limited fosfomycin susceptibility testing performed in Australia to date. Recommendations are based on studies performed overseas.

Activity *in vitro*

Bacterial species commonly susceptible to fosfomycin using European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standard Institute (CLSI) susceptibility testing guidelines:

Escherichia coli, *Proteus* spp, *Klebsiella* spp., *Citrobacter* spp., *Enterococcus faecalis*

Bacterial species variably susceptible or resistant to fosfomycin using EUCAST or CLSI susceptibility testing guidelines:

Enterobacter spp, *Serratia marcescens*, *Providencia* spp.

Bacterial species frequently resistant to fosfomycin using EUCAST or CLSI susceptibility testing guidelines:

Morganella morganii

Oral fosfomycin is not recommended in the treatment of the following bacterial species which do not have EUCAST or CLSI susceptibility testing guidelines:

Staphylococcus saphrophyticus, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter* spp, *Stenotrophomonas maltophilia*, *Bacteroides* spp and other anaerobic bacteria.

Resistance

Main mechanism of resistance is a chromosomal mutation causing an alteration of the bacterial fosfomycin transport systems. Plasmid-encoded mechanisms of resistance to fosfomycin have also been documented.

Table 1: Susceptibility testing

Breakpoints for Fosfomycin		
	EUCAST	CLSI
Enterobacteriaceae	≤32 mg/l (S)* >32 mg/l (R)*	
E.coli	≥24 mm (S)** <24 mm (R)**	≤64 mg/l (S)* 128 mg/l (I)* ≥256 mg/l (R)*
Enterococcus faecalis		≤64 mg/l (S)* 128 mg/l (I)* ≥256 mg/l (R)*

*MIC breakpoints
**disc diffusion zone diameter breakpoints

Based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, fosfomycin trometamol single 3 g oral dose is calibrated for the treatment of acute uncomplicated urinary tract infection (UTI) caused by Enterobacteriaceae. MIC breakpoints are ≤32 (less than or equal than) mg/l (S) and >32mg/l (R). EUCAST disc diffusion zone diameter breakpoints for *E. coli* only are >24 mm (S) and <24 mm (R). For other Enterobacteriaceae, an MIC method should be used. All methods require glucose-6-phosphate supplementation.

There are no EUCAST guidelines for other urinary pathogens such as *Pseudomonas*, *Staphylococcus saphrophyticus*, or *Enterococcus* spp.

Based on Clinical and Laboratory Standard Institute (CLSI) criteria, only *E coli* and *Enterococcus faecalis* from urinary tract isolates are calibrated. MIC breakpoints for both are <64 mg/l (S), 128 mg/l (I), and >256 mg/l (R). Disc and agar dilution MIC methods are approved provided there is supplemental glucose-6-phosphate. CLSI does not recommend broth dilution fosfomycin susceptibility testing.

There are no CLSI guidelines for any other bacteria apart from *E coli* and *Enterococcus faecalis*.

Clinical efficacy against specific pathogens

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable.

Oral fosfomycin should be used where there is resistance to other suitable antibiotics, including trimethoprim, cephalexin and amoxycillin/clavulanic acid.

Pharmacokinetic (PK)/pharmacodynamic (PD) relationship

Limited data indicate that fosfomycin most likely acts in a concentration-dependent manner. There are no known PK/PD breakpoints for fosfomycin.

Pharmacokinetics

Absorption

After oral administration, fosfomycin is well absorbed from the gut and has an absolute bioavailability of about 35-40%. Food delays absorption, not influencing urinary concentrations.

Distribution

Fosfomycin is distributed to the kidneys, bladder wall, prostate and seminal vesicles. Sustained concentrations of fosfomycin higher than the minimum inhibitory concentrations (MIC) are obtained in urine for 24-48 hours after oral administration.

Fosfomycin does not bind to plasma proteins, fosfomycin has been shown to cross the placental barrier in humans and animals.

Metabolism

Fosfomycin does not appear to be metabolised.

Excretion

Fosfomycin is excreted unchanged mainly via the kidneys by glomerular filtration (40-50% of the dose is found in the urine) with an elimination half-life of about 4 hours and to a lesser extent in faeces (18-28% of the dose). The appearance of a second serum peak 6 and 10 hours after drug intake suggests that the drug is subject to enterohepatic recirculation.

Special Populations

Geriatric

The pharmacokinetic features of fosfomycin are not modified by age.

Pregnancy

The pharmacokinetic features of fosfomycin do not appear to be modified by pregnancy in a study of 4 pregnant patients.

Hepatic Insufficiency

The pharmacokinetic features of fosfomycin have not been studied in patients with impaired hepatic function. However, fosfomycin does not undergo hepatic metabolism and clearance is known to be predominantly renal with urinary excretion. Limited studies confirm that there is an enterohepatic recirculation which does not influence bioavailability.

Renal Insufficiency

Renal Insufficiency: Peritoneal dialysis and haemofiltration.

The pharmacokinetics of fosfomycin trometamol have not been studied in patients undergoing peritoneal dialysis or haemofiltration.

Renal Insufficiency: Renal impairment and haemodialysis.

In 5 anuric patients undergoing haemodialysis, the $t_{1/2}$ of fosfomycin during haemodialysis 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.

The drug accumulates in patients with severe renal impairment but the significance of this is unknown. Linear relationships have been established between fosfomycin pharmacokinetic parameters and glomerular filtration rate.

In consideration of the safety profile of the drug and of single dose treatment, in patients with mild to moderate renal impairment (define as creatinine clearance >10 ml/min) it is not necessary to adjust the dose but these patients have to be carefully monitored.

Due to reduced excretion of drug and limited data, fosfomycin trometamol is contraindicated in severe renal failure (creatinine clearance <10 ml/min), haemodialysis, peritoneal dialysis and haemofiltration (see **CONTRAINDICATIONS**).

CLINICAL TRIALS

In three phase 3 prospective parallel multi-centre double-blind double-dummy randomised trials of acute uncomplicated urinary tract infection (UTI) performed in the 1990s, a single 3 g oral dose of MONUROL was compared to three other oral antibiotics (see Table 2 below). The study population consisted of female patients with symptoms and signs of acute lower UTI 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, 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 the first two studies (US-MON-01 comparator arm ciprofloxacin and US-MON-02 comparator arm trimethoprim/sulphamethoxazole), adult females aged 18 years and older were enrolled and patients with renal dysfunction (defined as serum creatinine clearance <30 mls/min) were excluded. In the third study (US-MON-03, nitrofurantoin comparator), females aged 12 years and older were enrolled and patients with severe renal dysfunction (defined as serum creatinine clearance <60 mls/min) were excluded. In all three studies, pregnancy, immunosuppression and neutropenia were exclusion criteria.

In these studies, the following clinical success (resolution of symptoms) and microbiologic eradication rates were obtained (Table 2):

Table 2: Clinical and microbiological efficacy of fosfomycin trometamol versus three comparator antibiotics, three pivotal studies of the treatment of females with acute uncomplicated lower UTI (studies MON-US-01, MON-US-02 and MON-US-03)

Treatment Arm	Treatment Duration (days)	Microbiologic Eradication Rate		Clinical Success Rate	Outcome (based on difference in microbiologic rates 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

In the 3 pivotal studies, median age of patients enrolled was 27-32 years (fosfomycin) and 27-31.5 years (comparator arms). In all 3 studies, approximately half the patients were aged 30 years or less. The most common pathogen in the three pivotal studies was *E coli*, which caused 82-86% of UTIs. Table 3 shows microbiological cure rates from pooled data from the 3 studies by pathogen.

Table 3: Dosing schedules and microbiological cure rates by pathogen at day 5-11 post-therapy, ITT and modified ITT populations, three pivotal studies of the treatment of females with acute uncomplicated lower UTI (studies MON-US-01, MON-US-02 and MON-US-03)

Pathogen	Fosfomycin 3 g single dose	Ciprofloxacin 250 mg bid x 7d	Trimethoprim/ sulfamethoxazole 160 mg/800 mg bid x 10d	Nitrofurantoin 100 mg 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%)

There have been no other phase 3 prospective, parallel, multicentre, double-blind, double-dummy randomised efficacy and safety trials for the treatment of acute uncomplicated UTI since the three pivotal studies US-MON-01, US-MON-02, and US-MON-03 performed in the 1990s.

INDICATIONS

MONUROL is indicated only for the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in females above 12 years of age caused by the following susceptible pathogens: Enterobacteriaceae (including *Escherichia coli*), *Enterococcus faecalis*.

MONUROL is not indicated for the treatment of pyelonephritis or perinephric abscess or where resistance is likely (previous treatment failure, infection due to non-susceptible organism).

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to MONUROL. However, therapy may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued. Consideration should be given to the relevant clinical guidelines on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

Hypersensitivity to fosfomycin trometamol or to any of the excipients.

Patients with severe renal insufficiency (creatinine clearance < 10 ml/min).

Patients undergoing haemofiltration, haemodialysis or peritoneal dialysis.

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.

Gender

The three pivotal trials US-MON-01, US-MON-02 and US-MON-03 were conducted in female patients only. However, there is extensive early clinical trial and post-marketing experience in males. There do not appear to be any gender-associated differences in the safety profile of MONUROL. Efficacy data in male patients with urinary tract infection (UTI) is limited so MONUROL is not recommended in males.

Hypersensitivity

Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment and may be life-threatening (see **ADVERSE EFFECTS**). If such reaction occurs, fosfomycin should never be re-administrated and an adequate medical treatment is required.

Antibiotic-associated Diarrhoea

Antibiotic-associated diarrhoea has been reported with use of nearly all antibacterial agents, including fosfomycin (see **ADVERSE EFFECTS**) and may range in severity from mild diarrhoea to fatal colitis. Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with MONUROL (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (CDAD). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with MONUROL. If CDAD is suspected or confirmed, appropriate treatment should be initiated without delay.

Renal Insufficiency

Urinary concentrations of fosfomycin remain effective for 48 hours after a usual dose if creatinine clearance is above 10 ml/min.

Effects on Fertility

Fosfomycin had no effect on fertility in male and female rats at doses up to 1000 mg/kg/day (3-times the clinical dose relative to body surface area). No data are available in humans.

Use in Pregnancy

Pregnancy Category B2

Fosfomycin was not found to be teratogenic in rats and rabbits when tested at doses of up to 1000 mg/kg/day and 500 mg/kg/day, respectively (3– and 3.8–times the clinical dose relative to body surface area, respectively). Fetoxicity was observed in rabbits at doses ≥1000 mg/kg/day, which was secondary to maternotoxicity (maternal deaths and body weight losses). No adverse findings were reported in peri-postnatal studies in rats treated at up to 1000 mg/kg/day (3-times the clinical dose relative to body surface area).

In early clinical trials and in the post-marketing period, at least 1400 pregnant human patients are known to have received fosfomycin during pregnancy, usually a 3 g single oral dose. Most patients received the drug during the second and third trimesters. There is no evidence based on review of human data that fosfomycin is associated with adverse foetal or maternal outcomes or teratogenicity. At the present time, single-dose antibacterial treatments are not considered suitable to treat urinary tract infections in pregnant women.

Use in Lactation

Fosfomycin is excreted in breast milk.

MONUROL therapy should therefore not be used in breastfeeding mothers unless the potential benefit outweighs the potential risks.

Paediatric Use

Experience in children with MONUROL 3 g is limited. The product is not recommended for children below the age of 12.

Use in the Elderly

Fosfomycin may be given in the elderly. In elderly patients with good renal function, pharmacokinetics, efficacy and safety appear similar to younger adults. For elderly patients with age-related or other renal insufficiency, see **Special Populations** section.

Genotoxicity

Fosfomycin was not found to be genotoxic under *in vitro* (bacterial reverse mutation assay, mammalian mutation assay, chromosomal aberration test) or *in vivo* conditions (mouse micronucleus test).

Carcinogenicity

Carcinogenicity studies in rodents have not been conducted. Based on the short-term use of fosfomycin and the lack of evidence of genotoxicity, fosfomycin is not anticipated to be carcinogenic.

Sucrose Content

MONUROL contains sucrose. Its use is not recommended in patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

Food

Food may delay the absorption of the active ingredient of MONUROL, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicine on an empty stomach or about 2 – 3 hours after meals.

Effects on Laboratory Tests

In post-marketing surveillance, three cases of increased INR (prothrombin time) and two cases of decreased INR (prothrombin time) were reported. No further clinical information is available regarding these patients. As fosfomycin does not bind to plasma proteins and does not undergo metabolism, an interaction with anticoagulant drugs of the coumarin type such as warfarin is not anticipated, although fosfomycin has not been studied in patients taking anticoagulants. Recommend monitoring of coagulation in patients receiving coumarins.

Effects on Ability to Drive and Use Machines

No specific studies have been performed but patients should be informed that dizziness has been reported. This may influence some patients' ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations of fosfomycin and should be avoided.

Other drugs that increase gastrointestinal motility may produce similar effects.

Cimetidine does not alter the pharmacokinetics of fosfomycin.

Interaction studies with metoclopramide and cimetidine have only been performed in healthy adult volunteers aged 20 years and over. No other drugs have been studied for potential interactions with fosfomycin. No drug interaction studies have been performed in humans aged less than 20 years.

Concomitant usage with urinary alkalinisers is not recommended. MONUROL is most bactericidal at typical urinary pH. Also, potential for resistance development appears less at acid pH.

ADVERSE EFFECTS

The majority of clinical trials have been conducted in adult or adolescent females aged 12 years or above. The most common adverse reactions following the single 3 g dose of fosfomycin trometamol involved the gastrointestinal tract, mainly diarrhoea. These events were usually self-limited in duration and resolve spontaneously. Table 4 lists drug-related adverse events which occurred in 1% or more of fosfomycin recipients in the three pivotal trials.

Table 4: Drug-related adverse events occurring in >1% of fosfomycin recipients in the 3 pivotal efficacy and safety trials US-MON-01, US-MON-02 and US-MON-03

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

Adverse Events	Fosfomycin 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

The following list displays ADRs that have been reported with the use of MONUROL from either clinical-trial or post-marketing experiences.

The displayed frequency categories use the following convention:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated form the available data).

Infections and infestations:

Common: vulvovaginitis

Immune system disorders:

Not known: anaphylactic reactions including anaphylactic shock, hypersensitivity

Nervous systems disorders:

Common: headache, dizziness

Uncommon: paraesthesia

Cardiac disorders:

Rare: tachycardia

Vascular disorders:

Not known: hypotension

Respiratory, thoracic and mediastinal disorders:

Not known: asthma

Gastrointestinal disorders:

Common: diarrhoea, nausea, dyspepsia

Uncommon: vomiting, abdominal pain, anorexia, dry mouth, flatulence

Not known: antibiotic-associated colitis (see **PRECAUTIONS**), oral paraesthesias (temporary tingling of mouth, tongue and cheek), temporary alterations of taste (dysgeusia and hypogeusia)

Skin and subcutaneous tissue disorders:

Uncommon: rash, urticaria, pruritus

Not known: angioedema

General disorders and administration site conditions:

Uncommon: fatigue, asthenia

One patient in a pivotal trial developed unilateral optic neuritis, considered possibly related to MONUROL therapy.

DOSAGE AND ADMINISTRATION

The recommended dose for the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) is a single MONUROL 3 g sachet in women above 12 years of age.

MONUROL is for oral administration.

It should be taken on an empty stomach or about 2 – 3 hours after meals, preferably before bedtime and after emptying the bladder.

The dose should be dissolved into a glass of water and taken immediately after its preparation.

MONUROL should not be taken in its dry form. Always mix MONUROL with water before ingesting. Do not use hot water. MONUROL should be taken immediately after dissolving in water.

Paediatric population

The safety and efficacy of MONUROL 3 g in children below 12 years have not been established. No data are available.

OVERDOSAGE

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

Repeated dose studies by oral route showed that the no-effect dose was between 100 and 200 mg/kg after 4 weeks of treatment in dogs and rats, respectively.

Experience regarding the overdose of oral fosfomycin is limited. The following events have been observed in patients who have taken MONUROL 3 g in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception.

Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin.

In the event of overdose, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.

In case of overdose, immediately contact the Poisons Information Centre for advice (13 11 26).

PRESENTATION AND STORAGE CONDITIONS

MONUROL contains 3 g fosfomycin (as fosfomycin trometamol), presented as white granules for oral solution in single use sachet. The sachet is a four layer laminate comprising of paper, polyethylene, aluminium and polyethylene, and is supplied in an outer cardboard carton, one sachet per carton.

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR

Mayne Pharma International Pty Ltd

ABN 88 007 870 984

1538 Main North Road

Salisbury South, SA 5106

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

4 September 2017

Monurol is a registered trade mark of Zambon SpA used under licence.