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Fosfomycin – what was old is new again

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Introduction

With the rising prevalence of antibiotic resistance in bacteria, there is a need to develop new antibiotics and re-visit older antibiotics where there are no available alternatives. Fosfomycin, first discovered in the 1960s[1] has a long history of use in some countries (including the United States, Japan and several European countries), particularly for urinary tract infections.[2] In Australia oral fosfomycin trometamol, previously only available via the Special Access Scheme, has recently been approved by the Therapeutic Goods Administration (TGA) for the management of acute uncomplicated urinary tract infections, in females over 12 years of age, caused by Enterobacteriaceae (including *Escherichia coli*) and *Enterococcus faecalis* where the standard recommended agents are not effective. Currently, it is not subsidised by the Pharmaceutical Benefits Scheme (PBS).

Mechanism of Action and Antimicrobial activity and resistance

Fosfomycin is a bactericidal antibiotic agent. It inhibits UDP-GlcNAc enolpyruvyl transferase, the first step of the synthesis of the bacterial cell wall.[3] This unique mechanism of action makes cross-resistance unlikely and allows fosfomycin to retain significant *in-vitro* activity against many gram positive and gram-negative pathogens, including multidrug resistant (MDR) strains.[4]

Fosfomycin is primarily active against gram negative urinary pathogens (Table 1).[5] It has poor activity against *Pseudomonas aeruginosa* and *Acinetobacter* spp.[6] Fosfomycin is active against both susceptible and multi-resistant strains of *E. coli* and *Klebsiella* spp., including strains producing extended spectrum beta-lactamases (ESBLs). In general fosfomycin is more active against *E. coli* than *Klebsiella* spp. producing ESBLs.[7] The drug also retains activity against some carbapenem-resistant *Enterobacteriaceae*.[5]

Obtaining fosfomycin susceptibility testing results in a clinically relevant time-frame can be a challenge for clinicians in Australia. It is also important to consider some technical concerns when interpreting susceptibility testing results. The two most commonly used testing standards in Australia, the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), offer simplified methods, which can be completed by most laboratories. The CLSI, but not EUCAST, offer disk zone diameter breakpoints for *Enterococcus faecalis* urinary isolates only[8] Both EUCAST and CLSI provide disk zone diameter breakpoints only for *E. coli* but recommend using a minimum inhibitory concentration (MIC) method of testing for other *Enterobacteriaceae*. It should be noted that the breakpoints for oral fosfomycin have been calibrated only for the treatment of uncomplicated urinary tract infections and are not applicable to more complex disease (e.g. bacteraemia). Furthermore, the only reliable method for

testing the MIC of fosfomycin is agar dilution, with the addition of glucose-6-phosphate[9, 10], which is rarely available in clinical laboratories. Fosfomycin susceptibility testing may therefore require referral to a reference laboratory, further delaying results, as fosfomycin is not typically included in 'first-line' testing and may only be completed once other resistance is detected or on request by the clinician.

Resistance mechanisms for fosfomycin are usually chromosomally encoded.[6] High mutational frequency *in vitro* does not often result in resistance or treatment failure *in vivo* probably due to the reduced fitness of the strains associated with mutation, particularly in *E. coli*. This could explain why the resistance rates for fosfomycin against common urinary pathogens such as *E. coli*, *Citrobacter* species, and *Proteus mirabilis* are low (i.e. less than 10%), even in countries where the antibiotic is commonly used.[5] There have been case reports of failure Klebsiella pneumoniae Carbapenemase (KPC)-producing *K. pneumonia when* fosfomycin is used as an adjunct therapy due to rapid selection of resistant variants.[11] Although plasmid-mediated resistance is rare, fosfomycin-modifying enzymes may also be encoded on transferable plasmids, especially in *E. coli*. This was initially reported in Japan and subsequently shown to be more pervasive in East Asia and China.[12, 13] Widespread penetration of these highly mobile plasmids, and the fosfomycin resistance genes they carry, has the potential to limit the efficacy of fosfomycin in the future. While it

is likely that fosfomycin resistance rates in Australia are currently low, we lack systematic microbiological surveys to evaluate this. Plasmid-mediated resistance appears to be increasing in neighbouring regions, and additional studies are required to understand the local resistance profile

Paediatrics

Fosfomycin has not been systematically studied in children and neonates, but numerous reports have documented success for various indications.[14-18] Significant adverse effects have not been reported in this population, despite prolonged courses in some cases.[19,14, 20] Dosing regimens used in children vary considerably. Oral doses of 100–200mg/kg/day (3-4 divided doses) have been used with good effect and without evidence of toxicity.[18]

Pregnancy

The pharmacokinetics of fosfomycin are unchanged by pregnancy.[21] Fosfomycin has been shown to be effective in the treatment of cystitis and asymptomatic bacteriuria in pregnancy and adverse events are uncommon.[22] It has been shown to cross the placenta. Although, available data is limited, fosfomycin has not been associated with teratogenicity (category B2). There are no reliable data on the use of fosfomycin during lactation.[23]

Renal Failure

Fosfomycin does not undergo hepatic metabolism and is primarily eliminated as unchanged drug by the kidneys through glomerular filtration. About 38% of the administered dose is eliminated in the kidneys.[23] Limited information is available regarding dosage adjustment in renal failure. The half-life of fosfomycin increases and urinary excretion decreases as renal function decreases.[24]

Pharmacokinetics and Toxicity

After a 3g oral dose administered to healthy female volunteers with normal renal function , large variability in urinary concentrations were reported. Concentrations remained above the EUCAST breakpoint of 32 mg/L in 100% of the volunteers over the first 24 hours, 67.5% for 48 hours, and 30% for 72 hours. This high variability observed in the pharmacokinetics of fosfomycin can potentially lead to inadequate drug exposure and a lack of clinical response.[25] In general, fosfomycin has good distribution into tissues, achieving clinically relevant concentrations in serum, kidneys, bladder wall and the prostate.[5, 24,26] Fosfomycin has also demonstrated antimicrobially effective concentrations in infected lung tissue of septic patients.[27]

The toxicity and adverse events associated with fosfomycin have not been investigated as rigorously as for newer agents, however most reports suggest a favourable safety profile.[5] The most common adverse effects are gastrointestinal with symptoms such as diarrhoea and nausea being reported with oral preparation in 2-8% of patients.[28] The adverse effects have mainly been evaluated following a

single oral dose, higher rates of gastrointestinal side effects may be seen with longer treatment courses.

Clinical use

Urinary tract infections are the most common infections worldwide, and members of the family *Enterobacteriaceae* are the main pathogens responsible. With the increase in antibiotic resistance there are limited treatment options, particularly for oral agents. Fosfomycin has been evaluated for the treatment of these infections when first line agents are no longer an option. [29]

Uncomplicated urinary tract infections (cystitis)

Most of the studies relating to fosfomycin efficacy have focused on uncomplicated urinary tract infection (cystitis) in adult females. Several comparative studies in patients with cystitis, using fluoroquinolones, trimethoprim–sulfamethoxazole, nitrofurantoin, amoxicillin-clavulanate and oral cephalosporins for 5 to 7 days compared to single dose oral fosfomycin, have shown similar clinical and microbiologic cure rates of between 75-95%.[2, 30, 31] Most of these studies have been performed with less stringent criteria and endpoints than would be typically used today. It should also be noted, that some of the antibiotics in the comparator arm of these studies are not recommended as first line therapy for the management of uncomplicated urinary tract infections in Australia. In addition, the duration of therapy is longer than the recommended guidelines.[32]

In a recently published randomized study by Huttner *et al*., nitrofurantoin administered 100 mg 3 times a day for 5 days was compared to a single 3-g dose of oral fosfomycin in women with uncomplicated cystitis. The authors reported clinical resolution of 70% in those patients receiving nitrofurantoin as compared to 58% for the fosfomycin group.[33] Although the findings of this study suggest that nitrofurantoin may have better clinical effectiveness compared to a single dose of fosfomycin, whether or not a multiple dose regimen of fosfomycin would have been more effective is not clear.[34]

Pyelonephritis and Prostatitis

Fosfomycin is primarily recommended (and registered) for use in females with uncomplicated cystitis. However, in patients with other types of urinary tract infection caused by multi-drug resistant bacteria it may be the only potential oral option for therapy. There is limited data available for the 'Off Label' use of fosfomycin. Management of these patients should be decided on an individual basis, weighing the potential advantages versus the risk posed by the lack of evidence related to both safety for longer durations of therapy as well as efficacy. In addition, treatment of these patients are complex and the treatment of these patients should be done in consultation with an expert in infectious diseases and/or clinical microbiology.

Falagas *et al*, in a systematic review of observational studies, reported that oral treatment with fosfomycin was clinically effective against cystitis and pyelonephritis caused by ESBL-producing *E. coli* .[35] However, the evaluation of patients in the sub group with pyelonephritis was only based on limited patient numbers and no randomized trials were included. For pyelonephritis, administration of multiple doses of oral fosfomycin seems appropriate, but this is based on limited pharmacokinetic data and the timing of the dosing intervals has not been defined. Even though it may be the only oral option in some cases, there are insufficient data to recommend fosfomycin for pyelonephritis or more severe manifestations, such as bacteraemia. In addition, clinicians should be aware of the higher likelihood of clinical failure with fosfomycin, and a higher risk of resistance developing, when treating urinary tract infections caused by gram-negative bacteria other than *E. coli*.[36]

Fosfomycin can be considered an alternative for the treatment of prostatitis because of its high oral bioavailability and ability to attain concentrations in prostatic tissue.[26] There have been case reports of patients with failure to first-line therapy for acute prostatitis caused by ESBL-producing *E. coli* who were subsequently cured with a prolonged course of 3 grams once daily oral fosfomycin.[37] A retrospective case series evaluated patients who failed first line treatment for chronic bacterial prostatitis

including patients with MDR *Enterobacteriaceae*. The patients received 3 grams oral fosfomycin every 48 to 72 h for 6 weeks. After a median follow-up of 20 months, 7 patients (47%) had a clinical response.[38] Fosfomycin may also prove to be a useful alternative in the prevention of trans-rectal ultrasound-guided prostate biopsy related infectious complications in patients with a high risk of quinolone-resistance.[39]

Infections outside of the urinary tract

The in vitro activity of fosfomycin against MDR gram-negative organisms raises the hope that the drug may be used as oral therapy of infections outside of the urinary tract. From a clinical perspective, there are a small number of case reports in which orally administered fosfomycin has been used as follow-on therapy to intravenous antibiotics for significant extra-urinary infections.[40] However, it is not recommended except in exceptional circumstances, under very close monitoring. Based on the maximum concentrations reported for oral doses of fosfomycin it would appear unlikely that oral fosfomycin alone would prove useful for most non-urinary infections.[41] In these patients, intravenous fosfomycin may be considered. Intravenous fosfomyicn has been administered in critically ill patients with sepsis or nosocomial-acquired infections due to MRSA, vancomycin-resistant *Enterococcus*, and multidrug-resistant (MDR) Gram negative bacteria, especially carbapenem-resistant *K. pneumoniae*, in combination with other antibiotics.[42]

The effectiveness of intravenous fosfomycin has been evaluated in many studies which is beyond the scope of this review.[43, 44] The intravenous formulation in Australia can only be accessed as an unapproved medications utilising the following mechanisms:

- The Special Access Scheme in Australia allows prescription of an unapproved drug to a named patient where there are no currently available treatment options. There are provisions to supply drugs urgently for life threatening infections (category A applications).
- An "authorized prescriber" status can be designated for expert physicians to prescribe unapproved antimicrobials where indicated. Although approval is not required for each patient individually, reports must be provided 6 monthly on the number of patients treated.

How should oral fosfomycin be used in Australia?

Most of the evidence for oral fosfomycin relates to its use in uncomplicated urinary tract infections, for which this agent has a long history of use in other countries. The availability of another therapeutic option in the era of increasing antimicrobial resistance is welcome. It is recognized that older generic antibiotics, such as fosfomycin, are rarely commercially viable. However, while it would seem an attractive option as a single dose treatment, the available evidence suggests that it

may not be as effective as other agents for uncomplicated urinary tract infections. Therefore, its use should be reserved for patients where there is resistance to other first-line antibiotics, or where other agents are not tolerated. Although evidence for the use of fosfomycin for more complicated infections is limited, its use can be considered where resistance limits the use of other options, particularly in ESBL-or carbapenemase producing organisms.

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Table 1. Spectrum of fosfomycin activity

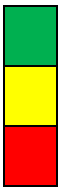
	Organism	Susceptibility
Gram positive	*Staphylococcus* spp.	
	Enterococcus faecalis	
	Enterococcus faecium	
Gram negative	*Escherichia coli*	
	Klebsiella spp.	
	Acinetobacter spp.	
	Pseudomonas aeruginosa	
	Citrobacter species	
	Proteus spp.	
	Providencia spp.	
	Bacteroides fragilis	

Code:

Highly susceptible

Moderately susceptible

Poor activity



References

1 Hendlin D, Stapley EO, Jackson M, Wallick H, Miller AK, Wolf FJ*, et al.* Phosphonomycin, a new antibiotic produced by strains of streptomyces. *Science*. 1969; **166**: 122-3.
2 Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI*, et al.* Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2010; **65**: 1862-77.
3 Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci*. 1974; **235**: 364-86.
4 Bergen PJ, Landersdorfer CB, Lee HJ, Li J, Nation RL. 'Old' antibiotics for emerging multidrug-resistant bacteria. *Curr Opin Infect Dis*. 2012; **25**: 626-33.
5 Frimodt-Moller N. Fosfomycin. In: Grayson LM (ed.). *Kucers' the use of antibiotics*. Vol. 6. London: Hodder Arnold 2010; 935-44.
6 Pogue JM, Marchaim D, Kaye D, Kaye KS. Revisiting "older" antimicrobials in the era of multidrug resistance. *Pharmacotherapy*. 2011; **31**: 912-21.
7 Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. *Clin Microbiol Rev*. 2016; **29**: 321-47.
8 Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 28th ed.

CLSI supplement M100 (ISBN 1-56238-838-X [Print]; ISBN 1-56238-839-8 [Electronic]). Clinical and Laboratory Standards

Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2018.
9 van den Bijllaardt W, Schijffelen MJ, Bosboom RW, Cohen Stuart J, Diederen B, Kampinga G*, et al.* Susceptibility of ESBL Escherichia coli and Klebsiella pneumoniae to fosfomycin in the Netherlands and comparison of several testing methods including Etest, MIC test strip, Vitek2, Phoenix and disc diffusion. *J Antimicrob Chemother*. 2018.
10 van Mens SP, Ten Doesschate T, Kluytmans-van den Bergh MFQ, Mouton JW, Rossen JWA, Verhulst C*, et al.* Fosfomycin Etest for Enterobacteriaceae: Interobserver and interlaboratory agreement. *Int J Antimicrob Agents*. 2018.
11 Karageorgopoulos DE, Miriagou V, Tzouvelekis LS, Spyridopoulou K, Daikos GL. Emergence of resistance to fosfomycin used as adjunct therapy in KPC Klebsiella pneumoniae bacteraemia: report of three cases. *J Antimicrob Chemother*. 2012; **67**: 2777-9.
12 Sastry S, Doi Y. Fosfomycin: Resurgence of an old companion. *J Infect Chemother*. 2016; **22**: 273-80.
13 Jiang Y, Shen P, Wei Z, Liu L, He F, Shi K*, et al.* Dissemination of a clone carrying a fosA3-harbouring plasmid mediates high fosfomycin resistance rate of KPC-producing Klebsiella pneumoniae in China. *Int J Antimicrob Agents*. 2015; **45**: 66-70.

14 Corti N, Sennhauser FH, Stauffer UG, Nadal D. Fosfomycin for the initial treatment of acute haematogenous osteomyelitis. *Arch Dis Child*. 2003; **88**: 512-6.
15 Taylor CG, Mascaros E, Roman J, Paz M, Santos M, Munoz A*, et al.* Enteropathogenic E. coli gastroenterocolitis in neonates treated with fosfomycin. *Chemotherapy*. 1977; **23 Suppl 1**: 310-4.
16 Wu TH, Huang FL, Fu LS, Chou CM, Chien YL, Huang CM*, et al.* Treatment of recurrent complicated urinary tract infections in children with vesicoureteral reflux. *J Microbiol Immunol Infect*. 2016; **49**: 717-22.
17 Li G, Standing JF, Bielicki J, Hope W, van den Anker J, Heath PT*, et al.* The Potential Role of Fosfomycin in Neonatal Sepsis Caused by Multidrug-Resistant Bacteria. *Drugs*. 2017; **77**: 941-50.
18 Careddu P, Borzani M, Varotto F, Garlaschi L, Fontana P. Trometamol salt of fosfomycin (Monuril). Preliminary pharmacokinetic and clinical experience in the treatment of urinary tract infections in children. *Eur Urol*. 1987; **13 Suppl 1**: 114-8.
19 Baquero F, Canedo E, Rodriguez A, Jaso E. Enteropathogenic Esch. coli gastroenteritis in premature infants and children treated with fosfomycin. *Arch Dis Child*. 1975; **50**: 367-72.
20 Katznelson D, Yahav Y, Rubinstein E. Fosfomycin in the treatment of cystic fibrosis. *Eur J Clin Microbiol*. 1984; **3**: 213.
21 Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clinical therapeutics*. 1999; **21**: 1864-72.
22 Keating GM. Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. *Drugs*. 2013; **73**: 1951-66.
23 Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *Int J Antimicrob Agents*. 2009; **34**: 506-15.
24 Michalopoulos AS, Livaditis IG, Gougoutas V. The revival of fosfomycin. *Int J Infect Dis*. 2011; **15**: e732-9.
25 Wijma RA, Koch BCP, van Gelder T, Mouton JW. High interindividual variability in urinary fosfomycin concentrations in healthy female volunteers. *Clin Microbiol Infect*. 2018; **24**: 528-32.
26 Gardiner BJ, Mahony AA, Ellis AG, Lawrentschuk N, Bolton DM, Zeglinski PT*, et al.* Is fosfomycin a potential treatment alternative for multidrug-resistant gram-negative prostatitis? *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014; **58**: e101-5.
27 Matzi V, Lindenmann J, Porubsky C, Kugler SA, Maier A, Dittrich P*, et al.* Extracellular concentrations of fosfomycin in lung tissue of septic patients. *J Antimicrob Chemother*. 2010; **65**: 995-8.
28 Mayama T, Yokota M, Shimatani I, Ohyagi H. Analysis of oral fosfomycin calcium (Fosmicin) side-effects after marketing. *Int J Clin Pharmacol Ther Toxicol*. 1993; **31**: 77-82.

29 Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG*, et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011; **52**: e103-20.
30 Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. *International journal of antimicrobial agents*. 2007; **29**: 62-5.
31 Rodriguez-Bano J, Alcala JC, Cisneros JM, Grill F, Oliver A, Horcajada JP*, et al.* Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. *Archives of internal medicine*. 2008; **168**: 1897-902.
32 Antibiotic Experts Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Limited 2014.
33 Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N*, et al.* Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial. *Jama*. 2018; **319**: 1781-89.
34 Datta R, Juthani-Mehta M. Nitrofurantoin vs Fosfomycin: Rendering a Verdict in a Trial of Acute Uncomplicated Cystitis. *Jama*. 2018; **319**: 1771-72.
35 Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis*. 2010; **10**: 43-50.
36 Matthews PC, Barrett LK, Warren S, Stoesser N, Snelling M, Scarborough M*, et al.* Oral fosfomycin for treatment of urinary tract infection: a retrospective cohort study. *BMC Infect Dis*. 2016; **16**: 556.
37 Grayson ML, Macesic N, Trevillyan J, Ellis AG, Zeglinski PT, Hewitt NH*, et al.* Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs. *Clin Infect Dis*. 2015; **61**: 1141-3.
38 Los-Arcos I, Pigrau C, Rodriguez-Pardo D, Fernandez-Hidalgo N, Andreu A, Larrosa N*, et al.* Long-Term Fosfomycin-Tromethamine Oral Therapy for Difficult-To-Treat Chronic Bacterial Prostatitis. *Antimicrob Agents Chemother*. 2015; **60**: 1854-8.
39 Roberts MJ, Scott S, Harris PN, Naber K, Wagenlehner FME, Doi SAR. Comparison of fosfomycin against fluoroquinolones for transrectal prostate biopsy prophylaxis: an individual patient-data meta-analysis. *World J Urol*. 2018; **36**: 323-30.
40 Roberts MJ, Parambi A, Barrett L, Hadway P, Gardiner RA, Hajkowicz KM*, et al.* Multifocal abscesses due to multiresistant Escherichia coli after transrectal ultrasound-guided prostate biopsy. *The Medical journal of Australia*. 2013; **198**: 282-4.
41 de Cueto M, Lopez L, Hernandez JR, Morillo C, Pascual A. In vitro activity of fosfomycin against extended-spectrum-beta-lactamase-producing Escherichia coli and

Klebsiella pneumoniae: comparison of susceptibility testing procedures. *Antimicrob Agents Chemother*. 2006; **50**: 368-70.
42 Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant Klebsiella pneumoniae in critically ill patients: a prospective evaluation. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2010; **16**: 184-6.
43 Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis*. 2008; **46**: 1069-77.
44 Grabein B, Graninger W, Rodriguez Bano J, Dinh A, Liesenfeld DB. Intravenous fosfomycin-back to the future. Systematic review and meta-analysis of the clinical literature. *Clin Microbiol Infect*. 2017; **23**: 363-72.

Abstract

In Australia oral fosfomycin trometamol has recently been approved by the Therapeutic Goods Administration (TGA) for the management of acute uncomplicated urinary tract infections, in females over 12 years of age, caused by Enterobacteriaceae (including *Escherichia coli*) and *Enterococcus faecalis* where the standard recommended agents are not effective. In this review we summarise the place in therapy for oral fosfomycin trometamol and highlight the pharmacokinetic, resistance characteristics and potential toxicities of this agent.

Key words: fosfomycin, fosfomycin trometamol, urinary tract infections, cystitis

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