Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fosfomycin trometamol

Proprietary Product Name: Monurol

Sponsor: Mayne Pharma International Pty Ltd

September 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AGAR	Australian Group on Antimicrobial Resistance
AE	Adverse event
ARESC	Antimicrobial Resistance Epidemiological Survey on Cystitis
AUC_{24h}	Area under the concentration-time curve at 24 h
AURA	Antimicrobial Use and Resistance in Australia
Ccr	Creatinine clearance
CFU/mL	Colony forming units per millilitre
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration or peak
C_{min}	Minimum concentration or trough
ESBL	Extended spectrum betalactamase-producing
ESCAPPM	Enterobacter, Serratia, Citrobacter, Aeromonas, Proteus vulgaris, Providencia, Morganella species
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDIU	Fetal death in utero
FT	Fosfomycin
G6PD	Glucose-6-phosphate dehydrogenase
IDSA	Infectious Diseases Society of America
INR	International normalised ratio
ITT	Intention to treat
MIC	Minimum inhibitory concentration
MITT	Modified intention to treat
MRSA	Methicillin-resistant Staphylococcus aureus

Abbreviation	Meaning
MSSA	Methicillin-susceptible Staphylococcus aureus
NCCLS	National Committee for Clinical Laboratory Standards
NF	Nitrofurantoin
PD	Pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
RMP	Risk management plan
SAE	Severe or serious adverse event
SAS	Special Access Scheme
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
spp.	Species
$T_{1/2}$	Half-life
T_{max}	The amount of time that a drug is present at the maximum concentration in serum
TMP / SMX	Trimethoprim / sulfamethoxazole
UTI	Urinary tract infection
VRE	Vancomycin-resistant enterococci
VSE	Vancomycin-susceptible enterococci

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	31 August 2017
Date of entry onto ARTG	4 September 2017
ARTG number:	278658
Active ingredient:	Fosfomycin trometamol
Product name:	Monurol
Sponsor's name and address:	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South SA 5106
Strength / dose form:	Eight (8) g sachet containing 5.6 g fosfomycin trometamol salt granules equivalent to 3 g fosfomycin free base for preparation in water and administration as oral solution
Approved therapeutic use:	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.
Route of administration:	Oral
Dosage:	Single dose once daily

Product background

This AusPAR describes the application by the sponsor to register Monurol (fosfomycin trometamol) as a new chemical entity for the following indication:

> *Monurol is indicated only for the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in women 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.*
>
> *Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Monurol. However, when there is reason to believe an infection may involve any of the susceptible organisms (see PHARMACOLOGY), therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate. If persistence or reappearance of bacteriuria occurs after treatment with Monurol, other therapeutic agents should be selected (see PRECAUTIONS and CLINICAL TRIALS section).*

Acute uncomplicated lower UTI (acute cystitis) is very common (around 6% of adult women per year). The most common single uropathogen in uncomplicated lower UTI across all ages is Escherichia coli (70 to 95%), followed by Staphylococcus saphrophyticus (5-10%) in younger women with other Gram negative bacilli such as Proteus, Klebsiella, Enterobacter and Pseudomonas spp. becoming implicated with increasing age especially in institutional care situations. Symptomatic UTI is very common in women aged 20-50 years but it is rare in men under 50 years. Australian laboratories currently do not routinely test sensitivity to fosfomycin.

A single dosage form and strength is proposed for marketing, that is, a sachet weighing 8 g containing 5.6 g fosfomycin trometamol salt, equivalent to 3 g free fosfomycin base, presented as white granules. Each sachet contains more than 2 g sucrose.

The recommended dose in acute, uncomplicated, lower UTIs is a single Monurol sachet in women above 12 years of age. It should be taken on empty stomach or about 2 to 3 h after meals, preferably before bedtime and after emptying the bladder. A single Monurol sachet is dissolved in a glass of water and taken immediately after preparation.

The formulation proposed for marketing is the same as that used in the pivotal efficacy trials with the exception of the flavouring agent. The proposed formulation has been used for many years without modification in several countries. This is the first ever submission of this agent in Australia. In Australia, fosfomycin oral sachet has had limited availability on the individual named patients Special Access Scheme (SAS) for unregistered medicines, but that has usually been in cases of failed treatment with the available agents and usually more than one dose is requested. The most frequently requested dose under SAS has been once daily on alternate days for a total of 3 doses.

Regulatory status

At the time of this submission to TGA, fosfomycin trometamol had been available for use in lower UTIs in many overseas jurisdictions since 1980s and is approved in the US, UK, Canada, Switzerland and Singapore, among numerous countries.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Registration timeline.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 August 2016
First round evaluation completed	15 February 2017
Sponsor provides responses on questions raised in first round evaluation	18 April 2017
Second round evaluation completed	26 May 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	30 June 2017
Sponsor's pre-Advisory Committee response	18 July 2017
Advisory Committee meeting	4 August 2017
Registration decision (Outcome)	31 August 2017
Completion of administrative activities and registration on ARTG	4 September 2017
Number of working days from submission dossier acceptance to registration decision*	209

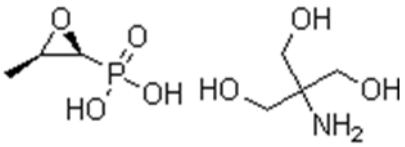
* Legislative timeframe is 255 working days

III. Quality findings

Introduction

Fosfomycin is an irreversible inhibitor of bacterial enolpyruvate transferase. The chemical structure of the trometamol salt is as shown below. The molecular formula is $C_7H_{18}NO_7P$ and the molecular weight is 259.2.

Figure 1: Chemical structure of trometamol salt.



The maximum daily dose in the proposed PI is 3 g of the free base (equivalent to 5.6 g of the trometamol salt) taken as a single dose.

The product is to be packaged in laminated PE/Al/PE/paper sachets in packs of one sachet.

Drug substance (active ingredient)

Fosfomycin trometamol is very soluble in water, slightly soluble in 95% ethanol and methanol, and almost insoluble in acetone, ether, and chlorinated solvents. It has a melting range between 116 °C and 122 °C and pKa values for the phosphonic acid moiety of 2.5 and 6.7, and a 5% aqueous solution has specific optical rotation of -13.5° to -12.5° and a pH of 4.0-5.0. The structure contains two stereogenic centres and the drug substance is the 2*R*,3*S* isomer. The drug substance is obtained as a single crystalline form.

Particle size is not controlled by the drug substance manufacturer. This is acceptable as the product is dissolved in water before administration.

Polymorphic form is not controlled by the drug substance manufacturer. This is acceptable as the product is dissolved in water before administration.

The drug substance complies with the BP/Ph Eur monograph.

Drug product

Fosfomycin trometamol was chosen as the drug substance on the basis of its solubility and literature reports of its use in products for oral administration.

The excipients were chosen to provide rapid dissolution and a pleasant taste to the finished product.

A detailed description of the development of the drug product has not been provided as the formulation proposed for registration in Australia has been marketed for many years in a number of other countries. This is acceptable as the manufacturing process is relatively simple.

The formulation used in all clinical trials is the same as that proposed for registration with the exception of a change to the orange flavouring ingredient.

No evidence has been provided to demonstrate the stability of the drug product after reconstitution. This will not be pursued as the directions for use in the PI state that the dose should be taken immediately after preparation.

The product is manufactured by a standard process for granules for oral solution and packaged in a suitable container system.

The proposed shelf life for the unopened product is 18 months when stored below 25°C.

Biopharmaceutics

Peak urinary concentrations of fosfomycin trometamol occur within 4 h after administration of a 3 g oral dose. Absolute bioavailability after oral administration is 31 to 58%.

Food delays absorption, but does not affect its extent. Fosfomycin does not appear to be metabolised.

Fosfomycin is distributed to the kidneys, bladder wall, prostate, and seminal vesicles, and urine concentrations are above the minimum inhibitory concentration (MIC) for 24 to 48 h after oral administration. Fosfomycin is not bound to plasma proteins.

No information on the potential for in vivo interconversion of enantiomers has been provided. The evaluator considers that in vivo interconversion of enantiomers is unlikely as any conditions or reactions that could conceivably lead to this would be more likely to result in ring-opening of the epoxide instead.

Fosfomycin is eliminated primarily via renal excretion as unchanged drug, with 40 to 50% of an oral dose recovered in urine. The appearance of a second serum peak between 6 and 10 h after administration suggests that fosfomycin is subject to enterohepatic recirculation. The mean terminal half-life is about 4 h.

The rate of elimination is proportion to glomerular filtration rate.

Absorption of an oral dose may be dose-dependent, with one study reporting approximately 51% of a 2 g dose, 32% of a 3 g dose, 24% of a 4 g dose, and 22% of a 5 g dose recovered in urine, although another study reported dose proportionality.

Conclusion

During the initial evaluation stage, the study report provided was more than twenty years old and some aspects of the conduct of the study were not consistent with current requirements. Key details that were missing from the study included the quality control documents for the products used in the study, the washout period between treatments, and individual patient data.

In addition, the assay method validation report did not adequately demonstrate the specificity of the method or the stability of the analyte under the conditions experienced during sample analysis and long-term storage, the acceptance criteria for analytical runs did not meet current standards, and the statistical analyses performed did not include calculation of confidence intervals for the results.

Given the age of the study, it was unlikely that these issues could be satisfactorily addressed. While there was no evidence to suggest that the results and conclusions of the study were incorrect, and the results appeared to be broadly consistent with results reported in literature references provided, the information and data provided were not sufficient to confirm that the results were correct.

The evaluator concluded that the clinical consequences were a matter for the clinical evaluator to assess.

Quality summary and conclusions

The stability data are sufficient to support the proposed shelf life provided the limits for assay and related substances are amended to be consistent with the observed trends.

The dossier includes a report of a bioavailabilty/bioequivalence study which concluded that the absolute bioavailability (AUC_{oral}/AUC_{iv}) of a 3 g oral dose of fosfomycin (as trometamol) was 37% under fasted conditions and 30% under fed conditions, and that the relative bioavailability under fed conditions (AUC_{fed}/AUC_{fasted}) was 81%.

The sponsor was asked a number of questions regarding the drug substance, drug product, and bioequivalence. On provision of this data, the information was considered acceptable, and approval of the registration was recommended with respect to pharmaceutical chemistry aspects.

IV. Nonclinical findings

Overall quality of the dossier

The overall quality of the nonclinical dossier was generally consistent with the International Conference on Harmonisation (ICH) guideline for the nonclinical assessment of pharmaceuticals (ICH M3).[1] However, the resistance data did not appear to have been updated from the original overseas submissions. Due to the age of many of the submitted toxicology studies (that is, around that is, 1980), only a few were conducted according to Good Laboratory Practice (GLP). Several study reports stated that GLP regulations came into effect in Italy in 1986. During evaluation of the Investigational New Drug by the FDA in 1991, the FDA requested that several toxicology study reports be rewritten to identify areas of non-GLP compliance. Toxicokinetic data were lacking for most studies, as well, the report for the safety pharmacology studies did indicate GLP compliance. Nevertheless, design aspects (that is, group sizes, dose ranges, dose timing, and use of control groups) of all these studies were considered acceptable and generally consistent with recommendations from the relevant guidance documents.

Primary pharmacology

Mechanism of action

Fosfomycin is a phosphonic acid antibiotic of natural origin that confers bactericidal activity by inhibiting cell wall biosynthesis via the enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), which catalyses the initial step in the synthesis of peptidoglycan. Cell permeability governs the extent of sensitivity of a bacterium to fosfomycin. Specifically, fosfomycin is primarily taken up by cells by the L-α-glycerophosphate transport system (GlpT), or by the phosphate uptake system (hexose phosphate system, UhpT), which is dependent on the presence of glucose-6-phosphate. Hydrolysis of the epoxide ring of fosfomycin results in its inactivation, and occurs at low pH; therefore, its development as a trometamol salt is intended to offer protection against acidic hydrolysis in the gastric environment.[2] Other factors also influence fosfomycin activity (albeit under in vitro conditions) including the use of urine as culture medium where minimum inhibitory concentrations (MICs) are higher than when nutrient broth is used. MIC levels are also higher (and therefore antimicrobial activity is lower) with higher pHs, as well as higher levels of phosphate. High levels of phosphate in testing media inhibit the primary mechanism for fosfomycin uptake by bacterial cells, but this is circumvented by the inclusion of glucose-6-phosphate which activates an alternative fosfomycin uptake mechanism, the hexose phosphate system.

Susceptibility testing

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set fosfomycin clinical MIC breakpoints for the Enterobacteriaceae (Escherichia coli, Proteus mirabilis, Klebsiella, Serratia and so on) of ≤ 32 µg/mL (susceptible) and >32 µg/mL (resistant). These apply only to uncomplicated UTI, and a single oral dose of 3 g of fosfomycin. In 2017, fosfomycin zone diameter breakpoints of ≥ 24 mm (susceptible) and

[1] M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

[2] Bundgaard H. (1980). Acid catalysed hydrolysis of fosfomycin and its implication in oral absorption of the drug. Intl. J. Pharmaceutics, 6, 1–9.

< 24 mm (resistant), for E. coli only, have been added. For other Enterobacteriaceae, an MIC method should be used.

The current USA CLSI breakpoints are ≤ 64 (susceptible), 128 (intermediate) and ≥ 256 µg/mL (resistant), and zone diameters of ≥ 16 (susceptible), 13 to 15 (intermediate), and ≤ 12 mm (resistant). These refer only to Enterococcus faecalis and Escherichia coli urinary isolates.

Antimicrobial susceptibility in vitro

The most common pathogen causing UTI is E. coli, other causative pathogens are P. mirabilis and Klebsiellia pneumonia (Enterobacteriaceae), Staphylococcus saprophyticus, Pseudomonas aeruginosa, and Enterococcus faecalis. Antimicrobial susceptibility to fosfomycin was assessed against a panel of bacterial isolates associated with UTIs.[3] Susceptibility was most apparent against E. coli, P. mirabilis, Haemophilus spp., methicillin-sensitive S. aureus, Citrobacter spp., and Group D streptococci (MIC_{90} values ≤ 16 µg/mL). Negligible activity was noted against Pseudomonas spp., Clostridium spp., Bacteroides spp., Proteus spp., Serratia spp., Acinetobacter spp., S. saprophyticus and M. morganii. Fosfomycin exhibits moderate antimicrobial activity relative to other antibiotic agents. Norfloxacin, enoxacin and ciprofloxacin had greater activity than fosfomycin in susceptible strains, whereas trimethoprim, ampicillin, azlocillin, cefuroxime and cotrimoxazole showed lower activity.

An ECO-SENS survey encompassing a number of European nations and Canada evaluated the susceptibility of bacteria that cause uncomplicated UTIs to fosfomycin and found a favourable profile against known susceptible strains (E. coli 0.7%; P. mirabilis 3.1% resistant) but less favourable against other strains (Klebsiella spp 56.7%; S. saprophyticus 100% resistant). Compared to other antimicrobial agents, resistance to fosfomycin by E. coli and P. mirabilis was lower than resistance to ampicillin, sulfamethoxazole or trimethoprim but higher than resistance to ciprofloxacin and Co-amoxiclav.[4]

More recent studies were reported in the Antibiotic Resistance Risk Assessment. In a review;[5] of 17 susceptibility studies with a total of 5057 clinical isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs (4448 were EBSL-producing), 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin. Using a breakpoint of < 64 µg/mL, 96.8% of 1657 E. coli isolates producing EBSL, and 81.3% of Klebsiella pneumoniae isolates were susceptible to fosfomycin. Zhanel;[6] summarised 11 papers on fosfomycin susceptibility using isolates from various sources, including urine. Fosfomycin MICs for E. coli (MIC_{90} = 2 to 16 mg/L), Citrobacter spp. and Proteus spp. were lower than for Klebsiella spp., Enterobacter spp. and Serratia spp. Most isolates of P. aeruginosa were resistant, Acinebacter spp. appeared inherently resistant.

The EUCAST Rationale for clinical breakpoints (online version 1.0, 15 February 2013) has a table of MIC distributions from multiple sources and time periods. Applying the fosfomycin susceptibility breakpoint of < 32 mg/L, the table indicates susceptibility for

[3] Reeves DS, Holt HA, Bywater MJ (1987). In vitro study of fosfomycin trometamol. New Trends in Urinary Tract Infections. Neu, Williams (eds.), 224–231; Barry AL & Fuch PC (1991). In vitro susceptibility testing procedures for fosfomycin trometamol. Antimicrob Agents Chemother., 35(6), 1235–1238; Brown AL & Brown SD (1995). Antibacterial spectrum of fosfomycin trometamol. J. Antimicrob. Chemother., 35, 228–230.
[4] Kahlmeter G (2002). An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECOS-SENS project. J Antimicrob Chemother 51: 69-76.
[5] Falagas ME et al (2010). Fosfomycin for the treatment of multidrug-resistant, including extended–spectrum btea-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis 10(1): 43-50.
[6] Zhanel GG et al (2016). Fosfomycin: a first-line oral therapy for acute uncomplicated cystitis. Canadian Journal of Infectious Diseases and Medical Microbiology Article ID 2082693, 10 pp.

Citrobacter spp, Escherichia coli, Klebsiella spp., Proteus spp., and Staphylococcus aureus, whereas Actinobacter spp. were usually resistant.

No fosfomycin susceptibility data specific to Australia were submitted, fosfomycin has only been available under the SAS in Australia.

Resistance development in vitro

The Antimicrobial Resistance Risk Assessment identified 9 studies on the development of fosfomycin resistance mutations in vitro. In general, resistant mutants developed rapidly, particularly for strains of P. aeruginosa or K. pneumonia compared to E. coli strains. Mutation frequencies were high in relation to comparator antibiotics.

Despite the relatively high rate of fosfomycin resistance development in vitro, major decreases in clinical isolate susceptibility to fosfomycin over time have not been reported (see below). This may be due to the high concentrations of fosfomycin achieved in urine (mean peak 706 ± 466 µg/mL, US label) 20 to 4 h after a single 3g oral dose (fasted state). Fosfomycin resistance mutations may also reduce bacterial fitness,[7] and/or adhesion to epithelial cells. However, Rodriguez-Rojas[8] reported that fosfomycin resistance in Pseudomonas aeruginosa was not associated with a fitness cost in a mouse model of lung infection.

Changes in fosfomycin susceptibility with clinical use over time

Fosfomycin has been registered in a number of countries since the 1990s (Switzerland 1988, U.K. 1992, USA 1996, Netherlands 1997, Canada 1999), and the Antibiotic Resistance Risk Assessment identified 12 European studies which examined susceptibility rates over time, mainly for E. coli urinary isolates. Eight of these studies were conducted in Spain, 3 in France, and 1 in Italy between 1977 and 2009. In all 3 countries fosfomycin is also used IV for treatment of systemic infections. None of the studies reported major declines in fosfomycin susceptibility over time. However, one Spanish study[9] of UTIs caused by ESBL-producing E. coli found an increase in fosfomycin resistance in from 4.4% in 2005 to 11.4% in 2009, which correlated with a 50% increase in nationwide community use of fosfomycin. In the sponsor's post-first round response, the sponsor provided a review;[10] of 84 studies of fosfomycin susceptibility published between January 2010 and June 2015. Susceptibility of S. aureus ranged between 33.2 to 100% (frequency 91.7%, 95% CI 88.7 to 94.9%), Enterococcus spp. 30 to 100% (92.6%, 95% CI 85.2 to 100%), Enterococcus faecalis 96.8%, 92.5 to to 100%), ESBL-producing E. coli 81 to 100% (95.1%, 94.3 to 95.9%), ESBL-producing Klebsiella pneumoniae 15 to 100% (83.8%, 78.7 to 89.4%), and carbapenem-resistant K. pneumoniae 39.2 to 100% (73.5%, 66.4 to 81.4%). The review identified two studies in Spain in which an increasing trend in resistance in E. coli was identified. Rodriguez-Avail[11] reported a decrease from 100%

[7] Karageorgopoulos et al (2012). Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J. Antimicrobial Chemotherap. 67(2): 255-268; Nilsson AI et al (2003). Biological costs and mechanisms of fosfomycin resistance in Eschericia coli. Antimicrob. Agents and Chemotherapy 47(9): 2850-2858.
[8] Rodriguez-Rojas A et al (2010). Assessing the emergence of resistance: the absence of biological cost in vivo may compromise fosfomycin treatments for P. aeruginosa infections. PLOS ONE 5(4): e10193. doi: 101371.
[9] Oteo J et al (2010). Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum-β-lactamase (ESBL)-producing Escherichia coli. J. Antimicrobial Chemother. 65(11): 2459-2463.
[10] Vardakas KZ et al (2016). Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature. Int J of Antimicrobial Agents 47:269-285.
[11] Rodriguez et al (2013). Increasing prevalence of fosfomycin rsistance in extended-spectrum β-lactamase (ESBL-producing Eschericia coli urinary isolates (2005-2009-2011). Dept Microbiology, Complutense University in Madrid.

susceptibility in 2005 to 85.6% in 2011, and Tena[12] reported a decrease in E. coli susceptibility from 97.8% in 2003 to 95.5% in 2007. Two Japanese studies were also submitted, where fosfomycin is also used IV. Shimizu[13] reported little change in 412 clinical isolates of Pseudomonas aeruginosa from across Japan in 1996 from that reported in 1975, and Hara[14] reported that strains of methicillin-sensitive S. aureus, methicillin-sensitive coagulase-negative Staphylococci and E. coli isolated during 2000-2001 had similar sensitivity to fosfomycin as isolates collected in 1975. These studies were limited by lack of information on fosfomycin usage.

Bactericidal activity

Fosfomycin was bactericidal against sensitive strains at close to MIC levels.[15] Bactericidal activity was evident against a number of strains of E. coli, P. mirabilis, E. cloacae, Proteus spp., K. pneumonia, S. faecalis and S. aureus at fosfomycin concentrations ≥ 1000 µg/mL under in vitro conditions. This compared favourably to norfloxacin bactericidal activity against these species. Complete sensitivity to fosfomycin was evident by 8 h exposure (> 99% kill rate).

It is unclear whether fosfomycin exhibits time- or concentration-dependent killing,[16] and data are limited. Primarily concentration-dependent fosfomycin killing of a single strain each of E. coli and Proteus mirabilis in vitro, with a post-antibiotic effect, was reported by Mazzei.[17] MacLeod;[18] reported time-dependent killing and a PAE for single strains each of S. aureus and P. aeruginosa.

Effect on adhesion to uroepithelial cells

Adhesion of bacteria to urinary epithelial cells is a key step in bacterial colonisation of the urinary tracts and accounts for the persistence of urinary tract infections. Fosfomycin reduced adhesive activity of bacterial strains E. coli, P. mirabilis and S. agalactiae to < 50% of control levels at subminimal MIC levels and to a comparable extent as norfloxacin.[19] This effect was evident within an h of exposure to fosfomycin trometamol when tested on human uroepithelial cells under in vitro conditions.

[12] Tena D et al (2010). Changes in the antimicrobial susceptibility of Eschericia coli isolates from community-diagnosed urinary tract infections during the period 2003-2007. Multicentre study in Castile la Mancha (Spain). Rev Esp Quimioter 23(1): 36-42.
[13] Shimizu M et al (2000). Novel fosfomycin resistance of Pseudomonas aeruginosa clinical isolates recovered in Japan in 1996. Antimicrob. Agents Chemother. 44(7): 2007-8.
[14] Hara T et al (2002). Antibacterial activities of fosfomycin against several fresh clinical isolates – comparison of the test methods for antibacterial activity. Japan J. Antibiotic 55(6): 844-854.
[15] Albini E, Arena E, Belluco G, Marca G (1987). Adhesion of bacteria to human uroepithelial cells and bactericidal activity of fosfomycin trometamol. New Trends in Urinary Tract Infections. Neu, Williams (eds.), 250–254; Cornaglia G, Pompei R, Foddis G, Satta G (1987). Antibacterial activity of fosfomycin trometamol in an in vitro model of the urinary bladder. New Trends in Urinary Tract Infections. Neu, Williams (eds.), 255-260; Lerner SA et al (1988). Microbiological studies of fosfomycin trometamol against urinary isolates in vitro. Neu, Williams (eds) New Trends in Urinary Infections. Int Symp. Rome 1987. Pp 121-129, Basel; Pinasi C, Albini E, Marca G (1987). Correlation between bactericidal activity of fosfomycin trometamol in an in vitro model of the urinary bladder and susceptibility testing. Eur. Urol., 13(1), 80–85; Ravizzola G et al (1987) In vitro study of the antibacterial activity of fosfomycin trometamol against microorganisms of the urinary tract. BML Quarterly Review of Laboratory Science 3: 53-62.
[16] Perdigao-Neto LV et al (2014). Susceptibility of multiresistant Gram-negative bacteria to fosfomycin and performance of different susceptibility testing methods. Antimicrob Agents Chemotherap 58(3): 1763-1767.
[17] Mazzei T et al (2006). Pharmacokinetic and pharmacodynamics aspects of antimicrobial agents for the treatment of uncomplicated urinary tract infections. Int J Antimicrob Agents 28 Suppl 1: S35-41.
[18] MacLeod DL et al (2009). Antibacterial activities of a fosfomycin/tobramycin combination: a novel inhaled antibiotic for bronchiectasis. J of Antimicrobial Chemotherapy 64: 829-836.
[19] Carlone et al (1987). Effect of fosfomycin trometamol on bacterial adhesion in comparison with other therapeutic agents. Eur. Urol. 13(1): 86-91.

Mechanisms of resistance

Fosfomycin resistance mechanisms have been reviewed by Castaneda-Garcia.[20] Mechanisms underlying the development of resistance to fosfomycin are:

- Reduced permeability due to chromosomal mutations that affect genes associated with fosfomycin uptake into cells that is, the L-α-glycerophosphate and hexose phosphate[21] transport systems, GlpT and UhpT, respectively. This is the main mechanism of fosfomycin resistance. GlpT is the only fosfomycin transporter in Pseudomonas aeruginosa.[22] Transporter expression is regulated by uhpA, uhpB and uhpC, and inactivation of any of these genes can prevent fosfomycin uptake by E. coli.
- Antibiotic modification by catalytic opening of the epoxide ring.[23] Three such resistance proteins, fosA, fosB and fosX have been identified, they are divalent metal-ion dependent metalloenzymes. FosA is a plasmid-encoded glutathione S-transferase. The fosB gene occurs in plasmids and chromosomes and is a thiol-S-transferase. FosX is located chromosomally and is a Mn^{2+}-dependent epoxide hydrolyase. Another enzyme, fosC, inactivates fosfomycin by the addition of a phosphate group. Two novel enzymes, fosA3 and fosC2 have been described among CTX-M producing E.coli isolated in Japan.[24] Multi-resistant plasmids encoding fosA3 have emerged among CTX-M β-lactamase producing E. coli and K. pneumonia isolates in Asia. The fosA gene has recently been reported in Enterobacteriaceae clinical isolates (E. coli, K. pneumoniae, Morganella morganii) in Portugal, probably imported by travel from Asia.[25]
- Modification of the target enzyme MurA. This is reportedly a rare mechanism in clinical isolates. In E. coli, fosfomycin binds to the cysteine-115 residue of murA in the active site, and substitution of cysteine with aspartate confers resistance.[26] Other substitutions (Asp369 to Asn or Leu370 to Ile) might also confer E. coli resistance. Resistance can also occur by over-expression of MurA[27] in some clinical E. coli isolates.

Cross-resistance

Fosfomycin has a unique mechanism of action, targeting the MurA enzyme, it is the only member of its class, and significant cross-resistance has not been observed. A Canadian study[28] of E. coli isolates collected from UTI patients from 2010-2013 reported respective susceptibility rates of 99.4%, 97.9%, 99.1%, 100%, 100% and 100% for all, ciprofloxacin-resistant, TMP-SMX-resistant, ESBL-producing, AmpC-producing, and MDR isolates.

[20] Castaneda-Garcia A et al (2013). Molecular mechanisms and clinical impact of acquired and intrinsic fosfomycin resistance. Antibiotics 2(2): 217-236.
[21] Kadner RJ, Winkler HH (1973). Isolation and characterisation of mutations affecting the transport of hexose phosphates in Escherichia coli. J. Bacteriol. 113(2): 895-900.
[22] Castaneda-Garcia A et al (2009). The glycerol-3-phosphate permease GlpT is the only fosfomycin transporter in Pseudomonas aeruginosa. J. of Bacteriology 191(22): 6970-6974.
[23] Arca P et al (1988). Formation of an adduct between fosfomycin and glutathione: a new mechanism of antibiotic resistance in bacteria. Antimicrobial Agents and Chemotherapy 32(10): 1552-1556.
[24] Wachino J-I et al (2010). Prevalence of fosfomycin resistance among CTX-M-producing Eschericia coli clinical isololates in Japan and identification of novel plasmid-mediated fosfomycin-modifying enzymes. Antimicrob Agents and Chemotherapy 54(7): 3061-3064.
[25] Mendes AC et al (2016). Importation of fosfomycin resistance fosA3 gene to Europe. Emerging Infectious Diseases 22(2): 346-348.
[26] Kim DH et al (1996). Characterisation of a Cys115 to Asp substitution in the Escherichia coli cell wall biosynthetic enzyme UDP-GlcNAc enolpyruvyl transferase (MurA) that confers resistance to inactivation by the antibiotic fosfomycin. Biochemistry, 35(15), 4923-4928.
[27] Takahata S et al (2010). Molecular mechanisms of fosfomycin resistance in clinical isolates of Eschericia coli. Int. Journal of Antimicrobial Agents 35: 333-337.
[28] Karlowsky JA et al (2014). In vitro activity of fosfomycin against Escherichia coli isolated from patients with urinary tract infections in Canada as part of the CANWARD surveillance study. Antimicrobial Agents and Chemotherapy 58 (2): 1252-1256.

Fosfomycin retained activity against ESBL-producing, AmpC-producing, carbapenem-non-susceptible, and multidrug-resistant E. coli, as well as KPC-producing K. pneumonia.[29] Linsenmeyer[30] reported that fosfomycin resistance among E. coli and Klebsiella uropathogens collected between 2010 and 2013 in 3 US facilities was not significantly associated with resistance to other oral antibiotics (fluroquinolone, trimethoprim-sulfamethoxazole).

Antimicrobial effects in animal models of infection

In vivo demonstration of the antimicrobial effects of fosfomycin trometamol was provided in mouse and rat models of cystitis. Animals inoculated with E. coli, P. mirabilis or K. pneumonia were orally administered antimicrobial agents 2 h later and bacterial counts relative to untreated controls were assessed a further 24 h later, with bacterial counts $<10^3$ cfu/mL considered a measure of a resolved infection. In rats, fosfomycin reduced bacterial counts for E. coli and P. mirabilis, but only norfloxacin (200 mg/kg, PO) satisfied this benchmark against P. mirabilis (slightly less for K. pneumonia and E. coli).[31] As the intended site of antimicrobial action is the urinary bladder, measures of urinary recovery of fosfomycin indicated that mouse bladders were exposed to fosfomycin trometamol concentrations (0-6 h: 603 µg/mL; 6-24 h: 291 µg/mL) well above the MIC_{90} for E. coli (2 µg/mL) and P. mirabilis (64 µg/mL) but not for Klebsiella spp. (> 512 µg/mL) over the 24 h period. Overall, fosfomycin trometamol exhibited moderate antimicrobial activity in in vivo mouse and rat models of urinary tract infections.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic studies were not conducted. Specialised safety pharmacology studies assessed the pharmacological actions of fosfomycin trometamol in the CNS, cardiovascular, renal and gastrointestinal organ systems. The 1991 report did not indicate that the safety pharmacology studies were GLP-compliant. Studies on the CNS in mice found no evidence of effects on body temperature control, on spontaneous activity, motor coordination or pain reactivity by fosfomycin administered orally or through the intraperitoneal route. For cardiovascular system functions, fosfomycin administered by intravenous infusion in rats had no effect on ECG (although QTc prolongation was not determined) or respiratory parameters. Modest changes to blood pressure were noted from 45 minutes onwards but overall, were not considered biologically significant. Similarly no effects on respiratory or blood chemistry parameters (pH, pO_2, pCO_2) were observed in rabbits. In rats a modest reduction in diuresis was noted at fosfomycin doses ≥ 30 mg/kg, which resolved by 2 h post-dose. No treatment-related effects on gastrointestinal transit were evident in mice or rats. Overall, fosfomycin trometamol was found to exert minimal effects to organ system functions in mice, rats and rabbits.

A series of pharmacodynamic interaction studies were also provided that assessed antimicrobial activity of fosfomycin against commonly prescribed agents under in vitro and in vivo conditions. Interactions were assessed on whether they showed attributes denoting synergism, additive, absent interaction or antagonism. None of the tested antimicrobial agents (ciprofloxacin, cefonid, cotrimoxazole and nitrofurantoin) or hydrochlorothiazide showed evidence of antagonism of fosfomycin trometamol or vice

[29] Zhanel GG et al (2016). Fosfomycin: a first-line oral therapy for acute uncomplicated cystitis. Canadian Journal of Infectious Diseases and Medical Microbiology Article ID 2082693, 10 pp.
[30] Linsenmeyer K et al (2016). Activity of fosfomycin against extended-specturm-β-lactamase-producing uroopathogens in patients in the community and hospitalized patients. Antimicrobial Agents and Chemotherapy 60 (2):1134-1136.
[31] Dubini F & Riviera L (1988). Treatment of experimental cystitis in the rat with a single dose of fosfomycin trometamol. Chemioterapia. 7(1), 24–28.

versa. Similarly co-administration of paracetamol, aminophylline, diazepam or scopolamine did not affect the antimicrobial activity of fosfomycin trometamol in inoculated mice. Likewise, fosfomycin trometamol did not affect the pharmacological activities of aminophylline, butylscopolamine, morphine, paracetamol, diazepam or hydrochlorothiazide. Overall, fosfomycin trometamol is not anticipated to interact with the tested substances in a way that would affect their respective pharmacological activities.

Pharmacokinetics

The serum kinetics of fosfomycin, as the trometamol, calcium or disodium salt, were assessed in mice, rats and dogs. Single oral dose studies in mice and rats (conducted in female animals only) showed similar absorption profile between the calcium and trometamol salt form of fosfomycin. Absorption was rapid and attained maximum serum levels by 15 mins post-dose in mice and 1 to 2 h post-dose in rats. Repeat oral dose studies in rats showed no differences between male and females with regard to absorption. As well, serum exposure (as AUC) exhibited dose proportionality with increasing doses and there was no evidence of accumulation. Half-lives were however increased at higher doses. In dogs, absorption was slightly accelerated when the trometamol salt was used compared with calcium or disodium salt (2 versus 3 h); as well peak serum levels were higher compared to the calcium salt form.

Fosfomycin did not exhibit any appreciable protein binding when assessed using pooled human sera. In rats, tissue distribution of fosfomycin was rapid and wide with tissue T_{max} achieved in most tissues by 1 h. Trace levels were detected in brain tissues from a few animals but only at 1 h and 2 h post-dose. The set of tissues examined was not exhaustive and reproductive tissues and pigmented tissues (skin, eyes, uveal tract) were not assessed. Levels were highest in small intestine and kidneys, which decreased substantially by 4 h and was mostly eliminated by the end of the 24 h collection period. For the remainder tissues fosfomycin was mostly eliminated by 24 h with trace levels detected in the stomach, small intestine, lungs and plasma.

Metabolism of fosfomycin was not investigated. In a rat mass balance study most of the fosfomycin dose was shown to be excreted in urine unchanged (> 88%) with the remainder (also unchanged) excreted in the faeces (about 9%) by 48 h post-dose. Thus, it was surmised that fosfomycin is also likely to be excreted unchanged in other species, including in humans. Another rat study in which samples were collected up to 24 h showed 49.2% recovery of unchanged fosfomycin in the urine (fosfomycin levels were not assessed in faeces). In the mouse, dog and human recovery of fosfomycin was only examined in urine. In the mouse recovery of unchanged fosfomycin in urine was up to ~56%, in dog it was up to 72% while in healthy volunteers, recovery was up to 58% of dose administered at 48 h post-dose. Excretion of fosfomycin was predominantly through the urinary route. It was noted in the Clinical Overview that patients with renal insufficiency (CL_{CR} < 50 mL/min) may experience substantial increases in exposure and elimination half-life.

Overall, in the limited investigations on the pharmacokinetic profile of fosfomycin, there were sufficient similarities between the laboratory animal (rat and dog) and human pharmacokinetic parameters to serve as appropriate models for the toxicity studies.

Pharmacokinetic drug interactions

There were no nonclinical studies on PK drug interactions submitted.

Toxicity

Acute toxicity

Single dose toxicity studies were conducted in mice, rats, rabbits and dogs using the oral and intraperitoneal routes. No mortalities were observed when the oral route was used and the maximum non-lethal doses were the highest tested doses (≥ 5000 mg/kg in mice & rats, ≥ 2000 mg/kg in rabbits and dogs). Clinical signs were generally minor or relatively benign in nature (sporadic observation of piloerection, watery stools/diarrhoea that resolved a few days post-dose).

The intraperitoneal route used in rodents resulted in a number of dose-dependent mortalities. Treatment-related deaths occurred within 2 to 4 days post-dose in rats and at up to 7 days post-dose in mice. Clinical signs included reduced spontaneous activity and changes to breathing (shallow breathing). Cause of death could not be determined in mice and there were no treatment-related effects evident at necropsy. In rats, post-mortem analysis found blood in the urinary bladders of animals from the 4400 and 5000 mg/kg dose groups. As well, there was evidence of haematuria in some males on the day of dosing, which resolved in surviving animals by Day 4.

Based on these observations fosfomycin trometamol exhibited a low to moderate order of acute toxicity when administered by the clinical (oral) route and a moderate order of toxicity with the intraperitoneal route in rodents.

Repeat dose toxicity

The sponsor submitted seven repeat dose toxicity studies that were conducted in rats and dogs. All studies used the clinical route (oral administration: gavage, intragastric tube) with the longest dosing period in rats being 13 weeks and 26 weeks in dogs. Only one study (4 weeks in rats) was conducted according to the principles of GLP. Nevertheless, design aspects of the studies (group sizes, parameter assessed) were generally consistent with the relevant guideline on repeat dose toxicity testing (CPMP/SWP/1042/99).[32]

Relative exposure

Exposure ratios are calculated based on plasma exposure (as AUC) determined in healthy human subjects given a 3 g oral dose of fosfomycin trometamol.

Table 2: Relative exposure in repeat-dose toxicity studies.

Species	Study No.	Dose (mg/kg/day)	AUC (µg.h/mL)	Relative exposure#
Rat (Crl:CD BR VAF/Plus)	**HWI-6277-123** (2 weeks)	250	95	0.5
		500	238	1.4
		1000	457	2.6
		2000	798	4.6
Dog (Beagle)	**3**(1 week)	50 [in corn starch	150	0.9

[32] Committee for Human Medicinal Products (CHMP): Guideline on repeated dose toxicity; 18 March 2010 CPMP/SWP/1042/99 Rev 1 Corr*.

Species	Study No.	Dose (mg/kg/day)	AUC (µg.h/mL)	Relative exposure#
		cachets]		
Human^	MRHD 3 g daily	60 mg/kg/day	174	–

Relative exposure = animal AUC: human AUC; based on PK parameters determined in healthy (fasted) subjects given 3 g oral dose.

Major toxicities

No specific or targeted toxicities were identified in the repeat dose toxicity studies and there were no mortalities that could be ascribed to fosfomycin trometamol treatment. Clinical signs were generally minor (for example, soft faeces, diarrhoea, excess salivation, emesis in dogs) and resolved when treatment ceased.

Clinical pathology findings indicated a dose-related effect on transaminases in rats (increased ALT in males at 4000 mg/kg, increased AST and OCT in females at ≥ 250 mg/kg, increased ALT in male and females at 3200 mg/kg), which suggested a fosfomycin-related effect. Correspondingly, there were also small but significant increases in relative liver weights in these groups. However, histological findings (confined to high dose treated animals only) did not show any microscopic findings consistent with adverse hepatic changes. The only adverse pathology finding was marked dilatation of the caecum which was noted in rats at doses ≥ 1000 mg/kg. The toxicological significance of this observation is uncertain as it did not coincide with microscopic changes to the gastrointestinal tract. However, another study did note aberrant faeces and swollen abdomen in some high dosed rats. Urinalysis findings from the 13 week rat study found slightly higher specific gravity at 4000 mg/kg/day and also decreased urinary pH at doses ≥ 1000 mg/kg/day. Given the acidic nature of fosfomycin (base), this observation is not unexpected and it is noted that these effects were not evident once fosfomycin treatment ceased. In most of the rat studies the NOAEL was generally established at around 1000 mg/kg/day, with doses above this level associated with effects on body weight gain and elevated transaminases. In the 13 week study, these effects were not evident after a 4 week recovery period.

Neither of the two dog studies uncovered any major toxicity findings. However, there were significant effects on body weight in a more recent 4 week study (1994 in contrastto the older 26 week study dated 1982). In males lower body weight gain was noted in the HD group, while in females there was actual body weight loss that also corresponded to decreased food consumption. This may have been due to emesis being a frequent observation in HD animals. However, aside from these adverse responses to fosfomycin trometamol, there were no distinct pathological observations that could be associated to treatment. Haematological parameters in treatment groups were similar to controls, though serum chemistry assessments found elevated albumin (and corresponding decreases in globulin and A:G ratio) in HD dogs. The toxicological significance of this is uncertain as there were no other overt changes to organs. With the exception of a few minor incidental findings (discoloured foci in the colon and ileocolonic joint), there were no adverse macroscopic or microscopic findings reported. In the older 26 week study the NOAEL was established at the highest tested dose (≥ 1000 mg/kg/day), while in the second 4 week study the NOAEL was 300 mg/kg/day, based on effects on body weight gain and emesis seen at the higher dose.

Overall, the repeat dose toxicity studies did not uncover any specific toxicological hazards with treatment-related changes being relatively benign and reversible in studies that included a recovery period component. Given the short duration of clinical use (single

dose or pre- and post-surgery doses), it is unlikely that any of the treatment-related effects identified in the animal studies will be relevant under the conditions of clinical use.

Genotoxicity

The genotoxic potential of fosfomycin trometamol was assessed in a standard battery of in vitro (bacterial reverse mutation, mammalian forward mutation, chromosomal aberration assay) and in vivo assays (mouse micronucleus test). All studies were stated to have been conducted according to the principles of GLP. Bacterial reverse mutation assays were feasible since S. typhimurium are resistant to fosfomycin. Overall, there was no evidence of mutagenic or clastogenic potential by fosfomycin trometamol under in vitro or in vivo testing conditions.

Carcinogenicity

Carcinogenicity testing of fosfomycin trometamol was not conducted. The ICH guideline on the need for carcinogenicity studies for pharmaceuticals (ICH S1A);[33] stipulates that such studies should be performed for pharmaceuticals that have an expected continuous duration of use of at least 6 months. Thus, in view of the short duration of treatment (single dose or prophylaxis and post-surgical treatment), the lack of genotoxic potential, as well as no evidence of pre-neoplastic lesions in the repeat dose toxicity studies up to 12 weeks in rats and 26 weeks in dogs, the absence of carcinogenicity studies is considered acceptable.

Reproductive toxicity

Reproductive toxicity of fosfomycin trometamol was assessed in rats and rabbits in mostly GLP-compliant studies that encompassed all stages of development (fertility, embryofetal development, peri-/postnatal development). The study designs that were utilised were generally satisfactory with regard to group sizes, timing and duration of treatment (although for rats, the duration of exposure was marginally shorter than expected, up to GD 15 instead of GD 16/17), as per the nonclinical Note for Guidance on reproductive toxicity studies (ICH S5 R2).[34]

Relative exposure

Table 3: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day)	Dose (mg/m²/day)	Dose ratio#
Rat (SD)	Fertility [T/3700/0002]	250	1500	0.8
		500	3000	1.5
	Embryofetal development [T/3700/0003]	1000	6000	3
	Peri-/Postnatal development [T/3700/0005]			
Rabbit (NZW)	Embryofetal	250	3750	1.9

[33] S1A: Need for Carcinogenicity Studies of Pharmaceuticals
[34] S5(R2): Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

Species	Study [Study no.]	Dose (mg/kg/day)	Dose (mg/m^2/day)	Dose ratio#
	development [T/3700/0004]	500	7500	3.8
		1000	15000	7.8
	Embryofetal development [TR 37]	100	1500	0.8
		200	3000	1.5
		400	6000	3
Human	MRHD 3 g daily	60 mg/kg/day	1980	–

Dose ratio = animal dose (mg/m2/day):human dose (mg/m2/day).

Dose selection was generally acceptable; Relative exposures attained in these studies were based on dose comparisons relative to body surface area because toxicokinetic measurements were not provided for any of the reproductive toxicity studies. Overall, maximum exposures were low for both species (up to 3 times and around 8 times the MRHD dose in rats and rabbits respectively, based on BSA comparisons).

Maternal and fetal exposure to fosfomycin trometamol was not extensively examined. A limited investigation in which fetal levels of fosfomycin was based on measurements from pooled fetal tissue samples from rats established that placental transfer of fosfomycin occurs. Milk transfer of fosfomycin was not assessed.

None of the reproductive toxicity studies identified a treatment-related effect on fertility, embryofetal or neonatal development. In the rat fertility study reproductive performance was unaffected by fosfomycin, with no interruptions to oestrus cycling females or morphological changes to reproductive tissues in males. Litter values (number of corpora lutea and implantations) were also unchanged by treatment, with treated groups found to be similar to controls. The embryofetal development studies also did not reveal any adverse effects on embryogenesis. In the rat there were no maternal deaths and adverse observations were not related to treatment. Litter values were comparable to controls. Assessment for fetal variations found a slightly higher incidence of skeletal variations (incomplete ossification of pelvis ischia and sternal centra) in the HD group (1000 mg/kg/day) but was unlikely to be biologically significant as it fell within historical control incidences. As well, a second embryofetal development study in rats using the same doses did not find any treatment associated effects. In rabbits, a higher dose study (up to 1000 mg/kg/day) was associated with maternal deaths in the HD group and body weight losses in all treatment groups. Subsequently, all dose groups had incidences of fetal losses (as aborted litters or increased resorptions). Also, one HD doe had a litter that included pups found to have fetal variations/malformations (micrognathia, short snout). A NOAEL was not established in this study due to fetal losses that were most likely secondary to maternal toxicity. A second study that used lower doses at up to 400 mg/kg/day (although conducted on an earlier occasion) did not find a treatment-related effect on embryofetal development or fetal losses and thus the NOAEL was established at the highest tested dose (≥ 400 mg/kg/day). Although 2 does from the HD were found dead during the treatment period, a cause was not identified during necropsy. As well, there was no treatment-related effect on body weight gain. Thus, it can be inferred that the fetal losses seen in the higher dose study were entirely due to maternotoxicity-associated body weight loss.

In peri-/postnatal development studies in rats, no adverse findings were observed. Both studies used the same dose levels with the more recent study reporting a slight but significant increase in maternal body weight during the lactation period. The biological significance of this observation is uncertain but was observed in females in a 13 week repeat dose toxicity studies. Nevertheless, this was not seen in the second postnatal development study and there was no overall difference to developmental parameters. There was no treatment associated change to gestation or parturition. One dam from the MD group was observed to have dystocia but as this was not seen in any other dams or at higher doses, it is not regarded as a toxicologically significant finding. Pup viability indices and developmental milestones were not affected by treatment and F_1 generation pups went on to exhibit normal development complete up to F_2 generation necropsy assessments.

Overall, in rats the NOAEL for fertility, embryofetal and peri-/postnatal development was considered to be the highest tested dose (≥ 1000 mg/kg/day), while in rabbit the NOAEL for embryofetal development was up 400 mg/kg/day.

Pregnancy classification

The sponsor did not propose a pregnancy category. Relative to BSA comparisons, maternal exposures were low and it is the view of the evaluator that the adequacy of fetal exposures attained in the reproductive toxicity studies is uncertain. In view of the absence of adverse embryofetal and postnatal development findings, it is recommended that an Australian pregnancy category of B2 be assigned.[35] The US FDA category is B.[36]

Local tolerance

No dedicated studies on potential local reactivity to fosfomycin trometamol were conducted. None of the toxicity study findings denoted poor local tolerance of fosfomycin trometamol in the studied test species. It is noted that the RMP identifies hypersensitivity reactions as a potential hazard based on post-market reports.

Phototoxicity

Phototoxicity studies were not conducted with fosfomycin trometamol.

Impurities

The proposed specifications for impurities in the drug substance and drug product are considered adequately qualified. Two identified impurities were screened for mutagenic structural alerts and were considered non-mutagenic.

Paediatric use

Fosfomycin trometamol is not proposed for use in children under 12 years of age and as such the sponsor did not submit specific studies in juvenile animals.

[35] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
[36] Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Nonclinical summary and conclusions

Summary

- The submitted dossier was in accordance with ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3).[37] However, reflecting the age of many of the studies, conducted in the 1980s, very few were conducted according to GLP.
- Fosfomycin is taken up by cells by two active transporters, GlpT and UhpT, and confers bactericidal activity by inhibiting cell wall biosynthesis via the enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), which catalyses the initial step in the synthesis of peptidoglycan. Susceptibility and bactericidal activity was most apparent against E. coli, P. mirabilis, Haemophilus spp., methicillin-sensitive S. aureus, Citrobacter spp., and Group D streptococci (MIC_{90} values ≤ 16 µg/mL) but negligible against Pseudomonas spp., Clostridium spp., Bacteroides spp. and Serratia spp. Fosfomycin was shown to reduce adhesion of bacteria to urinary epithelial cells in vitro. Fosfomycin exhibited moderate antimicrobial activity against clinical isolates associated with urinary tract infections in in vivo animal models of cystitis in mice and rats.
- Fosfomycin resistance may be conferred by reduced cell uptake due to chromosomal mutations in either transporter (GlpT or U hpT), or mutations or overexpression of the target enzyme MurA. Plasmid-mediated resistance has been reported due to FosA, FosB, and FosX, which catalyse opening of the oxirane ring of fosfomycin. Fosfomycin has a unique mechanism of action, and is the only member of its class, hence cross-resistance has not been observed, and fosfomysin is active against most multidrug-resistant Enterobacteriaceae. In vitro studies indicate rapid development of resistance, however clinical surveillance data, mostly in European countries where fosfomycin is registered, generally indicate stable susceptibility rates over time. No Australian fosfomycin susceptibility data were submitted.
- Potential off-target effects of fosfomycin have not been investigated. Safety pharmacology studies did not reveal any significant or clinically relevant effects on CNS, cardiovascular, renal or gastrointestinal organ systems. No significant pharmacodynamic interaction between fosfomycin and commonly prescribed drugs was identified.
- Absorption of fosfomycin as the trometamol, calcium or disodium salt was rapid and maximum serum levels were attained by 1 to 2 h post-dose in rodents and dogs. Fosfomycin does not exhibit protein binding but is widely distributed to tissues, with the highest levels seen in small intestine and kidneys and only trace levels detected in brain tissue. There is no evidence to indicate that fosfomycin undergoes metabolic transformation. Unchanged fosfomycin is mostly excreted through the urinary route (mouse around 56%, rat around 88%, dog around 72%) with small amounts of unchanged fosfomycin excreted in the faeces. Pharmacokinetic drug interaction potential was not investigated.
- Fosfomycin exhibited a low to moderate order of acute toxicity when administered by the oral route in rodents, rabbits and dogs, and a moderate order of toxicity with the intraperitoneal route in rodents.
- Repeat dose toxicity studies using the clinical (oral) route were conducted in rats (up to 13 weeks) and dogs (26 weeks). No specific or targeted toxicities were identified and there were no mortalities ascribed to fosfomycin trometamol treatment.

[37] M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Treatment-related changes (for example, soft faeces, diarrhoea, excess salivation, elevated transaminases and relative liver weights, elevated albumin, discoloured foci in the colon and ileocolonic joint) were relatively benign and reversible in studies that included a recovery period. Because of the short duration of clinical use, observations from the animal studies are not considered biologically relevant to the conditions of clinical use.

- Fosfomycin was not found to be mutagenic or clastogenic in a standard battery of in vitro (bacterial reverse mutation, mammalian forward mutation, chromosomal aberration tests) and in vivo (mouse micronucleus assay) assays. The carcinogenic potential of fosfomycin trometamol was not assessed, which is acceptable given the expected short duration of treatment.
- Fertility was not affected in male and female rats treated with fosfomycin at estimated exposure levels up to 3 times the human dose relative to body surface area. Placental transfer of fosfomycin was demonstrated in rats. Embryofetal development studies did not uncover adverse effects on embryogenesis in rats and rabbits. However, in rabbits fosfomycin was associated with maternal deaths and toxicities (body weight losses) at doses ≥ 500 mg/kg/day (around 4 times clinical dose relative to body surface area). Fetal losses that occurred at these doses were likely secondary to the maternotoxic effects of fosfomycin. There was no evidence of adverse effects on developmental milestones in rat pups exposed to fosfomycin during the peri-/postnatal period.

Conclusions and recommendation

- Primary pharmacology studies provided sufficient evidence of efficacy as an antimicrobial against bacterial species that cause urinary tract infections and support the use of fosfomycin trometamol for the proposed indication.
- Specialised safety pharmacology studies did not identify any clinically significant hazards to organ system functions.
- There were no significant toxicity findings in repeat dose toxicity studies and treatment-related changes were relatively benign, and reversible in studies that included a recovery period.
- The sponsor did not nominate a pregnancy category. Based on the absence of adverse findings in the reproductive toxicity studies and the low to moderate exposures attained (based on doses relative to body surface area comparisons), Category B2 is recommended.
- There are no nonclinical objections to the registration of fosfomycin.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Symptomatic urinary tract infections (UTI) are a very common disease, with particularly high incidence in women of child-bearing age. These infections occur in 1 to 3% of schoolgirls and then increase markedly in incidence with the onset of sexual activity in adolescence. Symptomatic UTI is very common in women aged 20-50 years, but it is rare

in men under 50 years. UTIs are usually classified as either complicated or uncomplicated. The diagnosis of uncomplicated UTI is made if there is no evidence of pyelonephritis or upper UTI, no renal or urological abnormalities, no urinary retention or urinary catheter. The most common organisms causing uncomplicated UTI are Escherichia coli, Proteus species, Klebsiella pneumoniae, other Enterobacteriaceae and Staphylococcus saprophyticus. Acute uncomplicated lower UTI is extremely common, being estimated to occur in about 6% of adult women per year.

Most uncomplicated UTIs respond well to oral antimicrobial treatment when the appropriate compounds are taken as directed. Traditionally, treatment duration was of 5 to 10 days, but there has been a noticeable trend towards shorter courses (three days or less) in recent years. With a multi-day antibiotic regimen, poor compliance, favoured by the rapid resolution of clinical symptoms, is well documented. Response to therapy may be compromised in non-compliant patients, and this noncompliance may be, in part responsible for increasing bacterial resistance.

A single-dose antibiotic that is both safe and effective would, therefore, be a significant therapeutic advance in the treatment of uncomplicated UTI, since it would increase patient convenience, enhance compliance, minimise adverse events, and reduce the potential for selection of antibiotic resistant bacteria.

Fosfomycin is currently being used to treat multi-resistant isolates such as these on the SAS scheme in Australia.[38] It is active against the most common urinary pathogens involved in uncomplicated UTI. It appears to have no cross-resistance with other antibiotic agents as it is the first and only agent in its class. It also appears to have few adverse effects.

Additionally fosfomycin is a potentially useful therapy for uropathogens which carry resistance genes such as ESBLs or inducible-betalactamases (ESCAPPM Gram negative bacilli). These isolates may be resistant to all other oral antibiotics available in Australia. It also may have activity against carbapenem-resistant Enterobacteriaceae and carbapenem-resistant non-fermentative Gram negative bacilli such as Pseudomonas.[39]

Fosfomycin has been included in a list of 33 'forgotten antibiotics' drawn up by infectious diseases specialists, microbiologists and hospital pharmacists in 38 countries from Europe, United States, Canada and Australia. Fosfomycin has been included on the list with 2 particular qualities highlighted: (1) that it is the only available antibiotic of its class, and (2) for its favourable pharmacokinetic criterion of requiring only 1 dose to treat uncomplicated cystitis. Another favourable quality its potential to treat infections caused by carbapenem-resistant Gram negative bacilli.[40]

The clinical rationale for the proposed introduction into the Australian market is to improve and broaden the therapeutic options for the treatment of acute uncomplicated lower UTI in adult females. The second proposed indication aims to improve and broaden the prophylaxis options for urinary tract infections in surgery and diagnostic procedures involving the lower urinary tract in adult males and females.

Guidance

Pre-submission advice from TGA was that the sponsor should submit a conventional dossier. No pre-submission meeting was required or held. TGA have also advised the

[38] The TGA's Special Access Scheme (SAS) provides access to unapproved therapeutic goods for patients in exceptional clinical circumstances.
[39] Pulcini C, Bush K, Craig WA et al. Forgotten antibiotics: An inventory in Europe, the United States, Canada and Australia. Clin Infect Dis. 2012, 54;268-274.
[40] Pulcini C, Bush K, Craig WA et al. Forgotten antibiotics: An inventory in Europe, the United States, Canada and Australia. Clin Infect Dis. 2012, 54;268-274.

sponsor that the two flavouring agents are already in use in other oral medicines and as such have already been approved by TGA. The sponsor has advised TGA that microbial resistance risk will be based on overseas resistance data due to lack of local Australian data, with this data to be generated in the future. The evaluator agrees that this is likely to be the case.

Contents of the clinical dossier

The submission contained the following clinical information:

- Three pivotal efficacy/safety studies: Studies MON-US-01, MON-US-02, and MON-US-03.
- Eight clinical pharmacology studies providing PK data.
- Seventeen other efficacy/safety studies.
- Nine periodic safety update reports (PSURs) covering the period from January 1995 to January 2016.
- There were no good dose-finding studies.
- 76 Literature references. These were composed of review articles, background information, PK and PD studies, and other efficacy/safety studies.
- All studies for the proposed 5 prophylaxis indication were contained in 'Literature references'. These therefore required detailed review but none are considered pivotal and they also did not meet GCP principles.
- One meta-analysis[41]
- 18 PK studies providing supporting data.
- All the PD data in the dossier, 4 studies only.
- 9 studies which included pregnant women. These required detailed review especially for safety in pregnancy.
- There were no studies which included lactating women.
- The following efficacy/safety studies in special populations: the elderly, 2 studies; chronic renal impairment 1 study, ESBL-producing bacteria or fosfomycin-resistant bacteria, 4 studies.
- 4 good review publications and 2 papers providing background microbiology information.

Paediatric data

A paediatric indication was not requested. The age group requested for the first indication is females 12 years or older. Sufficient data has been provided in the dossier for this age group.

Good clinical practice

Only the 3 pivotal efficacy and safety Studies MON-US-01, MON-US-02 and MON-US-03 meet the principles of GCP. The other studies in the submission were mostly conducted prior to the adoption of GCP principles. Despite this, as a group, they provide useful and relevant information.

[41] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr;29(2):321-47.

Evaluator's commentary on the clinical dossier

The submission was generally well-presented.

Pharmacokinetics

Studies providing pharmacokinetic data

Below shows the studies relating to each PK topic.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	Kisicki 1994[42] Borgia 1982[43] Borgia 1984[44] Thorsteinsson 1992[45]	 * * *
	- Multi-dose	Not provided	
	Bioequivalence † - Single dose	Not provided	
	- Multi-dose	Not provided	
	Food effect	Kisicki 1994[46]	*
PK in special populations	Target population § - Single dose	Not provided	
	- Multi-dose	Not provided	
	Hepatic impairment	Not provided	
	Renal impairment	Fillastre 1988[47]	*
	Neonates / infants / children / adolescents	Careddu 1987[48]	*
	Elderly	Fillastre 1988[49]	

[42] Study objectives: 1. To determine the absolute bioavailability of oral fosfomycin tromethamine and to evaluate the effect of food on oral absorption. 2. To evaluate a new microbiologic assay of fosfomycin.
[43] Study objectives: To evaluate serum concentrations and antibiotic urinary recovery after an oral 3g dose of fosfomycin trometamol.
[44] Study objectives: To assess the oral bioavailability of calcium fosfomycin in healthy volunteers and compare it to the bioavailability of trometamol fosfomycin (FZ588 or Monuril)
[45] Study objectives: To compare the PK parameters of a single oral administration of different doses of fosfomycin trometamol (FZ588) with those of a single intravenous injection of fosfomcyin disodium salt and to evaluate the bioavailability.
[46] Study objectives: 1. To determine the absolute bioavailability of oral fosfomycin tromethamine and to evaluate the effect of food on oral absorption. 2. To evaluate a new microbiologic assay of fosfomycin.
[47] Study objectives: To compare the PK of fosfomycin trometamol in elderly subjects and uraemic patients.
[48] Study objectives: To assess the PK of fosfomycin trometamol in children on treatment with fosfomycin for UTI.
[49] Study objectives: To compare the PK of fosfomycin trometamol in elderly subjects and uraemic patients.

PK topic	Subtopic	Study ID	*
		Salvioli 1985[50] Janknegt 1994[51]	*
	Pregnancy	De Cecco 1987[52]	
Genetic/gender related PK	Males versus females	yes	
	Other genetic variable	Not provided	
PK interactions	Metoclopramide	Bergan 1988[53]	*
	Cimetidine	Bergan 1988[54]	*
Population PK analyses	Healthy subjects	Not provided	
	Target population	Not provided	
	Other	Not provided	
Tissue distribution	Prostate	Moroni 1984[55]	
	Bladder tissue	Scaglione 1994[56]	
	Placenta	Ferreres 1977[57]	

* Indicates the primary PK aim of the study.

None of the studies had deficiencies that excluded their results from consideration. Some studies compared fosfomycin trometamol with the less bioavailable calcium fosfomycin salt which has an inferior PK profile to fosfomycin trometamol. In the study summaries, the evaluator has chosen to focus on the PK of fosfomycin trometamol, as it is the formulation proposed by the sponsor.

Evaluator's conclusions on pharmacokinetics

Summary of pharmacokinetics

Sachet composition

- A sachet of Monurol contains 5.631 g fosfomycin trometamol (equivalent to 3.0 g active fosfomycin), mandarin and orange juice flavour, saccharin and sucrose.

[50] Study objectives: To evaluate pharmacokinetics and bioavailability after an oral 3g dose of fosfomycin trometamol (Z1282 or Monuril) in elderly hospitalised patients.
[51] Study objectives: To assess the PK of fosfomycin trometamol in elderly patients with impaired renal function.
[52] Study objectives: To investigate the PK of fosfomycin trometamol during pregnancy.
[53] Study objectives: To investigate any PK interaction of fosfomycin with metoclopramide and cimetidine.
[54] Study objectives: To investigate any PK interaction of fosfomycin with metoclopramide and cimetidine.
[55] Study objectives: To investigate tissue distribution of fosfomycin into the prostate.
[56] Study objectives: To investigate tissue distribution of fosfomycin into the bladder mucosa.
[57] Study objectives: To evaluate the placental transfer of fosfomycin trometamol.

Absorption

- A single Monurol granules for oral solution sachet is dissolved into a glass of water and taken immediately after preparation. Fosfomycin trometamol salt is rapidly absorbed in the gut and converted to the active drug fosfomycin.
- The mean absolute bioavailability of fosfomycin trometamol in three studies of fasting healthy adult volunteers was 33 - 46%.
- Fosfomycin trometamol is substantially more orally bioavailable than calcium fosfomycin based on comparative early studies.
- The proposed formulation is the same as that used in the majority of PK, efficacy and safety studies with only the orange flavour agent changed.
- The proposed formulation with the current orange flavouring agent has been commercially available in Europe since the 1980s and is the same formulation currently used in Australia under the SAS scheme.
- Only a single dosage form and strength is proposed.
- In fasting healthy adult volunteers, mean C_{max} of 20.9–32.0 µg/mL was reached within about 2 h following administration of a single sachet of Monurol (active drug 3g fosfomycin).
- AUC_{24} for this dose is 120-184 ug.h/ml in fasting healthy adult volunteers.
- High fat food reduced the bioavailability of fosfomycin trometamol in healthy adult volunteers from 37% to 30% and decreased the rate and extent of absorption. It lowered Cmax by approximately 25% and delayed peak drug levels by a further 2 h with T_{max} at 4.0 h. It lowered AUC_{24} from 184 µg.h/mL to 154 µg.h/mL.

Distribution

- The apparent volume of distribution of fosfomycin in healthy volunteers was 16 to 21 litres, approximately the size of the extracellular fluid compartment indicating that the drug distributes widely into extra-vascular compartment.
- Plasma protein binding was 0% in a study of 10 healthy adult volunteers. No other data is available on plasma protein binding.
- Fosfomycin penetrates the prostate well achieving 57 to 100% serum levels (mean 90%) in 6 males undergoing prostectomy for adenomas.
- Fosfomycin achieves high levels in bladder tissue.
- Fosfomycin is transferred via the placenta in pregnancy with fetal serum levels a mean of 68% 2 to 3.5 h after maternal intramuscular dosage of sodium fosfomycin. There are no studies of placental transfer of the oral formulations but as the parenteral and oral formulations convert to fosfomycin active drug, presumably the oral formulation also has high placental transfer although the PK of this is unknown.

Metabolism

- Fosfomycin does not undergo metabolism and is primarily excreted unchanged in the urine.

Renal clearance and urinary excretion

- Total body clearance and renal clearance are similar so non-renal clearance is thought to be negligible.
- Total clearance of fosfomycin corresponds closely to the glomerular filtration rate, so neither tubular secretion nor reabsorption are thought to occur.

- In healthy adult volunteers, up to 40% of an orally administered dose of fosfomycin tromethamine equivalent to 3g fosfomycin is excreted in the urine within 48 h and, of this, approximately 85 to 95% is excreted in the first 24 h.
- Excretion of drug into urine is minimal after 48 h in healthy adult volunteers and in this group when tested 7 days after dosing, serum levels were undetectable.
- Food delays drug absorption but the total amount of drug excreted in the urine over time is the same. This means that the drug can be administered without regard to meals.
- For the first 4 h after a dose, higher urinary concentrations of fosfomycin are noted in fasting states compared to fed states. After 4 h, urinary concentrations are similar in either fasting or fed states.
- Mean urinary fosfomycin concentrations after a single 3 g oral dose peak at 400 to 700 µg/mLl 2 h (fasting) to 6 h (fed state) after the dose.
- Fosfomycin concentrates in urine, with mean peak urinary concentrations typically 100 times more than the mean peak serum concentrations.
- Mean urinary fosfomycin concentrations are maintained above an MIC threshold of 128 µg/mL for at least 24 h post 3 g oral dose in either the fasting or fed state.
- Fosfomycin is a good candidate for treatment of UTIs due to its marked urinary concentration.

Other forms of excretion

- Mean faecal recovery at Day 4 after the 3g oral fosfomycin dose was 28.0 ± 11.8 % in 6 healthy adult volunteers.
- Total faecal excretion of drug was not affected by dosing with or without food.
- Faecal excretion of the drug over a 5.5 day period was relatively linear by 24 h period commencing 24 h after the dose.
- Data on biliary excretion of fosfomycin provided in the dossier is limited. The presence of two serum peaks in one PK study suggests that fosfomycin could undergo enterohepatic circulation.
- In two volunteers undergoing cholecystectomy, biliary concentrations varying between 25% and 118% of serum concentrations were found 2 to 12 h after unknown oral or IV dosage of fosfomycin.
- Further information on biliary concentrations of fosfomycin in subjects without biliary inflammation has been requested from the sponsor.

Intra and inter individual variability of PK

- No data is available on intra-subject variability of PK.
- In healthy adult volunteers after a 3g oral dose, bioavailability of the drug in one study was a mean of 32.88% with a standard deviation of 2.3%. Mean plasma AUC was 139.08 µg.h/ml with a standard deviation of 11.376 µg.h/ml and urinary recovery of drug was 39.109% with a standard deviation of 1.93%. Hence, at least in healthy volunteers, the inter subject variability in PK does not appear significant.
- There are no significant differences in the PK between male and female healthy adult volunteers.

Pharmacokinetics in the target population

- Target population for the first proposed indication (treatment) is females with acute uncomplicated symptomatic UTI aged 12 years and older. No PK data has been presented in this target population but younger adult females are likely to have similar PK to healthy adult female volunteers. PK data has been presented in elderly females without UTI and in patients with renal impairment without UTI, see below.
- Target population for the second proposed indication (prophylaxis) adult males and females requiring prophylaxis. PK data has not been presented for this target population but has been presented in the elderly and in patients with renal impairment, see below.

Pharmacokinetics in subjects with impaired hepatic function

- No data.

Pharmacokinetics in subjects with impaired renal function

- Fosfomycin primarily undergoes renal excretion with a linear relationship between pharmacokinetics and glomerular filtration rate.
- Fosfomycin PK has been studied after 25 mg/kg oral dosage fosfomycin trometamol in 23 subjects with mild, moderate or severe renal impairment. As renal function decreased (creatinine clearances varying from 54 mL/min to 7 mL/min), the $T_{1/2}$ of fosfomycin increased from 11 h to 50 h. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreases the excretion of fosfomycin.
- The linear relationship between fosfomycin PK and glomerular filtration rate data has been mathematically described:

  $t_{1/2}$ (h) = 0.06 serum creatinine (umol/l) + 0.04 (n = 23, r = 0.95, p < 0.001);
  ke (h^{-1}) = 0.001 C_{cr} (mL/min) + 0.02 (n = 23, r = 0.72, p < 0.01);
  Cr (mL/min) = 1.39 C_{cr} (mL/min) - 13.3 (n = 23, r= 0 .94, p < 0.001).

- In 5 anuric haemodialysis patients, serum concentrations decreased slowly. $T_{1/2}$ of fosfomycin during hemodialysis was 40 h. Serum fosfomycin was still detectable in haemodialysis patients after 2 successive haeodialysis sessions 48-72 h apart.
- Fosfomycin accumulates if renal function is impaired. The clinical significance of this accumulation is unknown.

Pharmacokinetics in pregnancy

- In a study of 4 pregnant females who received 50 mg/kg oral fosfomycin trometamol at 27 to 32 weeks gestation and one month after delivery, there were no apparent differences in the 24-h period after dosing in serum and urinary concentrations during pregnancy compared to post-delivery. Thus, it is not likely based on one small study that pregnancy significantly alters the PK of fosfomycin.
- Fosfomycin transfers across the placenta to a large extent.

Pharmacokinetics in the elderly

- In a study of 6 elderly fasting hospitalised patients aged 68-88 years, a single 3g oral fosfomycin trometamol dose was given. Patients with renal impairment were excluded. Mean creatinine clearance was 94.33 mls/min which is at the high end of the normal range for all adults but as expected for a group of elderly patients. Mean Cmax was 33.07, slightly higher than that seen in other studies in healthy young adults. Absorption of drug was slower than in young adults with mean Tmax at 3 h. Urinary recovery was 18.5-61% at 24 h, again less than in young adults.

- In a study of 7 elderly female volunteers living in a nursing home aged 71 to 90 years with impaired renal function (range 21 to 72 mL/min) a 3 g Monuril sachet was given. Urinary concentrations were measured over an 84 h period. Elimination half-lives ranged from 7 to 5 h with longer half-lives correlated with more impaired renal function.
- The PK of fosfomycin has been studied in 8 healthy elderly adult volunteers and compared to 5 young healthy adult volunteers. All received a single dose of 25 mg/kg body weight tromethamine fosfomycin. Peak serum concentrations and apparent volumes of distribution were not significantly altered by age. The mean elimination half-life in young adults was 5.37 h and 8.3 h in the elderly. Mean urinary excretion of fosfomycin by 24 h was reduced in the elderly at 27.5% compared to 57.7% in the young adults. Mean creatinine clearance was much lower in the elderly at 48.8 mL/min compared to young adults at 179.6 mL/min.
- The same study examined the same dose of fosfomycin in 7 patients with mild renal impairment (creatinine clearance 54.2 +/- 24.2 SD mL/min) aged a mean of 43.7 +/- 22.9 SD years. PK of fosfomycin in these mildly renally impaired patients was similar to the healthy elderly volunteers. Creatinine clearance in both groups was comparable in both groups. Hence, PK of fosfomycin is altered by the worsening of renal impairment that occurs naturally as a person ages.
- In summary, the PK of fosfomycin is likely dependent on renal function and independent of age itself.

Pharmacokinetics in children and teenagers

- The sponsor has not requested a paediatric indication, although teenage patients 12 years or greater are included in the proposed patient group.
- One study contains paediatric PK data for 43 children aged 1 month to 15 years (mean 5.7 years) on treatment with oral fosfomycin tromethamine for UTIs. In 6 children given a mean dose of 63.9 mg/kg (the closest to the usual adult dose of 3g, assuming a typical adult weight of 70 kg), PK parameters were very similar to adults in other studies. Urinary recovery at 24 to 48 h was 27.6 to 50.1%, similar to the range in other studies of adults.
- PK data is very limited in children and young adults, but in teenagers aged 12 or older, based on the limited data, PK at the same dose by body weight is likely similar to that seen in adults.

Pharmacokinetics related to genetic factors

- No studies provided.

Pharmacokinetics in lactation

- No data presented.

Pharmacokinetics in other special populations, with other population characteristics or in other acute or chronic disorders

- No data presented.

Pharmacokinetics and ethnicity

- No data presented.

Population pharmacokinetics

- No studies provided.

Effect of cimetidine on pharmacokinetics of fosfomycin

- No interaction noted in a study of 9 healthy adult volunteers.

Effect of metoclopramide on pharmacokinetics of fosfomycin

- In a study of 9 fasting healthy young adult male volunteers given 20 mg oral metoclopramide 30 minutes before a fosfomycin trometamol dose of 50 mg/kg, the rate of absorption of fosfomycin was slowed, serum concentrations were lowered, half-life was prolonged, and AUC was reduced.
- In the same study, urinary excretion of fosfomycin over a 48 h period was reduced if metoclopramide was given. Total urinary recovery of fosfomycin over a 48 h period was 36.1% for fosfomycin alone compared to 27.7% for metoclopramide with fosfomycin.
- The postulated mechanism is that metoclopramide increased gastric and intestinal motility with quicker passage through the area of the gut with maximum fosfomycin absorption. As a result, fosfomycin is absorbed at lower levels of the gut over a longer period of time.

Other possible pharmacokinetic interactions

- No data was presented, but other drugs which increase gastrointestinal motility could have a similar interaction with fosfomycin as does metoclopramide.
- Fosfomycin does not undergo metabolism within the body, so there are not likely to be any hepatic cytochrome P450 interactions with other drugs, although this has not been studied.
- Fosfomycin is not bound to plasma proteins, so there are not likely to be drug interactions with plasma protein-bound drugs, although this has not been studied.
- Apart from metoclopramide and cimetidine, no other data or studies on potential pharmacokinetic interactions with other drugs was presented in the dossier.

Limitations of PK studies

- Fosfomycin is the first and only drug in its class, so PK results cannot be extrapolated from any other drug.
- PK studies in the dossier are uniformly old, with all PK studies in the dossier published between 1977 and 1994. This means that our current knowledge of the PK of fosfomycin is based on data that is more than 20 years old, with all the limitations of the PK studies conducted mostly in the 1980s and early 1990s.
- There is no new PK data that the evaluator is aware of for single 3 g oral fosfomycin that has been published in the last 20 years.
- Despite these limitations, the PK of single 3 g oral fosfomycin dose has been sufficiently well-studied in healthy adult volunteers and results across studies were reasonably consistent.
- The PK of single 3 g oral fosfomycin has not been studied in the target treatment population, but the PK of young adult females with acute uncomplicated UTIs can be extrapolated from the PK studies in healthy adult volunteers.
- The PK of single 3 g oral fosfomycin has not been studied in older adult females with acute uncomplicated UTI, but data can be extrapolated from the three PK studies conducted in the elderly and the one PK study conducted in renally impaired subjects.

- Only one PK study has been conducted in patients with renal impairment or haemodialysis. This study was well-conducted but in small numbers of subjects. This study is quite old having been published in 1988.
- No data is available in patients undergoing peritoneal dialysis or haemofiltration methods.
- No data is available in patients with hepatic impairment but the drug does not undergo hepatic metabolism.
- The PK of fosfomycin in patients with other acute or chronic disorders is unknown.
- The data for PK in pregnancy is limited and is based on a single study published in 1987 of 4 pregnant patients only.
- The sponsor states in the proposed PI that fosfomycin is distributed into breast milk but the dossier does not appear to contain any human or animal data or studies to support this statement.
- The sponsor has requested a treatment indication for females aged 12 years or older. There is only one PK study in the dossier for children and teenagers. PK data in teenagers is limited but PK parameters at the same dosage by body weight as adults appear similar to adults.
- The PK related to ethnicity is unknown.
- The PK of multiple doses of fosfomycin has not been well-studied, and all PK studies in the dossier were for single dose fosfomycin only. The optimum dosage interval between a first, second and third dosage of fosfomycin is unknown, should more than one dose be required. The sponsor has requested a 3 g single dose for the treatment of uncomplicated UTI (indication 1), and there is sufficient PK data in the dossier to support this dose. However, the sponsor has requested a surgical prophylaxis indication of a 3 g dose 3 h prior to surgery followed by a second dose 24 h after surgery but has not provided any PK data for this dosage regimen.
- The plasma protein binding data is limited. It is based on a single study of 10 volunteers published in 1969.
- The proposed PI states that fosfomycin is distributed into the seminal vesicles, but this data has not been provided.
- Data on possible enterohepatic circulation of the drug is largely based on the presence of 2 peaks in serum with some supporting data missing from the dossier.
- Data on biliary excretion is largely based on biliary levels in 2 volunteers undergoing cholecystectomy with some supporting data missing from the dossier.
- Studies of possible PK drug interactions are limited to metoclopramide and cimetidine only.

Questions regarding the PK studies

- Could the sponsor please provide further animal or human data regarding the distribution of fosfomycin into breast milk? Note the differences between the proposed Australian data which states that the drug is distributed into breastmilk and the PI in the USA stating that it is unknown whether the drug is excreted into breastmilk.
- Could the sponsor please provide the full poster or publication by Chezzi (1989) regarding the penetration of fosfomycin into seminal vesicles? The abstract in the dossier does not contain sufficient information.
- Is the sponsor aware of any PK data in peritoneal dialysis or haemofiltration?

- Could the sponsor provide more data regarding the biliary excretion and enterohepatic circulation of drug, specifically the publications referred to in the paper by Segre (1987) contained in the dossier?
- Is the sponsor aware of any other studies regarding PK drug interactions? Why do some of the early publications refer to possible fosfomycin interactions for lithium or balsalazide? Could the sponsor provide these studies? If not, could the sponsor comment on whether there is a potential interaction?
- Fosfomycin accumulates in patients with renal impairment however the clinical significance of this appears to be unknown. The last sentence in the publication by Fillastre (1988) recommends dosage reduction in patients with chronic renal sufficiency however this has not been recommended in the proposed PI. Could the Sponsor comment further? Is the sponsor aware of any data regarding the accumulation of the drug in patients with renal failure and any negative potential consequences of this?

Pharmacodynamics

Studies providing pharmacodynamic data

Pharmacodynamic studies of fosfomycin are mostly included in the nonclinical study reports, which have been evaluated by the nonclinical evaluator. However, there are some important clinical pharmacodynamic issues and issues of microbiology and resistance development which require discussion and review in the clinical evaluation of fosfomycin.

The pre-clinical and clinical development of fosfomycin in the late 1970s and early 1980s predates the development of antimicrobial pharmacodynamics. At that time, it was not a regulatory requirement to have a detail assessment of the pharmacodynamics of any new candidate antimicrobial agents. Hence, the pharmacodynamics studies of fosfomycin are extremely limited.

Below shows the studies related to each pharmacodynamic topic.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	In vitro pharmacodynamics	Mazzei 2006[58]	*
		Wiedemann 1987[59]	*
		Greenwood 1987[60]	*
	Bacteriostatic effect	Bergan 1990[61]	*
	In vivo pharmacodynamics	Carlone 1987[62]	*

[58] Study objectives: To investigate the in vitro pharmacodynamics including postantibiotic effect (PAE) of fosfomycin.
[59] Study objectives: To assess the pharmacodynamics particularly bacterial kill in an in vitro model.
[60] Study objectives: To test the activity of fosfomycin against E. coli in an in vitro dynamic bladder model.
[61] Study objectives: To study the antibacterial effect of fosfomycin in urine.
[62] Study objectives: To assess the adhesive properties of fosfomycin on bacteria isolated from the urine of patients with UTIs, and to compare these properties to those of norfloxacin and cotrimoxazole.

PD Topic	Subtopic	Study ID	*
	Bacterial resistance development	Gupta 2005[63] Wiedemann 1987[64] Greenwood 1987[65]	*
Secondary Pharmacology	Secondary pharmacodynamic effects	No studies	
Gender other genetic and Age Related Differences in PD Response	Effect of gender	No studies	
	Effect of genetic characteristic	No studies	
	Effect of age	No studies	
PD Interactions	Any drug	No studies	
Population PD and PK-PD analyses	Healthy subjects	No studies	
	Target population	No studies	

* Indicates the primary PD aim of the study.

No PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Summary of pharmacodynamics

Mechanism of action

- Fosfomycin is a phosphonic acid antibiotic which acts on the first stage of bacterial cell wall synthesis.
- Fosfomycin inhibits the enzyme phosphoenolpyruvate UDP-GlcNac-3-enolpyruvyl transferase which is contained in the bacterial cell wall. This irreversibly blocks the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate.
- Fosfomycin is actively transported into the bacterial cell wall via two different transport systems. These are the L-alpha-glycerophosphate transport system or alternatively the hexose phosphate pathway.
- The activity of fosfomycin is augmented in the presence of glucose-6-phosphate.
- Fosfomycin acts at a different stage of cell wall synthesis than the beta-lactam antibiotics. It mechanism of action is unique and therefore cross-resistance with other antibiotics in unlikely.

Antimicrobial susceptibility testing

- Fosfomycin trometamol is not calibrated for antimicrobial susceptibility testing against many bacteria, according to current clinical microbiology guidelines.
- Using EUCAST methods and breakpoints, fosfomycin trometamol single 3g oral dose is calibrated for the treatment of acute uncomplicated UTIs caused by Enterobacteriacae

[63] Study objectives: To assess the relative effects of fosfomycin, ciprofloxacin and nitrofurantoin on E. coli isolated from bowel flora in women after treatment for uncomplicated UTI.
[64] Study objectives: To assess the pharmacodynamics particularly bacterial kill in an in vitro model.
[65] Study objectives: To test the activity of fosfomycin against E. coli in an in vitro dynamic bladder model.

genus (this genus of aerobic gram negative bacteria includes E. coli, Proteus mirabilis, Klebsiella, Serratia etc). MIC breakpoints are <32 µg/mL (susceptible) and >64 µg/mL (resistant).

- There are no EUCAST methods or breakpoints for other urinary pathogens such as Pseudomonas, Staphylococcus saphrophyticus, or Enterococcus.
- EUCAST methods that can be used are disc, gradient MIC strip, agar dilution, broth dilution or commercial systems. All methods must have additional glucose-6-phosphate supplementation.
- Using CLSI methods and breakpoints, only E. coli and Enterococcus faecalis from urinary tract isolates are calibrated. Current MIC breakpoints for both are < 64 µg/mL (susceptible), 128 µg/mL (intermediate), and > 256 µg/mL (resistant). Importantly, no other bacterial species apart from E. coli and Enterococcus faecalis have susceptibility testing guidelines by CLSI methodology.
- Studies that report fosfomycin susceptibility for other bacterial species usually extrapolate breakpoints from known E. coli breakpoints but this has not been validated.
- Disc and agar dilution CLSI methods are approved provided there is supplemental glucose-6-phosphate. CLSI does not recommend broth dilution fosfomycin susceptibility testing for fosfomycin.

Antimicrobial activity of fosfomycin

- Many of the studies of fosfomycin susceptibility contained in the dossier were performed studies when the drug was originally approved in Europe in the 1980s.
- In Australia, the drug has had limited availability on the SAS scheme only.
- Many Australian laboratories currently only test fosfomycin for urinary pathogens that are resistant to other oral antibiotics.
- A preclinical study of fosfomycin susceptibility performed in the United States prior to approval there in 1996 shows that E. coli is usually susceptible, but there is some intrinsic resistance in Enterobacter, Morganella morganii, Providencia, Staph saphrophyticus, Pseudomonas, Enterococcus and Stenotrophomonas. Acinetobacter spp. was usually resistant.
- The Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC) Study included 9 European countries and Brazil. In 2008, their study of 4,264 adult women with acute uncomplicated lower UTI showed that E.coli was most frequent uropathogen (76.7%). E. coli fosfomycin susceptibility was 98.1%. Only 0.6% of E. coli isolates had an MIC of >128 mg/L.
- In the ARESC Study, the most common uropathogens after E. coli were Klebsiella pneumoniae, Proteus mirabilis and Staphylococcus saphrophyticus, all of similar incidence at 3.4 to 3.6%. Fosfomycin resistance rates were 5.6% for Klebsiella pneumoniae and 9.7% for Proteus mirabilis, using an extropolated CLSI breakpoint of > 256 mg/L as resistant. Fosfomycin susceptibility could not be reported for Staph saphrophyticus as there are no known breakpoints.
- In a Taiwanese study published in 2011 of 960 bacteria associated with UTI, E. coli was uniformly susceptible, and Klebsiella pneumoniae and Enterobacter cloacae were usually although not always susceptible. Pseudomonas and Stenotrophomonas susceptibility was highly dependent on whether CLSI or EUCAST breakpoints were used (extrapolated from E. coli). Acinetobacter baumaniae was usually resistant. Fosfomycin was very active against Staphylococcus aureus (including methicillin-resistant strains) and E. faecalis (including vancomycin-resistant strains). Activity

against E faecium was very dependent on whether extrapolated CLSI or EUCAST breakpoints were used.

- There are no PK/PD breakpoints for fosfomycin.
- Bacterial species which are common uropathogens and are usually fosfomycin susceptible include E. coli (most common uropathogen), Citrobacter spp, Klebsiella spp, Proteus spp, Enterococcus faecalis, and S aureus.
- Bacterial species which are not uncommon uropathogens and are frequently fosfomycin resistant include Enterobacter spp, Serratia marcescens, Morganella morganii, Providencia spp, Pseudomonas aeruginosa, Staph saphrophyticus, Stenotrophomonas maltophilia and Enterococcus faecium.
- Bacterial species which are not uncommon pathogens and are usually fosfomycin resistant include Acinetobacter spp.
- Fosfomycin has useful activity against many ESBL-producing isolates of E. coli and Klebsiella pneumoniae.

Primary pharmacodynamic effects of fosfomycin

- There is very limited pharmacoydnamic data available for fosfomycin due to its initial early preclinical development in the 1980s prior to the modern development of antimicrobial pharmacodynamics.
- There are no good human or animal model studies of the pharmacodynamics of the drug and very limited in vitro data.
- Fosfomycin is rapidly bactericidal at concentrations close to the MIC.
- In an in vitro study, fosfomycin demonstrated a concentration-dependent bactericidal effect against P. mirabilis and E. coli. At concentrations ≥ 8 x MIC, there was no re-growth for more than 24 h. Against both bacterial species fosfomycin demonstrated a long concentration-dependent PAE of up to 4.7 h.
- In an in vitro PK model, fosfomycin showed concentration-dependent killing against Enterobacter cloacae, E. coli, and S aureus. Concentration-dependent killing also occurred for E. faecalis, but only at the highest 3 g dose. At lower doses (1g or less), fosfomycin was bacteriostatic against E. faecalis. For all strains, a 3 g dosage prevented regrowth of E cloacae, E. coli, S aureus and E. faecalis within 23 h after the dose.
- Suggest reword proposed PI to: 'Limited data indicate that fosfomycin most likely acts in a concentration-dependent manner.'
- In a study of 8 healthy male volunteers who received a dose of 50 mg/kg of fosfomycin, urinary concentrations of fosfomycin were very high and this dose was sufficient to inhibit bacterial growth at 48 h in urine diluted 256 times for E. coli, 32 times for Proteus mirabilis, 64 times for P aeruginosa, and 8 times for E. faecalis.
- In a study of the activity of fosfomycin pre-treated bacteria (P mirabilis, E. coli, E. faecalis and Strep agalactiae) isolated from the urine of patients with UTIs tested against human urinary epithelial cells, fosfomycin reduced bacterial adhesion.

Secondary pharmacodynamic effects

- No studies presented.
- Fosfomycin activity is augmented in the presence of glucose-6-phosphate and G6PD deficiency is an exclusion criterion in the most recent of the pivotal studies (Study US-MON-03). Is the sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in G6PD deficient patients? Why was G6PD deficiency an exclusion criterion in the Study US-MON-03?

Time course of pharmacodynamic effects

- No studies.

Relationship between drug concentration and pharmacodynamic effects

- Data in this area is extremely limited and is based on a small amount of in vitro data only.
- A dose of 3 g fosfomycin trometamol appears optimal in terms of bactericidal activity and resistance development. A dose of 1 g fosfomycin trometamol was inferior. Higher doses or sequential dosing has not been studied.
- The PK/PD parameters of safety and the PK/PD parameters and breakpoints of efficacy for fosfomycin have not been studied in vitro or in vivo and are unknown.

Genetic, gender and age related differences in pharmacodynamic response

- No studies.

Pharmacodynamic interactions

- No studies.

Epidemiology of fosfomycin resistance development and its relationship to fosfomycin usage

- In a study of 14,319 urinary isolates of E. coli in Spain, fosfomycin susceptibility was 99% in 1994 and 98.4% in 2001. Fosfomycin susceptibility to E. coli was maintained despite sales of 307,000 doses of fosfomycin in Spain in 1995 increasing to 455,000 by 1999.

Mechanisms of fosfomycin resistance

- Chromosomal or plasmid-mediated mechanisms of fosfomycin resistance may occur, including target site modification and inactivation.
- All resistance mechanism papers located were published in 1993 or earlier and the resistance mechanisms summary provided by the sponsor also does not reference any studies later than 1993. Review papers contained reference at least 13 papers on the resistance mechanisms of fosfomycin published since 1994. These papers should have been included in the dossier but were not.
- The resistance development data in the dossier is more than 20 year out of date. If the evaluator has not identified this deficiency and reviewed the missing papers, please ask the sponsor to provide a more recent summary of resistance mechanisms and provide any relevant papers including but not limited to the 13 papers discussed above. Also, please provide for review all 48 publications.

Pharmacodynamic studies of fosfomycin resistance development

- In an in vitro dynamic bladder model, surviving bacteria after a 3g dosage of fosfomycin were re-exposed to a second identical drug dose after bacterial regrowth had occurred. For two fosfomycin-susceptible strains, when the peak concentration achieved was 50 or 250 mg/L, bacterial growth was suppressed for 20 h or more, but a second dose had reduced effect and resistance readily emerged. When the peak concentration was 2500 mg/L, resistance did not develop.
- This is some interest currently in the concept of mutant selection windows (MSWs) and mutant prevention concentrations (MPCs) for fosfomycin. There are at least 3 recent in vitro studies published but not included. If the evaluator has not reviewed these, could the sponsor provide these for review please? Also, has the MPC and MSW study referred to in PSUR1 Aug 2015-31 Jan 2016 refers to a pre-clinical study started in May 2015 for the in vitro evaluation of the MPC (mutant prevention concentration)

and the MSW (mutant selection window) of fosfomycin on Gram negative bacterial strains (Escherichia Coli, Proteus Mirabilis and Klebsiella Pneumoniae). It states that the first available results show a powerful bactericidal activity of fosfomycin. Is the sponsor able to provide this for review?

Effect of fosfomycin on bowel bacterial flora

- What is the relative effect of fosfomycin on bowel bacterial flora in comparison to other antibiotics? In a study of women after antibiotic treatment for acute uncomplicated lower UTI, rectal colonisation with E. coli was present in 94% of women prior to treatment. There was a significant reduction in the prevalence of rectal E. coli after treatment with ciprofloxacin and fosfomycin, but not after treatment with nitrofurantoin. By Day 28 to 30 after therapy, rectal prevalence of E. coli had returned to baseline for fosfomycin patients but not for ciprofloxacin patients. All rectal E. coli strains isolated from the subjects in the nitrofurantoin and fosfomycin treatment groups were susceptible to the study drug with which the subject had been treated. One of 25 women in the ciprofloxacin group had isolation of fluoroquinolone-resistant rectal E. coli.

Limitations of PD studies

- There is very limited pharmacodynamic data available for fosfomycin as its preclinical development in the 1980s predated the advent of antimicrobial pharmacodynamics.
- There are no known PK/PD breakpoints for fosfomycin.
- Fosfomycin susceptibility testing methods and breakpoints only exist for Enterobacteriaceae (includes E. coli) and Enterococcus faecalis.
- There is only one study of the effect of fosfomycin on bowel bacterial flora
- There are no publications on fosfomycin resistance development and mechanisms that are more recent than 1993. There are a large number of studies in this area that have not been included in the dossier. These will require review if not already done so as an integral component of any possible approval process.

Questions regarding the PD studies

- Is the sponsor aware of any theoretical or actual secondary pharmacodynamic effects of fosfomycin in glucose-6-phosphate dehydrogenase deficient patients? Why was G6PD deficiency an exclusion criterion in the study US-MON-03?
- The sponsor has not included any studies of fosfomycin resistance development and mechanisms from 1994 onwards. At least 13 studies were identified easily from two review papers. These studies are the references in the paper by Keating (Karageorgopoulos et al, 2012; Marchese et al, 2003; Nilsson et al, 2003; Oteo et al, 2009; Rodriguez-Avial et al, 2013; Oteo et al, 2010) and the references in the paper by Michalopoulos (2011) (Beharry et al, 2005; Horii et al, 1999; Garcia et al, 1994; Cao et al, 2001; Bernat et al, 1997; Rigsby et al, 2005; Arca et al, 1997). The lack of recent studies on resistance mechanisms and development is a serious omission from the dossier. Has the sponsor taken care to update the dossier and ensure it is current since approval of fosfomycin by the FDA in 1996 and Canada in 1999? A current review of resistance development and mechanisms is critical to the approval process of any antimicrobial agents. Please ask the sponsor to provide the studies above and any other relevant studies published in the last 20 years for review by the reviewer, as appropriate.
- Could the sponsor provide the recent studies on mutant selection windows and mutant prevention concentrations for review to the evaluator, as appropriate (if not already reviewed by the evaluator)? The studies are Mei et al. Eur J Clin Microbiol

Infect Dis. 2015 Apr;34(4):737-44 ; Liu et al. J Antibiot (Tokyo). 2013 Dec;66(12):709-12; Pan et al. J Antibiot (Tokyo). 2016 Oct 19 epub.

Dosage selection for the pivotal studies

A single 3 g fosfomycin trometamol sachet (Monurol or Monuril) was used in all 3 pivotal studies and the vast majority of all the clinical trials. Some of the early trials used a 2 g sachet in adolescent females but there is limited PK data to support this.

Evaluator's conclusions on dose finding for the pivotal studies

There were no good dose-finding pivotal studies performed. This is because the dose of 3 g single oral dose had been well-established in many non-pivotal efficacy studies, which predated the 3 pivotal efficacy studies.

A single 3 g oral sachet appears an appropriate dose in all females 12 years and over with normal to moderately impaired renal function based on the PK and limited PD data available.

Efficacy

Indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

Pivotal studies

These include:

- Study MON-US-01
- Study MON-US-02
- Study MON-US-03

Conclusions

- Overall there is a large amount of data on efficacy of fosfomycin; the vast majority of this is for a single dose of the 3g oral fosfomycin trometamol sachet that the sponsor is seeking to have approved.
- There are 3 pivotal efficacy studies from the early 1990s which have been reasonably well-conducted according to GCP. They suggest that single dose 3g fosfomycin trometamol has a clinical and bacteriological efficacy rate of 83-89% in the treatment of females with acute uncomplicated lower UTI. This is as effective as 7 days of nitrofurantoin but less effective than 7-10 days of ciprofloxacin or TMP/SMX.
- The non-pivotal efficacy studies and meta-analysis provide supportive evidence of a similar bacteriological efficacy rate to the pivotal efficacy studies. Most of the studies predate GCP and are open-label with no or poor randomisation methods.
- Bacteriological efficacy of fosfomycin against E. coli is generally good and this organism is the most common uropathogen. Bacteriological efficacy against other uropathogens especially Staph saphrophyticus can be variable.

Limitations

- Potential for and ease of resistance development to fosfomycin after therapy has not been addressed in these studies and is of critical importance to this submission. More information on this area needs to be provided for review by the TGA.

Questions

- The placebo sachet in pivotal Studies US-MON-01, US-MON-02 and US-MON-03 was matched for appearance with the fosfomycin sachet. A mandarin and / or orange juice flavour plus sweetener was used. Was the placebo sachet also matched for taste?
- In pivotal Studies MON-US-01 and MON-US-02, why was it considered necessary to change from a one-tailed to a two-tailed 0.05 level of significance?
- In Study MON-US-01, recurrence rates for fosfomycin were higher than for ciprofloxacin. Could the sponsor provide the results of the susceptibility testing for ciprofloxacin and fosfomycin for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?
- For Study MON-US-02, could the sponsor provide the results of the susceptibility testing for fosfomycin and TMP/SMX for the recurrent isolates? Did the recurrent isolates develop resistance to the study drug?
- In Studies MON-US-01, are p values available for the comparison between ciprofloxacin and fosfomycin for bacteriological efficacy against E. coli?
- In Studies MON-US-02, are p values available for the comparison between TMP-SMX and fosfomycin for bacteriological efficacy against E. coli?
- Study US-MON-03 contains the following information: 'In its evaluation of the efficacy of FT in the MON-US-01 and MON-US-02 trials, the FDA presented results to an Advisory Committee based on criteria which differed in certain respects from those defined prospectively in the protocols. Primarily, the FDA included the use of antibiotics for UTI as a criterion for failure and data from patients with 'missing' visits were handled either by excluding the patient from the modified ITT analysis (for non-completers who discontinued for reasons other than treatment failure or related reasons) or by assigning outcomes on a case-by-case basis (for non-completers who remained in the modified ITT population because their discontinuation reason was related to treatment failure.)'
- Is the sponsor able to provide the full transcript of the FDA report and also the statistical repeat analysis done according to the FDA recommendations?
- None of the 3 pivotal Studies MON-US-01, MON-US-02 or MON-US-03 contain much data on antimicrobial susceptibility testing results after therapy and whether resistance development occurred to the study drug. There is some individual patient data in Appendix 6 of MON-US-03 but is difficult to tease out and appears incomplete. Of particular importance is MON-US-01 which showed a significantly higher recurrence rate for fosfomycin patients compared to ciprofloxacin patients (14% versus 4%, $p < 0.01$). Is the sponsor able to provide any further antimicrobial resistance data for any of the 3 studies in early and late follow-up urine cultures after therapy?
- In PSUR January 1995 to December 1999, the publication by Licciardello and Bignamini on the efficacy and safety of fosfomycin is missing all figures. Could the sponsor provide the full paper including all figures please?

Indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

Pivotal studies

There were no pivotal studies presented; only non-pivotal studies were presented.

Conclusions

- The main current indications in Australia and internationally for antibiotic prophylaxis in procedures involving the urinary tract are in transurethral resection of the prostate (TURP) and transurethral prostatic biopsy.
- There were no good quality studies in the dossier of fosfomycin compared to another appropriate antibiotic in the prophylaxis of TURP or transurethral prostatic biopsy.
- Fosfomycin has good prostatic penetration so a good quality study comparing fosfomycin to gentamicin in TURP or fosfomycin to ciprofloxacin in transurethral prostatic biopsy would be of interest.
- Efficacy studies contained in the dossier are of insufficient content and insufficient quality to approve this proposed indication.

Safety

Studies providing safety data

As both proposed indications utilised the same dosage of fosfomycin trometamol (3 g single dose), safety data for both indications has been amalgamated.

Pivotal studies that assessed safety as the sole primary outcome

No studies presented.

Pivotal and/or main efficacy studies

- Study MON-US-01- see Study ID MON-US-01 for more information
- Study MON-US-02- see Study ID MON-US-02for more information
- Study MON-US-03- see Study MON-US-03 for more information.

These 3 related pivotal studies had the same methods of collecting and reporting safety data. These are as follows:

- General adverse events (AE): Safety analyses were performed on all patients who received at least one dose of study medication. These were performed at Visit 2 (Day 5 to 10 of study), Visit 3 (Day 11 to 17 for Studies US-MON-01 and US MON-03 and Day 14 to 20 for Study US-MON-02) and Visit 4 (Day 18 or later for Study US-MON-01 and US-MON-03 and Day 21 or later for Study US-MON-02). Adverse events were elicited by open-ended questioning and were assessed, documented and reported in accordance with GCP and classified according to MedDRA criteria.
- AEs of particular interest: No adverse events were targeted for specific questioning.
- Laboratory tests: Patients had baseline urinary cultures and urinalysis performed within 96 h of starting treatment and repeated at Visits 2, 3 and 4. Urinalysis was repeated 4-6 weeks post therapy. Patients had clinical chemistry (urea, electrolytes, liver function, cholesterol and uric acid), full blood count and urinalysis performed within 96 h prior to starting therapy and repeated at Visit 2 and 3. A central laboratory was used for all 3 studies [information redacted] except for urinalyses and urine cultures which were performed by a licensed or accredited local laboratory.
- Other safety variables: Vital signs were recorded at each study visit. Physical examination and body weight were recorded at Visit 1 and the final visit.

Other efficacy studies

The non-pivotal efficacy studies listed below also provided safety data. Most of the studies were performed in the 1980s and early 1990s prior to the 3 pivotal studies and do not meet GCP guidelines. In general, reporting of safety data was poor and relatively brief and data on adverse events were only collected if the patient spontaneously reported them. Few if any of the studies performed clinical chemistry, haematology or ECG monitoring.

Many of the non-pivotal studies did not specifically list discontinuations due to AEs in the information (usually publications) provided in the dossier. AEs were often not stratified by whether they were probably, possibly or unlikely related to treatment. Hence, safety data from these studies is often limited at best.

Patient exposure

All patients in the pivotal studies were female. The majority of the patients in the other controlled and uncontrolled treatment trials were female although some included males. In the four surgical prophylaxis trials, there were both male and female patients. The majority of patients were Caucasian. Most patients had acute uncomplicated lower UTIs although some patients had chronic or recurrent UTIs or asymptomatic bacteruria. Pregnant patients and elderly patients were included in some trials.

The vast majority of patients received a 3 g dose of fosfomycin trometamol. A few adolescent females received a 2 g sachet in countries where this dosing strength was available. It is likely they received a similar mg/kg dose by body weight compared to adult females.

A few studies included patients dosed with more than one dose of fosfomycin. This was usually 3 g daily for 3 doses. Insufficient patients received more than one dose of fosfomycin to be able to make any recommendations or safety analysis for multiple doses of fosfomycin.

Table 6: Exposure to fosfomycin and comparators in clinical studies

Study type/ Indication	Controlled studies					Uncont-rolled studies	Total Fosfomycin
	Fosfomycin 3g single dose	Nitrofurantoin 100 mg bd x 7 days	Ciprofloxacin 250 mg bd x 7 days	TMP/SMX 1 bd x 10 days	Other compar-ator		
Indication 1 Pivotal/Main US-MON-01 US-MON-02 US-MON-03	 432F 426F 375F*	 374F*	445F	 428F			1233
Indication 1 Other trial	1810	114 (50 mg qid x 7 days)			1715	5580	7390
Subtotal indication 1	3043	488	445	428	1715	5580	8623
Indication 2 Prophylaxis of UTI Non-pivotal trial	1278				752		1278
TOTAL	**4321**	**488**	**445**	**428**	**2467**	**1480**	**9901**

* Aged 12 years or older; F=female

Safety issues with the potential for major regulatory impact

Unlike most new drug submissions, fosfomycin has been commercially available and widely used in many countries in Europe, the United States and elsewhere since the 1980s. Hence, in addition to the clinical trial data discussed, there is a very large post-marketing experience of the drug which is contained in the PSURs.

It should be noted that patients in the 3 pivotal studies had haematology and biochemistry testing performed at baseline and repeated at Day 5 to 9 and Day 11 to 15 only. Also, it was uncommon for haematology or biochemistry testing to be performed in the non-pivotal studies. No clinical study in the dossier including electrocardiographic monitoring. Most clinical studies in the dossier were performed in the 1980s or 1990s predating GCP. Hence, and unusually for a novel drug application, most rare issues with potential regulatory impact will likely be identified by the post marketing experience.

Liver function and liver toxicity

Pivotal efficacy studies

- Study US MON-01. A shift analysis was done for the twelve serum chemistry parameters (including liver function tests) evaluated to determine the number of patients in each treatment group who had normal pre-treatment values and abnormally elevated post-treatment values. In the fosfomycin and ciprofloxacin treatment groups, zero to five of the patients experienced a shift from a normal test value to an abnormally elevated value (pre-treatment to post-treatment) for eleven of the twelve serum chemistry parameters evaluated. Two fosfomycin patients had an elevated SGOT value that exceeded 150 U/L. One patient taking only the oral contraceptive pill with baseline normal liver function had hepatitis with liver enzymes of SGOT 666 IU/l and SGPT 213 IU/L and normal bilirubin and alkaline phosphatase at visit 3. The liver enzymes had normalised at week 12.
- Study US-MON-02. A similar shift analysis was done in the same manner as for US-MON-01. One fosfomycin patient had a mild elevation of SGOT and SGPT.
- Study US-MON-03. A similar shift analysis was done in the same manner as for US-MON-01. In the fosfomycin and nitrofurantoin treatment groups, zero to six patients experienced a shift from a normal test value to an abnormally elevated value (pre-treatment to post-treatment) for eleven of the twelve serum chemistry parameters evaluated. None appear clinically significant. There were no significant changes in liver function in the fosfomycin group.

Other non-pivotal studies

Liver function testing was rarely performed and / or reported. No reports of clinical hepatitis.

Post marketing experience

Twelve patients with hepatitis are recorded in the PSURs with each case discussed individually. Information on each case is variable. Hepatitis in the 12 cases typically occurs 1 to 7 days after the dose. Hepatitis cases in the PSURs were mostly acute and sometimes associated with jaundice. Some cases were cholestatic. Some but not all patients were taking concomitant medications. History of other confounding factors such as alcohol intake is not reported for any case and only 1/12 cases had viral hepatitis serology reported. Most cases were reported to resolve although that information was not uniformly recorded in the PSURs. There was one case of fatal hepatitis necrosis in a 38 year old female (case PSUR 1 January 1995 to 31 December 1999). No details of her clinical history are available except that it occurred 7 days after single dose of fosfomycin for UTI. No concomitant medications are listed for the fatal case.

Summary of Clinical Safety lists 22 serious cases and 3 non-serious cases of adverse reactions causing hepatobiliary injury from spontaneous reporting and literature review. No further details of cases are provided in the dossier apart from the listing in this table.

Summary of liver toxicity

According to the information contained in the dossier, fosfomycin is associated with hepatitis but it is rare. In the pivotal studies, only 3 fosfomycin patients had hepatitis based on abnormal liver function testing results. Two were asymptomatic and it is unclear whether the third patient had symptoms. In post marketing data contained in the PSURs, hepatitis is reported on 12 occasions with one fatal case. It is unclear whether the fatal case was taking other concomitant medications. There are 25 cases of adverse reactions causing hepatobiliary injury listed obtained from spontaneous reporting and literature review. The dossier does not provide further details of the other 13 cases apart from the listing in the table.

Renal function and renal toxicity

Pivotal efficacy studies

It should be noted that patients with significant renal impairment at baseline were excluded from the pivotal studies.

- Study US MON-01. No significant changes in shift analysis and no markedly abnormal results.
- Study US MON-02. No significant changes in shift analysis and no markedly abnormal results.
- Study US MON-03. No significant changes in shift analysis and no markedly abnormal results.

Other non-pivotal studies

Renal function testing was rarely performed and / or reported. No reports of clinical renal impairment.

Post marketing experience

There were no reports of renal impairment associated with fosfomycin in the PSURs. 14 serious cases and 27 non-serious cases of adverse reactions causing renal and urinary disorders were listed from spontaneous reporting and literature review. Two serious cases are listed as 'tubulointerstitial nephritis'. No further details of cases are provided in the dossier apart from the listing in this table.

Summary of renal toxicity

Based on the information contained in the dossier, fosfomycin does not appear to be have a significant association with renal toxicity. As the most common adverse reaction of fosfomycin is gastrointestinal intolerance, prerenal failure due to dehydration from nausea, vomiting and diarrhoea could occur. Details of the 14 serious renal and urinary adverse events were not provided.

Other clinical chemistry

Pivotal efficacy studies

- Study US MON-01. Thirty-three fosfomycin patients and 37 ciprofloxacin patients had a rise in serum cholesterol out of normal range at post-treatment evaluation. The number of shifts from normal to high values was similar in both the fosfomycin and ciprofloxacin treatment groups. The shift from normal to high (max 27.5 mEq/L) in the potassium tests was probably due to a laboratory error (receipt of hemolyzed specimens or plasma rather than serum).
- Study US-MON-02. Thirty-five fosfomycin patients and 21 TMP/SMX patients had a rise in serum cholesterol out of normal range. The number of shifts from normal to

high values was similar in both the FT and TMP/SMX treatment groups. The shift from normal to high (max 27.5 mEq/L) in the potassium test was probably due to a laboratory error as in Study US-MON-01.

- Study US-MON-03. Twenty-eight fosfomycin patients and 31 nitrofurantoin patients had a rise in serum cholesterol out of normal range. The number of shifts from normal to high values was similar in both treatment groups. There were no markedly abnormal results.

Other studies

Clinical chemistry results were rarely performed and / or reported. No reports of significant abnormalities.

Post marketing experience

There was a single case of pancreatitis in a patient which resolved after 3 days. It is unclear whether this was a clinical and / or biochemical pancreatitis. The patient was also taking an oral contraceptive pill. The following serious abnormalities are listed in the Metabolism disorders tabulation: 'hypernatremia 1 case, hyponatremia 4 cases, hypokalemia 2 cases, hypoglycaemia 1 case'. No further details are provided of these cases in the dossier.

Summary of clinical chemistry

Based on the information provided in the dossier, fosfomycin does not appear to have a significant association with clinical chemistry abnormalities (this does not include liver and renal function). The serum cholesterol abnormalities noted in the 3 pivotal studies are minor, of similar incidence to the 3 comparator antibiotic arms and do not appear clinically significant.

Haematology and haematological toxicity

Pivotal efficacy studies

In the pivotal studies, haematology tests were last performed at Day 11 to 15, so long-term haematology effects are unlikely to have been noted within this time interval.

- Study MON-US-01. The shift analysis of the haematology data showed that in both treatment groups there was a shift from normal to low levels for haemoglobin, red blood cells, haematocrit, white blood cells, neutrophils, and lymphocytes. The number of shifts from normal to low values were few with numbers similar in both treatment groups. Decreases of haemoglobin to below the normal range were the most common changes noted among haematology tests. It is of note, however, that among fosfomycin patients, haemoglobin levels were not very low, they ranged from 11-16.3 g/dL at baseline and from 10.7-16.3 g/dL after therapy (mean change -0.26 g/dL; $p < 0.01$) No markedly abnormal haematology values were noted in any of the fosfomycin patients evaluated.
- Study US-MON-02. Overall, the number of shifts from normal to low values were few. However, over three times as many shifts in haemoglobin from normal to low occurred in the TMP/SMX group (25) than in the fosfomycin group (7). Almost twice as many shifts in haematocrit from normal to low occurred in the TMP/SMX group (15) than in the fosfomycin group (8). Decreases of hemoglobin to below the normal range were the most common changes noted among haematology tests. It is of note, however, that among fosfomycin patients, haemoglobin levels were not very low; they ranged from 10.3 to 16.6 g/dL at baseline and from 10.2 to 15.7 g/dL after therapy (mean change -0.11 g/dL; $p < 0.01$). One fosfomycin patient had developed an eosinophilia of 14% at Visit 3. None of the marked elevations was considered to be clinically significant.

- Study US-MON-03. Overall, the number of shifts from normal to low values were few. Decreases of haemoglobin to below the normal range were the most common changes noted among haematology tests. It is of note, however, that among fosfomycin patients, average haemoglobin levels were not significantly low. Just over l% of fosfomycin patients had markedly abnormal WBC counts either high or low (1.4% vs. 0.6% for nitrofurantoin). Further details were not supplied. Eosinophilia is listed as occurring in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients (US-MON-03). These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with Studies MON-US-01 and Mon-US-02 in which eosinophilia rates were < 1%.

Could the sponsor please advise the correct rate of eosinophilia for both drugs in Study US-MON-03? If the rate has risen compared to the two earlier pivotal studies, has the formulation changed? Was any eosinophilia clinically significant?

Other studies

Haematology results were rarely performed and / or reported. No reports of clinical issues.

Post marketing experience

The PSURs report 3 cases of thrombocytopenia. In each case, the patient was taking another medication which could have caused thrombocytopenia (quinidine, nitrofurantoin, ciprofloxacin respectively). One of these patients also had neutropenia which responded to filgrastatim. Another patient with small cell lung cancer taking concomitant itraconazole developed aplastic anemia and died. Cause of death of this patient was unknown. Five patients developed decreased or increased INR, no further details were provided. There were 23 serious adverse reactions listed without further details, the most important of which were: agranulocytosis/neutropenia (4), aplastic anaemia/bone marrow failure/ pancytopenia (3), anaemia (1), immune thrombocytopenic purpura (2), leukocytosis (1), leukopenia (2), macrocytosis (1), polycythaemia (1), thrombocytopenia +/- purpura (7).

Summary of haematological toxicity

Fosfomycin has been associated with a range of haematological toxicities but all appear to be rare. The most common of the rare toxicities are eosinophilia, thrombocytopenia, neutropenia and panyctopaenia. Interestingly the high (if correct) rates of eosinophilia noted in pivotal Study US-MON-03 are not reflected in post-marketing surveillance, which have no reports of eosinophilia (possibly because eosinophilia is rarely symptomatic unless associated with allergic rash).

Electrocardiograph findings and cardiovascular safety

Pivotal efficacy studies

No electrocardiograph monitoring was performed in the 3 pivotal studies.

Other studies

No electrocardiograph monitoring was performed in the non-pivotal studies.

Post marketing experience

In the PSURs, 6 cases of tachycardia were noted, one of which recurred after challenge. There are 20 serious cardiac disorders listed without further details, the most important of which were arrhythmia (1), atrial fibrillation/tachycardia (2), bradycardia (1), tachycardia (6), sinoatrial block (1), torsades de pointes (1).

Summary of electrocardigraph findings and cardiovascular safety

Electrocardigraph monitoring was not performed during the clinical trials of fosfomycin. No QT/QTc studies were submitted. Based on the post-marketing data, the drug does not appear to be associated with significant cardiac toxicity.

8.6.6. Vital signs and clinical examination findings

Pivotal efficacy studies

- Study US-MON-01. In both the fosfomycin and ciprofloxacin populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for systolic blood pressure and temperature.
- Study US-MON-02. In both the fosfomycin and TMP/SMX populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for diastolic blood pressure and temperature.
- Study US-MON-03. In both the fosfomycin and nitrofurantoin populations, statistically significant, but clinically insignificant decreases from mean baseline values were noted for temperature. In the fosfomycin population, statistically significant decreases from mean baseline values were noted for diastolic blood pressure and sitting pulse. These decreases were not considered to be clinically significant.

Other studies

No reports of clinically important issues.

Post marketing experience

No reports of concern in the PSURs.

Summary of vital signs and clinical examination findings

No significant abnormalities noted.

Immunogenicity and immunological events including hypersensitivity

Pivotal efficacy studies

No immunological events apart from rash were noted in the 3 pivotal studies.

Other studies

No immunological events apart from rash were noted.

Post marketing experience

The PSURs contain 7 reports of anaphylactic shock and/ or hypotension following fosfomycin. Onset after dosing was usually not specified but one case occurred 5 minutes after IV fosfomycin, one case started 10 minutes after an oral dosage and another case 30 minutes after an oral dosage. Three cases of Quincke's oedema were noted and 6 cases of facial or lip oedema. There were also cases or urticaria, cyanosis and dyspnoea. Nine cases of angiooedema, 12 cases of anaphylaxis, 15 cases of dyspnoea and 10 cases of unspecified hypersensitivity are noted without further detail.

Summary of immunological events including hypersensitivity

Fosfomycin is clearly associated with immediate hypersensitivity in the form of anaphylaxis, angiooedema, urticaria and asthma-like reactions. These are well-described but appear rare from the data contained in the dossier.

Serious skin reactions

Pivotal efficacy studies

Rash was reported in the 3 pivotal studies but there were no serious skin reactions noted.

Other studies

Rash was reported but there were no serious skin reactions noted.

Post marketing experience

There were 3 cases of toxic skin eruptions noted in the PSURs. The following serious skin reactions were noted without further detail: photosensitivity (3), erythema multiforme (2), Stevens Johnson syndrome (1), drug reaction with eosinophilia and systemic symptoms (2) and toxic epidermal necrolysis (2).

Summary of serious skin reactions

From the data contained in the dossier, fosfomycin is associated with serious skin reactions but these are rare.

Severe gastrointestinal disturbance and / or clostridium difficile colitis

Pivotal efficacy studies

Eight patients in the pivotal efficacy studies who received fosfomycin discontinued due to gastrointestinal intolerance, with diarrhoea the most notable symptom. Duration of diarrhoea in these discontinued patients was 1-7 days. None of the patients required hospitalisation.

Other studies

No reports of note.

Post marketing experience

In the PSURs, there were 2 case reports of Clostridium difficile infection which resolved without surgery. There were 3 reports of this condition.

*Sum**m**ary of severe gastrointestinal disturbance or Clostridium difficile colitis*

Diarrhoea is a relatively common fosfomycin adverse reaction but severe gastrointestinal disturbance is uncommon and Clostridium difficile infection appears rare.

Vestibular disturbance and deafness

Pivotal efficacy studies

No reports noted.

Other studies

No reports noted.

Post marketing experience

The PSURs contain one report of vertigo, vestibular loss and horizontal nystagmus lasting several months. There was another case of non-serious vertigo. There were 2 cases of reversible hearing loss. There was another report of reversible hearing loss in a patient taking fosfomycin every 15 days over a 2-year period (for an off-label indication). The following serious adverse reactions are listed: deafness (4), tinnitus (2), vertigo/vestibular disorder (6).

Summary of vestibular disturbance and deafness

Fosfomycin is associated with deafness, tinnitus, and vestibular disorder but these adverse events appear rare.

Psychiatric disturbance

Pivotal efficacy studies

No reports noted.

Other studies

No reports noted.

Post marketing experience

No reports in the PSURs. The following important serious adverse reactions are listed: acute psychosis (1), agitation (1), confusional state (2), hallucination (1), hypervigilance (1), insomnia (2), restlessness (1).

Summary of psychiatric disturbance

No significant adverse reactions noted in the dossier.

Bone and joint disturbance

Pivotal efficacy studies

No reports noted.

Other studies

No reports noted.

Post marketing experience

The PSURs contain 2 case reports of arthralgia and 1 case of oligoarthritis. 4 cases of arthralgia are listed.

Summary of vestibular disturbance and deafness

No significant adverse reactions noted in the dossier.

Neurological disturbance including paraesthesias

Pivotal and/or main efficacy studies

No events noted except one patient diagnosed with optic neuritis in Study US-MON-02 at day 10. Their vision returned to normal after steroid therapy.

Other studies

No reports noted.

Post marketing experience

Seven cases of paraesthesias noted in the PSURs. The paraesthesias are most commonly noted as tingling in the mouth, tongue and cheek. There are 16 cases of paraesthesias noted although only 2 are severe. Dysgeusia was noted in 11 cases although only 1 case was severe. There was also one case of hypogeusia. There was one case of optic neuritis listed; it is not known if this was the case noted in the Study US-MON-02. No other neurological disturbances of concern in the dossier.

Summary of neurological disturbance including paraesthesias

Paraesthesias and abnormalities of taste occur but are usually mild and transient.

Post marketing data

There is a large amount of post-marketing experience with the drug worldwide. Monurol 3g sachet was approved for use in the Netherlands (1997), UK (1992), USA (1996), Canada (1999), Switzerland (1988) and Singapore (1999). According to the 'Summary of Clinical Safety', fosfomycin was approved for the first time in 1986 (Italy) and is authorised in more than 80 EU and non-EU countries. For example, from 1 August 2015 to 31 January 2016, a total of 9,015,221 packages (283,207 packages of 2 g sachets and 8,732,014 packages of 3 g sachets) were sold by affiliates and contractual partners worldwide. Taking into account that the Defined Daily Dose of fosfomycin for the treatment of non-

complicated lower urinary tract infections is 3 g/one sachet (2 g in paediatric use) as a single dose, the number of subjects who received fosfomycin trometamol during the marketed use is assumed to be approximately equal to the number of packages sold. Therefore, it can be estimated that 9,015,221 patients (283,207 paediatric subjects and 8,732,014 adults) were exposed to fosfomycin trometamol between 1 August 2015 and 31 January 2016.

Two post-marketing surveys enrolling 4295 were included.

Nine Periodic Safety Update Reports (PSURs) conducted by the drug company Zambon are included in the dossier. They cover a continuous period from 1 January 1995 to 31 January 2016.

Severe rare ADRs noted in the post marketing period possibly or probably related to fosfomycin usage

The following rare adverse events possibly related to fosfomycin therapy contained in the PSURs should be noted.

Hepatic adverse events

- PSUR 1 Jan 1995 to 31 Dec 1999. One case of fatal hepatic necrosis in a patient occurring 7 days after single dose of fosfomycin for UTI. Clinical history, concomitant treatments not available.
- PSUR 1 Jan 1995 to 31 Dec 1999. A case of cholestatic hepatitis in a patient occurring 24 h after single dose fosfomycin. Patient taking multiple other medications including clotiapine. Resolved within a few days. Patient had previously taken single dose fosfomycin 6 months earlier without incident.
- PSUR 1 July 2000 to 31 July 2005. A patient with cystic fibrosis without liver involvement developed mild to moderate hepatitis 4 days after starting fosfomycin 12 g daily (unclear whether oral or IV formulation of fosfomycin used). Resolution on ceasing drug, hepatitis recurred again after 2 further challenges with fosfomycin and resolved when drug ceased. Peak liver enzymes were ALT 921 IU/L, AST 482 IU/L, GGT 214 IU/L.
- PSUR 1 Jan 2005 - 31 Aug 2009. A case of jaundice and hepatitis in a patient two days after 3g fosfomycin. Peak liver enzymes were bilirubin 9.8 x normal, AST 6.3 x normal, ALT 12.4 x normal, GGT 10.8 x normal, ALP 1.4 x normal. Viral hepatitis serology negative.
- PSUR 1 Jan 2005 - 31 Aug 2009. Nonserious hepatic enzyme increase. No other details available.
- PSUR 1 June 2009 - 30 Nov 2009. Hepatitis in a patient without any underlying liver condition and no concomitant medication reported. Three days after fosfomycin administration (unspecified dose for 3 days), the patient experienced drug-induced acute mixed liver damage with peak value ALT 12.8 x upper limit of normal, peak value ALP 1.9 x upper limit of normal, peak value bilirubin 42 µmol/L and peak value GGT 4.9 x upper limit of normal. Therapy with fosfomycin was discontinued and the hepatic function tests normalized 1 week after the withdrawal of the drug.
- PSUR 1 June 2010 - 31 May 2015. Jaundice and hyperbilrubinaemia after 9g daily (i.e. 3x recommended daily dose) for an unknown amount of time. No other details available.
- PSUR 1 June 2010 - 31 May 2015. Jaundice 48 h after fosfomycin, patient also taking paracetamol and ibuprofen. Recovery after 2 months.

- PSUR 1 June 2010 - 31 May 2015. Acute hepatits one week after single fosfomycin dose. Liver biopsy showed drug-induced hepatitis.
- PSUR 1Feb 2015- 31 July 2015. Chronic hepatitis, assessed as unlikely related to Monuril, being more probably related to autoimmune origin. No further details provided.
- PSUR 1Feb 2015- 31 July 2015. Patient with medical history of cholecystectomy experienced hepatocellular injury after a single-dose of fosfomycin 3 g. No further details provided.
- PSUR 1Feb 2015- 31 July 2015. Hepatitis. No further details provided.

Anaphylaxis / hypersensitivity

- PSUR 1 Jan 1995 - 31 Dec 1999. A case of Quincke's oedema in a patient who received a single dose of fosfomycin and also received enoxacin 200 mg daily for 3 days starting at the same time. Patient recovered.
- PSUR 1 Jan - 30 June 2000 and PSUR 1 July 2000 - 31 July 2005. Two cases of Quincke's oedema which resolved. No other details available.
- PSUR 1 Jan 1995 - 31 Dec 1999. A case of bronchospasm and anaphylactic hypotension in a patient after treatment with single dose fosfomycin. Patient recovered with adrenaline and steroids. No other concomitant medications. Patient had previously had anaphylaxis with beta-lactams and subsequently developed an unspecified allergic reaction with Baycip (ciprofloxacin).
- PSUR 1 Jan 1995 - 31 Dec 1999. A pregnant patient (16 weeks gestation) who developed bullous rash and mild facial swelling 3 days after single dose fosfomycin. Recovered with steroids. Pregnancy otherwise uneventful.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with anaphylactic shock immediately after fosfomycin dose. Recovered. Concomitant long-term tricyclics not implicated and continued these.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with anaphylactic shock 5 minutes after receiving IV fosfomycin, aminophylline and hydrocortisone for asthma. Patient recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. Cyanosis and dyspnoea on the same day as 3g dose of fosfomycin. Fully recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. A case of swollen lip and cheeks and dyspnoea 24 h after 3 g fosfomycin. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Anaphylactic shock occurring 30 minutes after single fosfomycin dose. Recovered.
- PSUR 1 Jan 2005 - 31 Aug 2009. Anaphylactic shock and rash occurring one day after single fosfomycin dose. Recovered.
- PSUR 1 June 2009 - 30 Nov 2009. Lip swelling, non-serious. No other details.
- PSUR 1 Dec 2009 - 31 May 2010. Face angioedema, urticaria and dyspnoea on the same day as 3 g fosfomycin single dose. Recovered.
- PSUR 1 Dec 2009 - 31 May 2010. A patient with anaphylaxis 10 minutes after 3g single dose fosfomycin. This started as itchiness and exanthema on the trunk and legs 10 minutes after taking Monuril. Thereafter the patient started to feel narrowing of the throat followed by hypotension. The patient was brought to the hospital, where she was administered with anti-allergic agents, steroids and adrenaline. The patient recovered without sequelae within 24 to 48 h.

- PSUR 1 Dec 2009 - 31 May 2010. Non-serious throat tightness. No other details.
- PSUR 1 June 2010 - 31 May 2015. Anaphylactic shock after fosfomycin. Recovered.
- PSUR 1 June 2010 - 31 May 2015. Allergic reaction with urticaria and syncope the day after taking a single dose of fosfomycin. Recovered.

Cutaneous reactions

- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption requiring 7 days hospitalisation. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption starting 24 h after fosfomycin. Resolved.
- PSUR 1 June 2009 - 31 Nov 2009 p14. Toxic skin eruption and fever starting 24 h after fosfomycin, lansoprazole and trimebutine. Resolved.
- PSUR 1 June 2010 - 31 May 2015. 44 cases. Severe cutaneous adverse reactions.

Haematological adverse events

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with UTI took a single dose of fosfomycin and also took nitrofurantoin one day earlier and two subsequent nitrofurantoin doses. Three days after fosfomycin she was admitted to hospital with acute pyelonephritis and was noted to be moderately neutropaenic (white call count 1.7 x 10^3/mL) and mildly thrombocytopenic (platelet count 127 x 10^3/mL). Recovered with filgrastim. Neutropenia and thrombocytopenia are both well known as untoward effects following nitrofurantoin administration and they are reported in the information leaflet of Macrobid.[66]
- PSUR 1 Jan 1995 - 31 Dec 1999. One case of severe thrombocytopenia in a patient occurring 3 days after single dose fosfomycin. Patient was on multiple other medications including quinidine. Platelet count prior to fosfomycin unknown. Epstein-Barr virus serology IgM positive, later became negative. Thrombocytopaenia resolved after platelet transfusion.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with small cell lung cancer developed fatigue and was noted to have aplastic anaemia on bone marrow biopsy. This occurred about 2 weeks after single dose of fosfomycin with itraconazole 1g daily g for 6 days started on the same day. The patient died about 4 weeks after bone marrow biopsy with unknown cause of death.
- PSUR 1 Jan 2005 - 31 Aug 2009. Thrombocytopaenia. Patient also taking ciprofloxacin. No further details available.
- PSUR 1 Jan 2010- 31 May 2015. Increased INR (3 cases). No further details provided.
- PSUR 1 Jan 2010- 31 May 2015. Decreased INR. No further details provided.
- PSUR 1 Aug 2015 - Jan 2016. Decreased INR. No further details provided.

Cardiac adverse events

Many of the early reports of tachycardia occurred in association with a hypersensitivity reaction. However, from PSURs from 2010 onwards, cases of tachycardia without associated hypersensitivity were noted.

- PSUR 1 June 2010 - 31 May 2015. Nonserious tachycardia. No further details.

[66] PDR, 50th Edition, p. 1989, 1996/ABPI Compendium of Data Sheets and Summaries of Product Characteristics, p. 840, 1996/97.

- PSUR 1 June 2010 - 31 May 2015. Tachycardia, patient also taking Urispas. No further details.
- PSUR 1 June 2010 - 31 May 2015. Tachycardia judged related to fosfomycin in light of temporal association and positive rechallenge. No further details.
- PSUR 1 June 2010 - 31 May 2015. Tachycardia. No further details.
- PSUR 1 Feb 2015 - 31 July 2015. Nonserious tachycardia, fatigue, redness and swelling on the face. No further details.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with idiopathic cardiomyopathy and atrial tachcardia six days after single dose fosfomycin. No concomitant medication. Outcome unknown.

Vestibular disturbance and deafness

Serious cases of deafness reported in PSURs are:

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient took three 3g fosfomycin doses over a 6 day period and developed severe dizziness during therapy with vertigo and horizontal nystagmus. Bilateral vestibular loss was noted. The patient was referred to an otolaryngologist who noted symptom onset (mild) prior to fosfomycin. Vertifo was severe and lasted several months.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient who experienced hearing loss following 3 grams of fosfomycin trometamol every 15 days for prophylaxis of recurrent urinary infection for a 2 year period (off-label indication). Resolved.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient who experienced sudden deafness of left ear, resonance and tinnitus the day after Monuril intake (3 g single dose). Visit to an E.N.T. specialist revealed slightly cicatricial eardrum, decrease in hearing at the bass tones, with balance trouble. The event resolved completely. No further details are available.
- PSUR 1 Jan 2005 - 31 Aug 2009. One case of reversible hearing loss. No other details available.
- PSUR 1 June 2009 - 30 Aug 2009. Non-serious vertigo. No other details.

Clostridium difficile colitis

- PSUR 1 July 2000 - 31 July 2005. A case of severe *Clostridium difficile* pseudomembranous colitis in a patient occurring 3 weeks after single dose fosfomycin. Resolved without surgery.
- PSUR 1 Jan 2005 - 31 Aug 2009. Nonserious pseudomembranous colitis. No other details available.

Bone and joint adverse events

- PSUR 1 Jan 1995 - 31 Dec 1999. One case of fever, rash, arthralgia and myopathy in a 60-year old female occurring 4 days after fosfomycin. Resolved with corticosteroids and antihistamines. Clinical history, concomitant treatments not available.
- PSUR 1 Jan 2005 - 31 Aug 2009. Allergic cutaneous vasculitis with oligoarthritis in a patient occurring 24 h after single dose fosfomycin. Patient remained bedridden at the time of the writing of the report.
- PSUR 1 Jan 1995 - 31 Dec 1999. Arthralgia, no other details available.

Paraesthesias

Paraesthesias are noted in the early reports in the setting of hypersensitivity. However, from PSURs from 2010 onwards, a type of paraesthesia is noted which is frequently oral.

- PSUR 1 June 2010 - 30 May 2015. Paresthesia occurring 15 minutes following the intake of fosfomycin and paracetamol. The available information does not allow any evaluation regarding the nature of the reported events and their causality to fosfomycin.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia occurred in a patient with medical history of anxiety treated with citalopram and zolpidem. The available information does not allow any evaluation regarding the nature of the reported events and their causality to fosfomycin.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia judged possibly related to fosfomycin treatment in light of temporal relationship.
- PSUR 1 June 2010 - 30 May 2015. Paresthesia and diarrhoea judged possibly related to fosfomycin treatment in light of temporal relationship.
- PSUR 1 June 2010 - 30 May 2015. Oral paresthesia reported in a pattern of hypersensitivity.
- PSUR 1 June 2010 - 30 May 2015. Possible paresthesia due to fosfomycin.
- PSUR 1 Feb 2015 - 31 July 2015. Tingling in mouth and cheek. No further details.

Other miscellaneous adverse events

- PSUR 1 Jan 2005 - 31 Aug 2009. A case of pancreatitis which resolved after 3 days. Patient was also taking Cycleane 30 oral contraceptive.
- PSUR 1 Jan 2005 - 31 Aug 2009. A patient with Parkinson's disease on longterm levodopa and tramadol. Patient took single dose of fosfomycin with the laxatives macrogol and mebeverine. Diarrhoea with electrolyte disturbance (unspecified) occurred the same day with loss of consciousness requring 3 days intubation. Recovered.
- PSUR 1 Feb 2015 - 31 July 2015. Unilateral optic neuritis considered unlikely related to the single dose fosfomycin administration, taking into consideration that drug induced optic neuropathy usually occurs in both eyes. No further details provided.

Fosfomycin use in pregnancy

- PSUR 1 Jan 1995 - 31 Dec 1999. A case of fetal death in utero (FDIU) at 30 weeks gestation in a patient. Foetal hypotrophy noted on ultrasound at 26 weeks. Patient had had a car accident requiring hospital admission at 28 weeks and received a single dose of fosfomycin at 29.5 weeks, 5 days before ultrasound showing no fetal heart sounds. Patient had placenta praevia with multiple placental infarctions on delivery of the placenta. FDIU considered by the treating physician to be unrelated to fosfomycin.
- PSUR 1 Jan 1995 - 31 Dec 1999. A patient had a FDIU at 7 months gestation two days after two doses of nitrofurantoin and one day after a single dose of fosfomycin. Patient had dark urine and contractions prior to fosfomycin dose.
- PSUR 1 July 2000 - 31 July 2005. A patient with a history of 4 previous abortions, one of which was a trisomy 15 received fosfomycin trometamol 3 grams one dose at week 14 and one at week 18 of gestation. On June 2002, the patient delivered a baby with a congenital left pyelocalyceal dilatation. Pyelocalyceal dilatations are often an effect of a congenital vesico-ureteral reflux, a quite common disease diagnosed in 17 to 37% of prenatal ultrasounds. It is considered that an association with fosfomycin is possible but unlikely.
- PSUR 1 Jan 2005 - 31 Aug 2009. A pregnant patient took a single 3 g dose of fosfomycin at 12 weeks of gestation. Ultrasound performed the same week showed spina bifida.

- PSUR 1 Dec 2009 - 31 May 2010. A pregnant patient took a single 3 g dose of fosfomycin at 12 weeks of gestation. Child born with hydrocele and small penis size.

Prescription-event monitoring report

- PSUR 1 Jan 1995 – 31 Dec 1999 contains a 1997 prescription-event monitoring report from the Drug Safety Research Trust, a registered UK charity. This was conducted in a cohort of 3,363 patients. The exposure data was prescriptions collected by the Prescription Pricing Authority (PPA) in England. The outcome data were event reports obtained by sending questionnaires (green forms) to the general practitioners who issued prescriptions for fosfomycin. In this particular study, the fosfomycin prescriptions were written during the period February 1994 to June 1996 and the green forms were posted approximately 6 months later.
- 3,783 (45%) of the 8,303 green forms posted were returned. 929 (39%) of the 2,382 general practitioners (GPs) who were sent green forms failed to return any of them. 420 (11%) of the 3783 green forms that were returned were classified as void because they did not contain any clinical data. Therefore useful information is available on a cohort of 3,363 patients (41% of all fosfomycin prescriptions during in the 29-month period).
- Age and sex: Of the 3,363 patients, 286 (9%) were males with a mean age of 57 ± 19.4 years and 3,033 (90%) were females with a mean age of 46 ± 19.7 years.
- Indications: A study of the indications for which the drug was prescribed shows that the major usage was for urinary tract infection/cystitis (76%). The indication was not specified for 18% of the patients.
- Effectiveness: 2,993 (89%) of the total cohort included an opinion about the effectiveness of fosfomycin. Fosfomycin was perceived by GPs to have been effective in 2,668 (89%) of these and not effective in 325 (10.9%) of patients.
- Selected events of interest: The incidence of diarrhoea was more than 1.0 per 1000 patients. Two cases of skin reaction (one facial rash with eye swelling within 48 h of taking the drug and one body rash). One case *Clostridium difficile* diarrhoea, patient also received other unspecified IV antibiotic within the same 24 h period.
- Discontinuations: Not applicable as fosfomycin is administered as a single dose.
- Pregnancies: There were a total of 30 pregnancies reported. Thirteen women had taken fosfomycin during pregnancy, two of these were in the first trimester. The outcomes of these pregnancies were 12 live births and one spontaneous abortion. One baby exposed to fosfomycin four days before delivery was born with congenital adrenal hyperplasia.
- Deaths: There were a total of 57 deaths (1.7% of the cohort). No death was attributed to fosfomycin.

Evaluator's conclusions on safety

Clinical safety population and extent of exposure

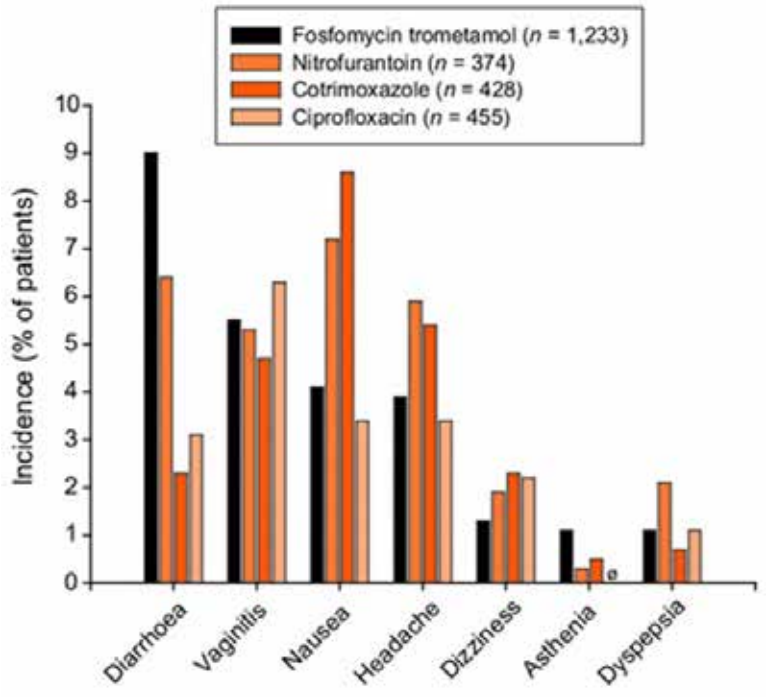
- Three pivotal efficacy and safety studies conducted according to GCP with 1233 fosfomycin subjects evaluable for safety against 3 comparator antibiotics.
- Multiple non-pivotal efficacy and safety studies most predating GCP guidelines with 8668 fosfomycin subjects evaluable for safety.
- All patients in the pivotal studies were female. The majority of the patients in the other controlled and uncontrolled trials were female although some included males. The majority of patients were Caucasian.

- Most patients evaluable for safety had acute uncomplicated lower UTIs although some patients had chronic or recurrent UTIs or asymptomatic bacteruria.
- Pregnant patients and elderly patients were included in some trials.
- The vast majority of patients received a 3 g dose of fosfomycin trometamol. A few adolescent females received a 2 g sachet in countries where this dosing strength was available. It is likely they received a similar mg/kg dose by body weight compared to adult females.
- A few studies included patients dosed with more than one dose of fosfomycin. This was usually 3 g daily for 3 doses. Insufficient patients received more than one dose of fosfomycin to be able to make any recommendations or safety analysis for multiple doses.

Common adverse events

- All 3 pivotal studies utilised the same 3 g single fosfomycin trometamol dosage and were of similar study design, hence pooled data for drug-related adverse events, that is, adverse drug reactions across the 3 studies is shown. Comparator antibiotics were appropriately chosen and were nitrofurantoin 100 mg bd for 7 days (Study US-MON-03), TMP/SMX 1 DS tablet bd for 10 days (Study US-MON-02) and ciprofloxacin 250 mg bd for 7 days (Study US-MON-01). Note discussion of the incidence in the next few paragraphs is for all adverse events rather than drug-related adverse events, so percentages on the bar graph and in the following discussions are not the same.

Figure 2: Tolerability of fosfomycin trometamol 3 g single dose in pooled data from the 3 pivotal efficacy and safety trials US-MON-01, US-MON-02 and US-MON-03.



* Shown are drug-related adverse events occurring in >1% of fosfomycin recipients. From Keating (2013) with original data from US prescribing information (FDA, 2011).

- The most commonly reported adverse event across the 3 pivotal studies was headache which was reported in 8.8 to 11.3% of fosfomycin patients. However in none of the studies was the rate significantly different in the comparator arm.
- The second most common adverse event across the 3 pivotal studies was diarrhoea which was reported in 7.6-14.7% of fosfomycin patients. In all 3 studies, this was a

significantly higher incidence in the fosfomycin group than in the comparator arm (4.3% ciprofloxacin; p = 0.04; 2.6% TMP/SMX, p < 0.01; 8% nitrofurantoin, p = 0.005).

- The third most common adverse event across the 3 pivotal studies was nausea which was 4.9 to 6.7% for fosfomycin. In the TMP/SMX study, TMP/SMX patients had a significantly higher rate of nausea 10%, p < 0.01). For the other 2 comparators, there were no significant differences in rates of nausea.
- There were no significant differences between fosfomycin and the comparator antibiotics in the next most common adverse reactions, vaginitis, dizziness, asthenia, dyspepsia.
- The incidence of rash was low in the fosfomycin groups at 0.7 to 2.3%. Significantly more TMP/SMX patients developed rash (5.1%, p < 0.01).
- Although diarrhoea is the most common adverse event, vomiting occurred in 0.9% and abdominal pain 1.9% of fosfomycin patients across the 3 studies.
- In the non-pivotal efficacy and safety studies (many of which were open-label), the most common fosfomycin adverse reaction was diarrhoea with incidence typically 5 to 10%. Other common adverse events in the fosfomycin arms of these studies were headache, nausea, rash and abdominal pain.
- In the meta-analysis by Falagas;[67] of patients with uncomplicated UTIs treated with either single dose 3 g fosfomycin (adults) versus single or multiple doses of comparator antibiotics, no difference was observed regarding the occurrence of adverse events in non-pregnant female patients treated with fosfomycin versus those treated with comparator(s) (13 RCTs, 2388 patients, RR = 1.25, 95% CI = 0.83 to 1.88).

Deaths and other serious adverse events

- There were no deaths in any of the clinical trials contained in the dossier.
- Serious adverse events were reported in 0.4% to 5% of fosfomycin patients in the 3 pivotal studies, most commonly gastrointestinal intolerance. Rates of SAEs were not significantly different in the comparator arms. One fosfomycin patient developed an optic neuritis which resolved after steroid therapy.
- In the non-pivotal efficacy studies (many of which were open-label), SAEs in the fosfomycin arms was < 1%. This was always due to gastrointestinal intolerance, usually diarrhoea.

Discontinuations due to adverse events

- In the 3 pivotal studies, 20 (1.4 to 1.9%) of fosfomycin patients discontinued due to adverse events. Common causes were diarrhoea (n = 9) and rash (3). Significantly more TMP/SMX patients discontinued due to rash and nitrofurantoin patients due to dizziness.
- Most of the non-pivotal studies did not report discontinuations separately from serious adverse events.

Post marketing experience

- Fosfomycin was first approved in 1986 (Italy) and is now authorised in more than 80 EU and non-EU countries. There is a large amount of usage and post-marketing experience with the drug worldwide. For example, from 1 August 2015 to 31 January 2016, a total of 9,015,221 packages (283,207 packages of 2 g sachets and 8,732,014 packages of 3 g sachets) were sold by affiliates and contractual partners worldwide.

[67] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr; 29(2):321-47.

- Nine Periodic Safety Update Reports (PSURs) conducted by the drug company Zambon are included in the dossier. They cover a continuous period from 1 January 1995 to 31 January 2016.
- Most safety issues with potential regulatory importance have been identified from post marketing experience.

Safety issues of potential regulatory importance

- Fosfomycin has a number of rare adverse events of potential regulatory importance. The most important of these are likely to be immediate hypersensitivity, hepatitis, vestibular disturbance and deafness, and severe rash.
- Immediate hypersensitivity (anaphylaxis, angiooedema, urticaria and asthma-like reactions) Fosfomycin is clearly associated with immediate hypersensitivity in the form of anaphylaxis, angiooedema, urticaria and asthma-like reactions. These are well-described but appear rare from the data contained in the dossier. There were 7 reports of anaphylactic shock and/ or hypotension following fosfomycin in the PSURs. Onset after dosing was usually not specified but one case occurred 5 minutes after IV fosfomycin, one case started 10 minutes after an oral dosage and another case 30 minutes after an oral dosage. Three cases of Quincke's oedema were noted and 6 cases of facial or lip oedema. There were also cases or urticaria, cyanosis and dyspnoea.
- Hepatitis. Mildly abnormal liver function tests without symptoms which resolve are not uncommon. Clinical hepatitis, according to the information contained in the dossier, is rare. Twelve patients with hepatitis are recorded in the PSURs. Hepatitis in the 12 cases typically occurs 1-7 days after the dose. Hepatitis cases in the PSURs were mostly acute and sometimes associated with jaundice. Some cases were cholestatic. Most cases were reported to resolve although that information was not uniformly recorded. There was one case of fatal hepatitis necrosis in a patient. No details of their clinical history are available except that it occurred 7 days after single dose of fosfomycin for UTI. No information was available for concomitant medications for the fatal case.
- Serious skin reactions. From the data contained in the dossier, fosfomycin is associated with serious skin reactions but these are rare. There were 3 cases of toxic skin eruptions noted in the PSURs.
- Vestibular disturbance and deafness. Fosfomycin has been associated with deafness, tinnitus, and vestibular disorder but these adverse events appear rare. The PSURs contain one report of vertigo, vestibular loss and horizontal nystagmus lasting several months. There was another case of non-serious vertigo. There were 2 cases of reversible hearing loss. There was another report of reversible hearing loss in a patient taking fosfomycin every 15 days over a 2-year period (for an off-label indication). In overdosage, one case of vestibular disturbance has been described.
- Severe gastrointestinal disturbance and / or Clostridium difficile colitis. Despite the frequent occurrence of diarrhoea, severe diarrhoea requiring hospitalisation is rare. In most patients, diarrhoea resolves 1 to 7 days after the dose. Clostridium difficile colitis has been reported but is also rare, perhaps due to the drug's relatively small impact on normal bowel flora.
- Haematological toxicity. Fosfomycin has been associated with a range of haematological toxicities but all appear to be rare. The most common of the rare toxicities are mild anaemia, eosinophilia, thrombocytopenia, neutropenia and panyctopenia.
- Cardiovascular toxicity. Electrocardigraph monitoring was not performed during the clinical trials of fosfomycin. No QT/QTc studies were submitted. Based on the

postmarketing data, the drug does not appear to be associated with significant cardiac toxicity.

- Renal toxicity. Based on the information contained in the dossier, fosfomycin does not appear to have a significant association with renal toxicity. As the most common adverse reaction of fosfomycin is gastrointestinal intolerance, prerenal failure due to dehydration could occur.

Safety in pregnancy

- Fosfomycin crosses the placenta with high resultant high levels in the fetus soon after maternal dosing.
- The dossier contains nine clinical studies in which at least 1387 pregnant patients with either symptomatic lower UTI or asymptomatic bacteruria were treated with fosfomycin, usually 3 g single dose. All of the studies were open-label and they were mostly small but they are important for consideration of safety of fosfomycin in pregnancy. Gestational age at treatment was not always specified but only two studies appear to include patients in the first trimester. Examination of offspring at birth or follow-up of the baby after birth was not commonly reported. In these studies, fosfomycin was generally well-tolerated in pregnancy and no adverse maternal or fetal outcomes were noted although the limited follow-up is noted.
- In the pivotal and main efficacy studies, 5 patients became unexpectedly pregnant. One patient was lost to follow up. Three patients had good maternal and fetal outcomes and one had early delivery for unrelated reasons.
- All PSURs contained in the dossier list only 5 patients with adverse pregnancy outcomes. All 5 pregnancy adverse outcomes were for different conditions. None of the adverse pregnancy outcomes appear related to fosfomycin.
- In a survey of family practitioners in the UK between February 1994 and June 1996, 30 patients treated with fosfomycin became pregnant with information available for 24 pregnancies. Thirteen mothers took fosfomycin during pregnancy, two during the first trimester. Sixteen conceptions occurred after the use of fosfomycin. There were 12 live births. Two abnormalities were reported, the first a case of congenital adrenal hyperplasia with delivery at term 4 days after fosfomycin dosing. After fosfomycin dosing in the 2nd trimester, the other baby had an apnoeic episode at day 4 and a febrile convulsion at just less than one year of age. None of the abnormalities appear related to fosfomycin. There was one spontaneous abortion at approximately 19 weeks gestation and an unplanned pregnancy resulting in a therapeutic termination.
- At least 1400 women have received fosfomycin during pregnancy, usually 3g single oral dose. There is no evidence based on review of the human data that fosfomycin is associated with adverse fetal or maternal outcomes or teratogenicity. The data in animal models will have been reviewed by the nonclinical evaluator.

Safety in lactation

- The dossier does not contain any information about safety in lactation. The 3 large pivotal studies and many of the other studies excluded nursing mothers.
- It is noted that proposed Australian PI states that fosfomycin is excreted in breast milk. However, the PI from the United States (dated 2011) states that it is not known whether fosfomycin tromethamine is excreted in human milk. Could the Sponsor please provide further information and / or human studies as to whether fosfomycin is excreted into breast milk? Is the comment based on studies in animals?

Safety in the elderly

- Based on limited data, it is anticipated that safety in the elderly with normal or mildly impaired renal function will not be substantially different from safety in younger adult populations.

Safety in patients with hereditary abnormalities of sugar metabolism

- The proposed Australian PI and foreign PIs state that 'This medicinal product contains sucrose. Patients with rare hereditary diseases as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase should not use this product'. Presumably this safety warning has been added because each sachet contains more than 2 g sucrose which patients with these hereditary deficiencies cannot metabolise. Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- The pivotal Study US-MON-03 excluded patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Presumably this is because the activity of fosfomycin is altered in the presence of glucose-6-phosphate. Neither the proposed Australian PI or the current American PI lists G6PD deficiency as a precaution or a contraindication. Is the sponsor aware of any safety issues in this patient population? Why was G6PD deficiency an exclusion criterion in the Study US-MON-03?

Safety in overdose

- Safety data in humans in overdosage is limited. One case was noted in a PSUR of vestibular disturbance after a supratherapeutic dose. From the proposed PI, there appears to be some data on overdose and safety in animal models which should have been reviewed by the nonclinical evaluator.
- The proposed PI includes the following wording, under section 'Overdose':

  > *The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.*

  What data are the taste disturbances based on?

Evaluator's overall conclusions on safety

- There is a large amount of safety data for fosfomycin trometamol available from clinical trials in humans and post-marketing experience. The drug has been available in many countries since the 1980s and 1990s.
- The majority of the safety data is for a single 3 g oral dosage of fosfomycin trometamol in the proposed Monurol formulation.
- At least 1400 women appear to have taken the drug during pregnancy, most commonly during the second and third trimesters. Based on this data, the drug does not appear to be associated with poor maternal or fetal outcomes or teratogenicity.
- The most common adverse event occurring with fosfomycin is diarrhoea which usually lasts 1-3 days but can last out to 7 days. It occurs in approximately 10% of patients. This is usually mild to moderate but can be severe.
- Other less common adverse events are headache, nausea, rash, vomiting, and lethargy. The incidence of these adverse events appears to the same or lower than common comparator antibiotics such as TMP/SMX, nitrofurantoin and ciprofloxacin.

- Serious but rare adverse events including anaphylaxis and other immediate hypersensitivity reactions. This appears much less common than for the beta-lactam class of antibiotics. Other rare serious adverse events include hepatitis, serious skin reactions, vestibular disturbance and deafness and haematological toxicity.
- There were no deaths in any of the clinical studies.

Limitations of safety studies

- Human safety data in the first trimester of pregnancy is limited.
- Human safety data in lactation is limited or non-existent.
- Safety data in populations apart from Caucasians and African-Americans and in males is limited.
- Safety data for other dosages apart from a single 3g oral fosfomycin trometamol dosage is limited.
- Safety data in some special populations such as hepatic impairment is limited.
- The development of the drug predated mandatory electrocardiograph monitoring or QT/QTc studies in clinical trials. However, a large amount of post marketing experience would suggest that the drug is not associated with significant cardiotoxicity.

Questions on safety studies

- In pivotal Study Mon-US-03, eosinophilia is reported in 57/362 (15.7%) of fosfomycin patients and 58/346 (16.8%) of nitrofurantoin patients. These are extraordinarily high results for both drugs. However, on review of the specific listing for eosinophilia in Appendix 14, 20 (5.3%) fosfomycin patients and 14 (3.7%) nitrofuranotin patients appear to have had eosinophilia. This is still higher and out of keeping with Studies MON-US-01 and Mon-US-02 in which eosinophilia rates were < 1%. Could the sponsor please advise the correct rates for eosinophilia for both study drugs? If the rates are till much higher than for fosfomycin in Studies MON-US-01 and MON-US-02, could the sponsor explain why? Was the formulation changed? Was any eosinophilia clinically significant?
- Is the warning in the PI about patients with rare hereditary diseases such as fructose intolerance, glucose-galactose malabsorption or deficiency of sucrase-isomaltase not using Monurol due to their inability to metabolise the sucrose in the product? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- Is this the case? If so, what adverse events have been noted in these patients? Or is it a theoretical risk only? Does the sucrose load alter serum glucose levels in diabetes mellitus?
- Is the sponsor aware of any safety issues in patients with hereditary abnormalities of sugar metabolism or G6PD deficiency?
- The proposed PI includes the following wording, under section 'Overdose':

  > *The following events have been observed in patients who have taken Monurol in overdose: vestibular loss, impaired hearing, metallic taste, and general decline in taste perception. In the event of overdosage, treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the drug.*

  Could the sponsor advise the source of the comments on taste alteration?

First round benefit-risk assessment

First round assessment of benefits

Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

The benefits of fosfomycin trometamol (Monurol) in the proposed indication are:

- In non-pregnant adult and adolescent females, Monurol is an efficacious single 3g dosage treatment for acute lower uncomplicated UTI.
- The bacteriological efficacy rate of Monurol was 83 to 89% in three pivotal efficacy and safety trials performed in the USA in the 1990s. These suggest that 3g single dose Monurol has similar efficacy to 7 days of nitrofurantoin (100 mg twice-daily), but that it is less effective than a 7-day oral regimen of ciprofloxacin (250 mg twice-daily) or a 10-day oral regimen of TMP/SMX (160 mg/800 mg tablet twice-daily). The three pivotal trials had some issues of design discussed below in 'Strengths and uncertainties of the evidence'.
- Evidence from multiple non-pivotal trials supports the bacteriological efficacy rate of 83 to 89% found in the pivotal studies.
- Fosfomycin has good efficacy against E. coli, which causes 70 to 95% of acute uncomplicated lower UTIs in adult and adolescent females.
- Fosfomycin is generally efficacious against other less common uropathogens in females such as Proteus and Klebsiella and has variable activity against other Gram negative uropathogens and Staph saphrophyticus.
- A single 3g oral dosage has favourable pharmacokinetics and is likely to improve patient compliance compared to multiple-daily dosing of other antibiotics.
- Fosfomycin has a favourable safety profile and was well-tolerated in the pivotal and non-pivotal trials. Diarrhoea was the most common adverse reaction occurring in approximately 10% of patients. This usually resolves within 1 to 3 days and was usually mild to moderate. Nausea, vomiting and abdominal pain occurred in < 5% of patients and were usually mild.
- Fosfomycin was better tolerated than TMP/SMX in a pivotal study and had similar tolerability in another pivotal study to nitrofurantoin.
- There is a large post-marketing experience with fosfomycin. Most severe adverse reactions, are rare. The most common of these are immediate hypersensitivity and hepatitis. Severe ADRs are not common enough to cause concern in the approval process.

The strengths and uncertainties of the evidence are:

- The first 2 pivotal Studies MON-US-01 and MON-US-02 incorrectly classified patients receiving concomitant antibiotics as discontinuations rather than treatment failures for the purposes of the efficacy analysis. There were no significant differences in concomitant antibiotic use in the two treatment groups of Study MON-US-02 but in the Study MON-US-01, 25% of fosfomycin patients used concomitant antibiotics compared to 13% in Study MON-US-01 ($p < 0.01$). This likely overestimated the efficacy rates for fosfomycin and the comparator antibiotics. In the later Study MON-US-03, efficacy variables were correctly assigned and the bacteriological efficacy of fosfomycin was 83%.

- There are no good pivotal trials comparing Monurol to trimethoprim or cephalexin, which are the recommended first or second line therapy of acute uncomplicated lower UTIs in Australia.[68]
- More than 1000 pregnant patients have been treated without any evidence of poor maternal or fetal outcomes or teratogenicity in humans. However, single dose therapy of UTIs is not recommended in international guidelines due to lower efficacy rates compared to multiple-day regimens. If pregnant patients receive fosfomycin single dose, it would be important to check post-treatment that bacteriological eradication has occurred by urine culture.
- The drug has been sufficiently studied in immunocompetent adult and adolescent females with acute uncomplicated lower UTI.
- There is a potential for off-label usage in the treatment of ESBL-producing and carbapenemase-producing Gram negative lower UTIs. The current SAS usage of the drug is usually in patients with uncomplicated or complicated lower UTI is caused by these organisms. This is in fact a potential benefit of approval of the drug in Australia. However, the dosing schedule of fosfomycin has not been properly studied in the treatment of complicated UTI or in patients who are immunocompromised such as renal transplant patients.

Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The major current Australian and international indication for antibiotic prophylaxis in surgical or diagnostic procedures involving the urinary tract is in the surgical prophylaxis of TURP and transurethral prostatic biopsy. Antibiotic prophylaxis is generally not indicated in minor urological procedures such as cystoscopy or ureteroscopy. The wording of the proposed indication is extremely general and would include many patients who do not require antibiotic prophylaxis.

The strengths and uncertainties of the evidence are:

- There were no good quality studies in the dossier comparing fosfomycin to another appropriate antibiotic in the prophylaxis of TURP or transurethral prostatic biopsy.
- In the prophylaxis of TURP, two relatively poor quality studies compared fosfomycin either to placebo or to a poor choice of comparator.
- In the other two surgical prophylaxis studies included in the dossier, most of the patients in these studies did not require surgical antibiotic prophylaxis as they underwent minor urological procedures only.
- Efficacy studies contained in the dossier are of insufficient content and insufficient quality to approve this proposed indication.

First round assessment of risks

Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

The risks of Monurol in the proposed usage are:

- As yet unidentified ADRs. However the large post-marketing experience in other countries for over 30 years makes this unlikely.

[68] Therapeutic Guidelines: Antibiotic v14.

- As yet unidentified drug interactions. In humans, data was only available for cimetidine and metoclopramide.
- No data is available in patients with hepatic impairment.
- No data is available in peritoneal dialysis or haemofiltration. Data in haemodialysis patients or significant renal impairment is very limited.
- Little or no data in lactating patients.
- No data is available in immunocompromised patients.
- Limited data in racial groups other than Caucasian or African-American.
- The dosing schedule in patients with complicated acute lower UTI is unknown.
- The dosing schedule in male patients with UTI is unknown.
- There is no data for patients with pyelonephritis so the drug should not be used to treat patients with upper UTI or bacteremia.
- The drug has limited and variable efficacy in the treatment of acute uncomplicated UTI caused by Staphylococcus saphrophyticus. This organism is usually the 2nd-4th most common uropathogen in adult and adoloscent females and is more common in a community than a hospital setting. It is most common in young sexually active females and, as the cause of 'honeymoon cystitis', it is a marker of onset and frequency of sexual activity.
- Susceptibility testing for fosfomycin is currently limited in Australia. However, this is likely to change if the drug is approved and there are no barriers to the occurrence of this.
- In 1997, soon after approval of fosfomycin in the United States, the drug was substantially more expensive than other common multiple-day antibiotic courses for acute lower UTI (Fosfomycin for UTI 1997). This may occur in Australia as well. It is noted that short courses of the first-line UTI agents (trimethoprim or cephalexin) are relatively inexpensive.
- The draft RMP Appendix Fosfomycin trometamol Australian post-marketing surveillance proposal refers to the drug being used as a first-line agent for the treatment of acute uncomplicated UTIs in Australia. In the United States, fosfomycin is not recommended for first-line therapy due to lower efficacy compared to comparator antibiotics. In the evaluator's opinion, fosfomycin should not be a first-line antibiotic for acute uncomplicated UTI treatment in Australia for reasons of lower efficacy and possibly higher cost. However, it could be a useful third-line agent or fourth-line agent or even a second-line agent, especially where resistance has occurred to first-line agents, allergies or in patients in whom compliance could be an issue (due to single dose).[69]
- The development of fosfomycin resistance as a possible result of therapy has been identified by the sponsor in the draft RMP as a key consideration. However, the sponsor has not provided sufficient material in the dossier in this area. Consideration of this issue is important to the approval process of any antimicrobial agent. The review paper in this area lists 53 references only 5 of which have been provided in the submission. The 5 publications provided are generally old and out of date. The missing resistance studies require review by the TGA and the sponsor is requested to provide these by the second round of the approval process.

[69] Please also refer to the second round assessment, Question 12.3.5. TGA Question 5, clarifying that the three recommended first-line therapies for acute uncomplicated lower UTI in the USA are fosfomycin, trimethoprim/sulphamethoxazole and nitrofurantoin. See Attachment 2 for further details.

Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The dossier contains insufficient evidence to support this proposed indication.
- Fosfomycin has good prostatic penetration so the sponsor is encouraged to perform good quality prophylaxis studies for single dose fosfomycin 3g against an appropriate comparator. These comparators might include single dose gentamicin for TURP prophylaxis or single dose oral ciprofloxacin for transrectal prostate biopsy prophylaxis.

First round assessment of benefit-risk balance

Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

- The benefit-risk balance of Monurol is unfavourable for the proposed usage, but could become favourable if the changes and additional information recommended in next section are adopted.

Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- The benefit-risk balance of Monurol for the proposed usage is unfavourable.

First round recommendation regarding authorisation

Proposed indication 1: Treatment of acute uncomplicated lower urinary tract infections in women above 12 years of age

- Approval is not recommended for the proposed indication at this time. The sponsor is requested to respond to the clinical questions and to provide all relevant studies in the area of fosfomycin resistance development for consideration by the TGA at the second round.
- Efficacy: Fosfomycin resistance development has the potential to compromise efficacy. The Sponsor is asked to provide all relevant studies in the area of fosfomycin resistance development for consideration by the TGA at the second round. Otherwise, sufficient has been provided for efficacy, subject to adequate response to clinical questions.
- Safety: Sufficient data provided subject to adequate response to clinical questions.

Proposed indication 2: Prophylaxis of urinary tract infections in surgical and diagnostic procedures involving the lower urinary tract in adult males and females

- Approval is not recommended for the proposed indication. There is insufficient efficacy data at the present time for the proposed indication.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of fosfomycin trometamol (Monurol) in the proposed usage are unchanged from those identified above apart from the issue of the potential for off-label usage of the drug in ESBL-producing or carbapenemase-producing Gram negatives. Provided that the organism is fosfomycin-susceptible and the UTI is acute and uncomplicated, single-dose fosfomycin is an appropriate choice for therapy in these patients. The evaluator reiterates that the correct dosing schedule for the drug in complicated UTI is unknown so in this condition the drug should not be used. The evaluator encourages the sponsor to undertake further clinical studies which include serum and urinary level monitoring in patients with complicated UTI (not pyelonephritis or perinephric abscess).

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of Monurol in the proposed usage are unchanged from those identified above, apart from the following points.

- Single dose Monurol has good clinical and bacteriological efficacy in the treatment of acute uncomplicated UTI, comparable to 7 days of nitrofurantoin. However, it has acceptable but lower bacteriological efficacy than 7-10 days of ciprofloxacin or TMP/SMX. Hence like all other single dose antibiotic therapies,[70] single dose Monurol should not be used in as a single dose in pregnancy and the PI should reflect this.
- Using EUCAST or CLSI guidelines (the common susceptibility testing methods in Australia), susceptibility testing for Monurol is only calibrated for Enterobacteriaceae (including E. coli) and Enterococcus faecalis. Also, some enterococci and some species of Enterobactericeae (for example Enterobacter spp, Serratia, Morganella) are frequently resistant. Staph saphrophyticus, a common pathogen in community-acquired UTI, can be quite resistant, when breakpoints are extrapolated from E. faecalis. Pseudomonas is frequently resistant to fosfomycin; in vitro mutants arise more readily after exposure than for E. coli and some studies suggest that unlike E. coli there is no biological cost associated with the development of fosfomycin resistant mutants in Pseudomonas (Karageorgopoulos et al, 2012).[71] Hence, the evaluator recommends that the proposed indication for acute uncomplicated lower UTI be narrowed to the treatment of acute uncomplicated lower UTI caused by susceptible strains of Enterobacteriaceae (including Escherichia coli) and Enterococcus faecalis.

  The evaluator notes that the PIs in countries who have most recently approved fosfomycin, for example USA (1996) and Canada (1999) have limited the approval to the pathogens E. coli and E. faecalis. This may in part reflect the predominance of CLSI as the susceptibility testing method most commonly used in those countries. Using CLSI methodology, E. coli and E. faecalis are the only urinary pathogens calibrated for fosfomycin susceptibility testing. However, given that EUCAST since 2013 has had susceptibility testing guidelines for other Enterobacteriaceae apart from E. coli, and that based on pivotal trial data, fosfomycin is likely to be efficacious in fosfomycin-susceptible Enterobacteriaceae apart from E. coli, species approval does not need to be limited to E. coli but can encompass the other Enterobacteriaceae.

[70] Therapeutic Guidelines: Antibiotic v14.
[71] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.

- Fosfomycin-resistant mutants of bacterial species including E. coli occur relatively frequently following therapy but the biological fitness of these mutants apart from possibly Pseudomonas appears lowered (see Karageorgopoulos, 2012).[72] In Europe and other countries with high historical fosfomycin usage, fosfomycin susceptibility has been preserved apart from a few resistant clones. The post-marketing surveillance RMP proposed (v1.2, April 2017) with the assistance of AGAR will be important to monitor resistance development.
- The relative place of fosfomycin in the treatment of acute uncomplicated UTI needs consideration. Therapeutic Guidelines: Antibiotic[73] is the appropriate Australian expert body to do this, taking into account efficacy compared to other agents, cost, convenience, potential for antimicrobial resistance and the threshold for acceptability of clinical failure.
- The paper by Falagas;[74] included by the sponsor states:

  > *Fosfomycin may increase the levels or effects of digoxin; patients should be monitored closely when digoxin and fosfomycin are coadminstered. A low risk for contraceptive failure exists when fosfomycin is coadministered with conjugated estrogens… Finally, fosfomycin trometamol should not be coadministered with probenecid which decreases renal clearance and excretion of fosfomycin (Paladin Labs, 2007, Monurol package insert, Canada).*

  Could the sponsor please advise whether there are clinically significant interactions of fosfomycin with digoxin, conjugated estrogens and / or probenecid? If so, statements will need to be added to the PI.
- In post-marketing surveillance, 5 cases of increased or decreased INR were noted. In the second round, the sponsor has added a comment to the draft PI 'Effects on laboratory tests' regarding alteration in INR. Is the sponsor able to provide more information on these 5 cases, specifically regarding possible interactions with anticoagulants?
- The nonclinical evaluator has noted that fosfomycin is most bactericidal at typical urinary pH.[75] Also, development of mutational resistance could be less at acid pH).[76] If this is correct, concomitant urinary alkalinisers would not be recommended. A statement has been added to the draft PI regarding this.
- The evaluator has reviewed the PI justification document in the response presented by the sponsor in the second round. In this document, the sponsor has requested that the following events be excluded from the PI: aplastic anemia, cholestatic jaundice, hepatic necrosis, toxic skin eruptions, and toxic megacolon. These events were requested for inclusion by the evaluator and are all included in the current US PI dated 2 Feb 2011 submitted by the sponsor in round 1.

Toxic megacolon

Gastointestinal disorders

The sponsor has advised in the PI justification document in the response that toxic megacolon has never been reported, but toxic megacolon is listed in the post marketing

[72] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.
[73] Therapeutic Guidelines: Antibiotic v14.
[74] Falagas ME, et al. Fosfomycin. Clin Microbiol Rev. 2016 Apr;29(2):321-47.
[75] Wise R, Andrews JM (1987). Fosfomycin trometamol: an in vitro study. New Trends in Urinary Tract Infections. Neu, Williams (eds.), 224–231.
[76] Karageorgopoulos DE, et al. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother. 2012 Feb;67(2):255-68.

experience section of the US PI dated 2 Feb 2011. Could the sponsor advise the source of the listing in the US PI, as toxic megacolon may be included as an adverse event of 'not known: frequency' category?

Aplastic anaemia

One case noted:

- PSUR 1 Jan 1995 - 31 Dec 1999. A patient with small cell lung cancer developed fatigue and was noted to have aplastic anaemia on bone marrow biopsy. This occurred about 2 weeks after single dose of fosfomycin with itraconazole 1g daily g for 6 days started on the same day. Patient also received ciprofloxacin and fluconazole the same week. The patient died about 4 weeks after bone marrow biopsy with unknown cause of death.

This case is also described in more detail in the PI justification document in the response received in the second round. The evaluator agrees with the sponsor that aplastic anaemia is unlikely due to fosfomycin based on the information provided. However, the US PI dated 2 Feb 2011 lists aplastic anaemia in the post-marketing experience section. Could the sponsor advise details of this post-marketing report? Is it based on the case in question or on additional cases? The evaluator agrees that this case in the PI justification document in the response is not assessable. If there are no other cases, recommend aplastic anaemia is not included as an adverse event in the PI.

Toxic skin eruption

Three cases of toxic skin eruption and 44 cases of severe cutaneous adverse events were noted, based on post-marketing reports:

- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption requiring 7 days hospitalisation. Resolved.
- PSUR 1 Jan 2005 - 31 Aug 2009. Toxic skin eruption starting 24 h after fosfomycin. Resolved.
- PSUR 1 June 2009 - 31 Nov 2009. Toxic skin eruption and fever starting 24 h after fosfomycin, lansoprazole and trimebutine. Resolved.
- PSUR 1 June 2010 - 31 May 2015. 44 cases. Severe cutaneous adverse reactions.

In post marketing surveillance, the following severe skin reactions were noted: erythema multiforme (2 cases), Stevens-Johnson syndrome (1 case), drug reaction with eosinophilia and systemic symptoms (2 cases) and toxic epidermal necrolysis (2 cases).

Based on this information, recommend listing 'Unknown frequency: toxic skin eruption' under the skin and subcutaneous tissue disorders heading. Recommend also advice from the TGA delegate and / or a dermatologist as to whether 'toxic skin eruption' is the best and most appropriate current dermatological summary wording to encompass the serious skin reactions reported.

Cholestatic jaundice, hepatic necrosis

The evaluator has reviewed the additional cases in the PI justification document. There are sufficient cases of liver injury temporally associated with fosfomycin without other cause to recommend listing as follows:

- Gastrointestinal disorders: 'Not known: cholestatic hepatitis, toxic hepatic necrosis'.

It is also noted that cholestatic jaundice, hepatic necrosis are listed in the post-marketing experience section of the US Product Information dated 2 February 2011.

Second round assessment of benefit-risk balance

The benefit-risk balance of Monurol, given the proposed usage, is favourable, provided the Sponsor provides a satisfactory response to the questions and issues discussed above.

Second round recommendation regarding authorisation

Subject to the sponsor's satisfactory response to the questions and issues raised, approval of Monurol (fosfomycin tromethamine) is recommended subject to narrowing of the indication to read as follows (note changes required are in **bold font**):

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

The reasons for narrowing the indication have been discussed in detail above, and also in the first round review, particularly Pharmacodynamics.

VI. Pharmacovigilance findings

Summary of RMP evaluation[77]

- The sponsor submitted EU-RMP version 0.1 (dated 13 July 2016; DLP 31 January 2016) and ASA version 1.1 (dated 26 July 2016) in support of this application. An updated ASA (version 1.2, dated April 2017) was provided with the Section 31 response of 11 April 2017.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 7: Summary of Safety Concerns.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	**Additional**	**Routine**	**Additional**
Important identified risks	Hypersensitivity reactions	ü	–	ü	–
	Antibiotic-associated diarrhoea	ü	–	ü	–
Important	INR alterations	ü	–	ü	–

[77] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	**Additional**	**Routine**	**Additional**
potential risks	Development of microbial resistance to fosfomycin (ASA only, not in EU RMP)	ü	ü	ü	–
Missing information	nil				

- The sponsor has proposed routine pharmacovigilance for all safety concerns. The Australian-specific safety concern of 'development of microbial resistance to fosfomycin' has additional pharmacovigilance proposed in the form of a targeted post-marketing surveillance program to detect any significant changes in the susceptibility to fosfomycin amongst bacterial infections in the Australian population. It is proposed that this activity will be undertaken on an annual basis for 3 years commencing approximately one year after Monurol becomes available on the Australian market.
- The sponsor has proposed routine risk minimisation for all safety concerns.

New and outstanding recommendations

There are no further issues outstanding after the evaluation.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *Implement EU-RMP (version 0.1, dated 13 July 2016, data lock point 31 January 2016) with ASA (version 1.2, dated April 2017) and any future updates as a condition of registration.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Fosfomycin was first isolated from Streptomyces fradiae in 1969 but is now manufactured synthetically. All issues have been resolved and approval is recommended.

Nonclinical

There are no nonclinical objections to the registration of fosfomycin. The sponsor did not specify a pregnancy category. The toxicology evaluators recommend category B2.

Clinical

Pharmacokinetics

Fosfomycin trometamol has simple pharmacokinetics. Oral fosfomycin trometamol is rapidly absorbed and converted to fosfomycin. Absolute bioavailability of 8g Monurol sachet containing 5.6g fosfomycin trometamol in healthy adult volunteers ranged from 32% to 46% in various studies. Cmax is reached within 2 h (Tmax). Plasma half-life is about 4 h. Fosfomycin is not metabolised and is excreted unchanged in the urine. Total fosfomycin Clearance corresponds to the glomerular filtration rate, so neither active tubular secretion nor passive reabsorption play any role. In general, up to 40% of dose is excreted renally within 48 h of which approximately 85 to 95% occurs within first 24 h of oral intake. Steady-state PK or dose proportionality does not apply as the drug is intended as a single dose. It does not bind to plasma proteins. Volume of distribution is 16 to 21 litres. There is evidence of high penetration in prostate and bladder tissue. There is a small food effect with reduction in bioavailability from 37% under fasting to 30% under fed state.

Mean urinary concentration of fosfomycin after a single 3 g oral dose peaks at 400 to 700 µg/mL 2 to 6 h after dosing which is typically 100 fold the concurrent serum concentration.

In a renal impairment study, as renal function decreased, $t_{1/2}$ of fosfomycin increased from 11 h to 50 h. The proportion of fosfomycin recovered in urine decreased from 32% to 11%. In 5 anuric haemodialysis patients, $t_{1/2}$ of fosfomycin during haemodialysis was 40 h. Serum fosfomycin was still detectable in haemodialysis patients after 2 successive haemodialysis sessions 48 to 72 h apart.

In elderly the pharmacokinetics are likely dependent on renal function and independent of age itself.

In 6 children given a dose of 64 ± 12 mg/kg (closest dose to the usual adult dose of 3 g, assuming a typical adult weight of 70 kg), PK parameters were very similar to adults.

No CYP P450 related drug interactions are expected. No data is available in patients with hepatic impairment. This is not considered a deficiency given the pharmacokinetics of fosfomycin. Metoclopramide affects fosfomycin absorption likely due to increased gastrointestinal motility.

Pharmacodynamics

Fosfomycin is the only antibacterial agent in its class and acts at the first stage of peptidoglycan synthesis in bacterial cell wall, that is, at a different stage of cell wall synthesis than the beta lactam antibiotics.

Fosfomycin has a wide spectrum including methicillin-resistant Staphylococcus aureus, enterococci and Gram negative bacilli including Pseudomonas spp. and many extended spectrum beta-lactamase (ESBL)-producing Gram negative bacteria.

Fosfomycin has rapid bactericidal activity at concentrations close to the MIC. Bacterial species which are common uropathogens and are usually fosfomycin susceptible include E. coli, Citrobacter spp, Klebsiella spp, Proteus spp, Enterococcus faecalis and S aureus. Bacterial species which are not uncommon uropathogens and are frequently fosfomycin

resistant include Enterobacter spp, Serratia marcescens, Morganella morganii, Providencia spp, Pseudomonas aeruginosa, Staph saphrophyticus, Stenotrophomonas maltophilia and Enterococcus faecium. Bacterial species which are not uncommon pathogens and are usually fosfomycin resistant include Acinetobacter spp. Fosfomycin has useful activity against many ESBL-producing isolates of E. coli and Klebsiella pneumoniae.

Fosfomycin susceptibility testing methods and breakpoints (MIC) only exist for Enterobacteriaceae (includes E. coli) and Enterococcus faecalis. Studies that report fosfomycin susceptibility for other bacterial species usually extrapolate breakpoints from known E. coli breakpoints but these have not been validated. There are no PK/PD breakpoints.

The bacterial resistance development against fosfomycin appears to be predominantly chromosomally mediated rather than plasmid-mediated.

There are no good human or animal model studies of the pharmacodynamics of the drug and very limited in vitro data. In in vitro PK model, fosfomycin was bactericidal in concentration-dependent manner. A dose of 3 g fosfomycin trometamol appears optimal in terms of bactericidal activity and resistance development. A dose of 1 g fosfomycin trometamol was inferior. Higher doses or sequential dosing has not been studied.

Efficacy

A single 3 g fosfomycin dose (8 g sachet) was used in the three pivotal Phase III clinical trials supporting this product. Dose finding in clinical studies was not systematically investigated.

The 3 clinical trials were similarly designed and have been summarised by the clinical evaluator for inclusion in the PI as follows:

> *In three Phase 3 prospective parallel multi-centre double-blind double-dummy randomised trials of acute uncomplicated UTI performed in the 1990s, a single 3g oral dose of Monurol was compared to three other oral antibiotics (See table 1 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 (for example,, 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/sulfamethoxazole), adult females aged 18 years and older were enrolled and patients with severe renal dysfunction (defined as serum creatinine clearance <30 mills/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 mills/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 8: 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 eradication 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/ sulfamethox-azole	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 to 32 years (fosfomycin) and 27 to 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 to 86% of UTIs. The table below shows microbiological cure rates from pooled data from the 3 studies by pathogen.

Table 9: 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	Fosfo-mycin 3 gm single dose	Cipro-floxacin 250 mg bid x 7d	Trimetho-prim/sul-famethо-xazole 160 mg/ 800 mg bid x 10 d	Nitrofur-antoin 100mg bid x 7d
E. coli	509/644 (79%)	184/187 (98%)	171/174 (98%)	146/187 (78%)
E. faecalis	10/10 (100%)	0/0	4/4 (100%)	1/2 (50%)

There have been no other Phase III 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.'

The non-pivotal efficacy studies and meta-analysis provide supportive evidence of a similar bacteriological efficacy rate (83 to 89%) to the pivotal efficacy studies.

Safety

Safety data for fosfomycin trometamol are available from clinical trials and post-marketing experience. The drug has been available in many countries since the 1980s. The majority of the safety data is for a single 3 g oral clinical dose of the proposed product (8 g sachet) for registration.

The most common adverse event occurring with fosfomycin is diarrhoea which usually lasts 1 to 3 days but can last up to 7 days. It occurs in approximately 10% of patients. This is usually mild to moderate but can be severe. Other less common adverse events are headache, nausea, rash, vomiting and lethargy. The incidence of these adverse events

appeared to be same or lower than the comparator antibiotics TMP/SMX, nitrofurantoin and ciprofloxacin.

Serious but rare adverse events include anaphylaxis and other immediate hypersensitivity reactions as reported during post-market safety surveillance. These appear less common than for the beta lactam class of antibiotics. Other rare serious adverse events include hepatitis, serious skin reactions, vestibular disturbance and deafness and haematological toxicity. There were no deaths in any of the clinical studies.

At least 1400 women appear to have taken the drug during pregnancy, most commonly during the second and third trimesters. Based on this data, the drug does not appear to be associated with poor maternal or foetal outcomes.

Risk-benefit analysis

Delegate's considerations

A single 3 g oral dose of fosfomycin (taken as trometamol) has simple pharmacokinetics with < 40% bioavailability and urinary excretion of the unchanged drug (fosfomycin) within 24 to 48 h.

It has bactericidal mechanism of action on the bacteria cell wall and is active against E. coli – the most common uropathogen in uncomplicated lower UTI and generally active against other less common uropathogens such as Proteus and Klebsiella and has variable activity against Staph saphrophyticus.

There is a large amount of data on efficacy and clinical safety of fosfomycin from non-pivotal published reports including meta-analysis and from extensive post-market experience. The vast majority of evidence is for a single oral dose of Monurol sachet (3g fosfomycin). The pivotal evidence is based on three old clinical trials.

The 3 pivotal efficacy studies are from early 1990s which showed that single 3g dose of fosfomycin has a clinical efficacy (around 70%) and bacteriological (around 80%) efficacy in the treatment of females with acute uncomplicated lower UTI. This is statistically as effective as 7 days of nitrofurantoin but statistically significantly inferior to 7 days of ciprofloxacin or 10 days of Trimethoprim/Sulfamethoxazole.

The first 2 pivotal studies (Study MON-US-01 (versus ciprofloxacin 250mg BID x 7 days) and Study MON-US-02 (versus TMP/SMX 160/800 BID x 10 days)) did not classify patients receiving concomitant antibiotics as treatment failures. There were no significant differences in concomitant antibiotic use in the two treatment groups of Study MON-US-02 but in the Study MON-US-01, a total of 25% fosfomycin patients used concomitant antibiotics compared to 13% in comparator ciprofloxacin arm. This design deficiency was rectified in the 3rd Study MON-US-03 (versus nitrofurantoin 100mg BD x 7 days) which also recruited younger age females and had more than half the patients in the 12 to 30 year age group.

Another notable deficiency was lack of resistance analysis in cases of treatment failures in all 3 clinical trials. This has been thoroughly discussed by the clinical evaluator who has also commented extensively on fosfomycin activity, susceptibility testing and potential for resistance development. Lack of data on resistance development has been addressed by the sponsor with an updated ASA to its RMP which proposes a 3 years active surveillance for resistance development.

This is considered a satisfactory proposal. The clinical evaluator has further proposed extension to 5 years rather than the proposed 3 years. The sponsor is requested to comment in its pre-ACM response to this overview.

The adverse effects profile of Monurol in the proposed clinical use (uncomplicated lower UTI) in the intended patient population (females >12 years of age) at the proposed dose (single oral dose) indicates favourable risk-balance. All changes to the PI recommended by the clinical evaluator following the second round report have been adopted by the sponsor.

Proposed action

Overall, the data package supports approval. The Delegate supports the clinical evaluator's view that susceptible uropathogens be specified in the indication. The following is recommended as the proposed therapeutic indication (some editorial changes):

> *Monurol is indicated 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.*
>
> *Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Monurol. Consideration should be given to the relevant clinical guidelines on the appropriate use of antibacterial agents*

Request for ACM advice

1. Consequent to evaluation of data by TGA, a restriction has been placed in the therapeutic indication in the form of specification of susceptible pathogens. For antibiotics, such information is usually placed under Pharmacodynamics section. However, in this instance it is considered appropriate and is supported. It is also consistent with overseas approval in the USA. Advice from the Committee is requested.
2. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor acknowledges that the Delegate has made updates to the proposed Indication and has referred the revised Indication to ACM for review and comments. The sponsor agrees with the revised Indication and would like to further include the wording 'suspected to be' in the Indication (see below). This is to assist with clarification of this single dose product use and align it with the empiric advice as mentioned in the Therapeutic Guidelines, Urinary Tract Infections (see statement: 'In symptomatic patients, treatment can be started empirically').[78] This clarification of empiric use, under the circumstances described in the Indication, is further recommended and supported by the infectious disease specialist and program author for the post-marketing resistance surveillance program for Monurol.

· Indication:

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

[78] Therapeutic Guidelines Ltd, Urinary tract infections

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

Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Monurol. Consideration should be given to the relevant clinical guidelines on the appropriate use of antibacterial agents.

Advisory Committee Considerations[79]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

- Proposed indication for consideration by the ACM:

  Monurol is indicated only for the treatment of acute uncomplicated lower urinary tract infections (acute cystitis) in women 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.

  Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Monurol. However, when there is reason to believe an infection may involve any of the susceptible organisms (see PHARMACOLOGY), therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies. Once these results are known, therapy should be adjusted if appropriate. If persistence or reappearance of bacteriuria occurs after treatment with Monurol, other therapeutic agents should be selected. (see PRECAUTIONS and CLINICAL TRIALS section).

- The ACM resolved to recommend the following indication:

  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: Enterobacteriacae (including Escherichia coli), Entercoccus 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 organisms).

  Appropriate culture and susceptibility studies should be performed to identify the causative organism(s) and determine its (their) susceptibility to Monurol. Consideration should be given to the relevant clinical guidelines on the appropriate use of antibacterial agents.

Specific advice

The Delegate requested advice on specific questions on this submission. ACM advised the following in response to the Delegate's questions:

[79] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

1. ***Consequent to evaluation of data by TGA, a restriction has been placed in the therapeutic indication in the form of specification of susceptible pathogens. For antibiotics, such information is usually placed under Pharmacodynamics section. However, in this instance it is considered appropriate and is supported. It is also consistent with overseas approval in the USA. Advice from the Committee is requested.***

The ACM agreed with the Delegate that it is appropriate to place susceptible pathogens in the therapeutic indication in the interest of decreasing the rate of inappropriate prescribing, however raised that:

- the list of pathogens could become outdated as use increases in the Australian context
- the restrictions should be made based on clinical trial evidence.

The indication recommended by the ACM is described above.

2. ***The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.***

The ACM discussed the potential inappropriate use of fosfomycin and the increased rate of resistance by complicating organisms. The view of the committee was that fosfomycin should be reserved as a second-line treatment, after the use of other more appropriate antibiotics, such as trimethoprim, cephalexin and amoxicillin/clavulanic acid which don't have activity against complicating pathogens.

The ACM also raised that that the indication should state use in 'females' above 12 years old, rather than 'women' above 12 years old, in agreement with the indication proposed by the Delegate. This has been described in the ACM proposed indication above.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Monurol [fosfomycin (as trometamol)] 3 g granules for oral solution sachet indicated for:

> *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.*

Specific conditions of registration applying to these goods

- The Monurol EU-RMP, version 0.1, dated 13 July 2016 (data lock point 31 January 2016), and any subsequent revisions, as agreed with the TGA will be implemented with ASA (version 1.2, dated April 2017) and any future updates as a condition of registration in Australia.

Attachment 1. Product Information

The PI for Monurol approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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