Fosfomycin tromethamine (MONUROL)

Abbreviated Drug Review

January 2023

**VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Introduction

Cystitis is a common infection in Veterans and can be associated with significant morbidity and mortality. Increases in drug-resistance have limited oral options available for the treatment of lower urinary tract infection. *Escherichia coli* (*E. coli)* and other gram-negative organisms that harbor extended-spectrum beta-lactamases (ESBLs) are often resistant to fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX) and oral beta-lactams. While many remain susceptible to nitrofurantoin, some patients cannot receive that product due to severe renal insufficiency or other contraindications. Guidelines on the management of cystitis only address women and are outdated. In addition to cystitis in men, management of acute and chronic prostatitis, and prophylaxis prior to urologic procedures are also impacted by increasingly resistant gram-negative organisms.

The purposes of this abbreviated review are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating fosfomycin for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Fosfomycin in the United States is only available as a 3-gram powder sachet, designed to be dissolved in 3-4 ounces of water. Oral bioavailability is 37-42%, with a mean C_{max} from 20-25 ug/mL within 2 hours (fasted). Mean urine concentrations of 706 (+/- 466) ug/mL were attained within 2-4 hours after a single oral 3-gram dose. Urine concentrations remain above 100 ug/mL for 24-30 hours in both fasted and fed states, and a mean urine concentration of 10 ug/mL persists at 72-84 hours post dose. Oral dosing does not result in systemic concentrations needed for urinary tract infections involving the upper urinary tract or with systemic manifestations.

In vitro activity

The CLSI breakpoint for Fosfomycin is ≤ 64 ug/mL, and only applies to *E.coli* and *Enterococcus faecalis* in urine cultures. Most VHA microbiology labs do not routinely test these organisms for susceptibility to fosfomycin but may do selective testing based on resistance profiles or on provider request.

In vitro, Fosfomycin has significant activity against many gram-negative pathogens, notably *E.coli* (including those producing extended-spectrum beta-lactamases or ESBLs), *K.pneumoniae, Enterobacter* spp*., Serratia* spp*., Citrobacter* spp*.,* and *Proteus mirabilis. Pseudomonas aeruginosa (P. aeruginosa)* is moderately and variably susceptible, while *Acinetobacter* spp*.* and *Stenotrophomonas* spp. are usually resistant to fosfomycin. In addition, emergence of resistance to fosfomycin, while uncommon with *E. coli,*

has also been reported, most notably with *K.pneumoniae* and *P.aeruginosa*, More contemporary reviews also show high activity against *E.coli*, including MDR and ESBL producing isolates. Activity against *K.pneumoniae* was more variable, but some carbapenemase producing isolates retain susceptibility to fosfomycin.

In terms of gram-positive organisms, fosfomycin is very active against *Enterococcus spp.* (including vancomycin-resistant *Enterococcus* or VRE), and *Staphylococcus aureus* (including methicillin-resistant or MRSA) but lacks activity against *Staphylococcus saprophyticus.*

Data from the national VHA ASTF/MedSAFE medication use evaluation of outpatient urinary tract infections, which included 1287 patients from over 30 VA facilities, fosfomycin demonstrated 95% susceptibility in *E.coli* isolates, although testing was only done in 40 of 1287 isolates.

Susceptibility testing of fosfomycin is not routinely done in most clinical microbiology labs and must be requested. CLSI breakpoints are only available for *E.coli* and *E.faecalis.* Approved methods for testing include disk diffusion and the agar dilution MIC method (agar media supplemented with 25 ug/mL of glucose-6-phosphate). CLSI explicitly states that broth microdilution MIC susceptibility testing should not be performed. In addition, CLSI advises that disk diffusion and MIC breakpoints apply only to E. coli urinary tract isolates and should not be extrapolated to other species of Enterobacterales.

Several studies cite issues with categorical agreement and report unacceptable major and minor error rates when evaluating E-test performance against the gold standard (agar dilution). Performing manual testing on isolates other than E.coli and E. faecalis should be discouraged, as the reliability is uncertain and clinical decisions should not be made based on these results. Infectious diseases specialists should work closely with their microbiology directors to determine when manual testing for Fosfomycin susceptibility is appropriate.

FDA Approved Indication(s) [2]

Fosfomycin is an antibiotic indicated for:

- Treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of *Escherichia coli* and *Enterococcus faecalis*.
- Fosfomycin is not indicated for the treatment of pyelonephritis or perinephric abscess.

Potential Off-label Uses

- Fosfomycin is often used off-label when other antibiotics are not available or appropriate due to resistance, allergy or route of administration. These include:
    - Management of cystitis in males
    - Management of acute and chronic prostatitis
    - Pre-operative prophylaxis (e.g. pre-transrectal prostate biopsy)
    - Rarely as chronic suppressive therapy in patients with recurrent symptomatic cystitis

It is important to recognize that many organisms, including *Pseudomonas aeruginosa, Morganella spp., Proteus vulgaris and Staphylococcus saprophyticus* have elevated MIC values and are unlikely to respond to Fosfomycin. In addition, as there are no susceptibility breakpoints for these organisms, labs cannot report susceptibility except for *E. coli* and *E. faecalis.* Several gram-negative organisms intrinsically possess the fosA gene, which may lead to clinical failure, including organisms at risk of AmpC production

Current VA National Formulary Alternatives (*for ESBL producing E.coli not susceptible to other oral agents such as nitrofurantoin, fluoroquinolones or TMP/SMX*)

- Aminoglycosides (e.g. amikacin)
- Carbapenems

Dosage and Administration

- FDA approved as a single 3-gram dose dissolved in water for uncomplicated cystitis
- Off-label dosing (varies by case series):
  - Cystitis in men: 3-grams every 24-72 hours x 3-4 doses (1-3 weeks total)
  - Prostatitis: 3-grams daily for one week followed by 3-gram every 48 hours OR 3-grams orally every 48-72 hours for 2-4 weeks (acute prostatitis) or 4-6 weeks or longer (chronic prostatitis)
  - Pre-transrectal prostate biopsy: single 3-gram dose

Efficacy

Table 1. Fosfomycin for treatment of UTI involving male patients or multidrug-resistant organisms

Study	Design	Organism	Dose	Outcomes
Quio et al., 2013	Adults in China with AUC, rUTI or cUTI* -Pyelo/fever excluded -**Included 105 males**, 230 females	Not noted Only 152/335 included in microbiologic analysis	3g on days 1,3,5	**Overall efficacy in males 73%** By diagnosis (both sexes) AUC: 95% rUTI: 77% cUTI: 63% micro eradication (n=152) AUC: 91% rUTI: 75% cUTI: 74%
Pullukcu et al. 2006	52 adults with uUTI or cUTI without fever/leukocytosis -Included **25 males** Many had urologic or other comorbidities	ESBL + *E.coli* Did not test for fosfomycin susceptibility but resistance very rare in ESBL *E.coli* in Turkey	3g on days 1,3,5	Clinical success: 94% Microbiologic success: 79% Of 28 patients with EOT cultures 0/28 relapsed with 3/28 reinfected
Neuner et al., 2012	41 adults with cystitis due to MDR pathogen, including **19 males** -included 15 solid organ transplant recipients and many other comorbidities and urologic risk factors	CR-Kp** (n=13) *P.aeruginosa* (n=8) ESBL *E.coli/Kleb* (n=7) VRE*** (n=7) *E.coli* (n=5) Other (n=4) 86% S / 7% I / 7% R	Not specified but average number of doses was 2.9 +/- 1.8	Microbiologic cure: 59% (less than 40% for *P.aeruginosa*, 46% for vs. 70% for VRE, ESBLs, 100% of *E.coli*/other Resistance in 3 patients, all with CR-KPC and new organisms with resistance in 2 patients **Results not separated by gender**
Senol et al., 2010	47 adults with cUTI (but no fever/leukocytosis) who received fosfomycin	ESBL + *E.coli* susceptible to both fosfomycin and	3g on days 1,3,5	Clinical success : 21/27 fosfomycin (78%) vs. 19/20 carbapenem (95%)

	(n=27) or carbapenem (n=20) -included **19 males** (13 fosfo and 7 carbapenem)	carbapenems		Microbiologic success: 16/27 fosfomycin (59%) vs. 16/20 carbapenem (80%) **Similar results by gender**
Nagel et al., 2015	43 patients who received fosfomycin for uUTI/cUTI matched to 43 control patients with alternative antibiotics (nitrofurantoin, TMP/SMX, doxycycline most common). **Only 8 males in fosfo group**	Did not specify other than to say their protocol was for fosfomycin for those with VRE or ESBL+ lower UTI	Single 3g dose in 35/43 patients with 3g every 48 hours x 3 doses for most others. Many patients received other antibiotics (mean 2.9 days)	Clinical success (not having a repeat positive urine culture with the same organism within 30 days): 95% in each group Fosfomycin associated with significantly lower antibiotic acquisition costs that control.
Veve et al., 2016	Retro review of patients who received fosfomycin (n=89) or ertapenem (n=89) for outpatient UTI due to ESBL+ organisms. **23/89 fosfo and 51/89 ertapenem were male.** CAUTI: 36% cUTI (cystitis): 32% uUTI: 17% 70% of fosfo and 96% ertapenem patients initially admitted with bacteremia in 1% vs. 26%.	*E.coli* 84% *Klebsiella spp* 15% *Enterobacter* 1% *Morganella* 1% Only 21% were assessed for fosfomycin susceptibility	60% fosfo and 96% ertapenem patients received a carbapenem Most got fosfo 3g q72h (62%), 3g q48h (23%), 3g single dose (13%) 3g daily (2%) Median duration 9 days	Primary outcome was readmission or unplanned visit within 30 days: Fosfomycin: 15% Ertapenem: 14% None of the fosfo patients with pyelo met primary outcome Majority of primary outcomes were due to infection recurrence (44%), clinical worsening (24%) or treatment intolerance (8%) with no difference between groups
Hatlen et al, 2020	Retrospective review of 99 patients who received fosfomycin for cUTI, including 37 males. 21% had fever and 13 patients had pyelonephritis	*E.coli* 77/99, 94% of which were ESBL+ 70/72 *E.coli* tested were susceptible to fosfomycin.	57% received IV antibiotics prior to fosfomycin, typically for 25-50% of intended course Dosing was 3g q48h or q72h	For the 63 patients who had follow-up, 78% had clinical success. Failure was associated with male sex, urologic abnormality, pathogens other than *E.coli*, and less than 25% of total duration with IV antibiotics 64 patients had positive urine cultures with *E.coli* during follow up and 9 were fosfomycin resistant (14%)
Doesschate et al., 2021	Randomized, controlled RCT of step-down therapy with fosfomycin (n=48) vs ciprofloxacin (n=44) in women with FEBRILE UTI Around 50% had bacteremia, around 27%	*E.coli* susceptible to fosfomycin and ciprofloxacin	Appropriate IV antibiotics for 2-5 days (median 3), then Fosfo 3g QD Cipro 500mg	Primary outcome clinical cure 6-10 days post end of treatment Fosfo: 75% Cipro: 65% Microbiologic cure Fosfo: 78%

	required IV fluid for hemodynamic instability		q12h Duration of oral 5-8 days	Cipro: 94%

*AUC = acute uncomplicated cystitis, rUTI = recurrent UTI, cUTI = complicated UTI, CR-Kp = carbapenem-resistant *K.pneumoniae*, ***VRE = vancomycin-resistant *Enterococcus*

Efficacy summary:

- Several case series containing 27-75 patients each evaluated use of varying doses of fosfomycin for lower UTI (usually ranging from 1-3 doses given every or every other day). The majority of patients were women, but a significant number of men were included, although some studies did not separate efficacy results by gender.
- Clinical and microbiologic outcomes were good for ESBL-producing *E.coli*, which was most common (typically > 70% clinical and/or microbiologic cure), but worse outcomes tended to be seen with *K.pneumoniae*. Emergence of resistance was likewise more common with non-*E.coli* gram-negative isolates, with *K.pneumoniae* most consistently reported.
- While not definitive, these studies suggest providers felt more complicated patients or more resistant organisms might benefit from additional doses beyond the single dose approved by the FDA, typically given as 3 g every 48 – 72 hours.

Off-label:

- **Prostatitis:**
  - Fosfomycin penetrates the prostate with mean concentrations of 4-8 ug/g, and a prostate to plasma ratio of 0.67, based on a pharmacokinetic study during prostate biopsy, typically by 1-4 hours post dose.
  - Several case report and small case series describe use of fosfomycin for chronic bacterial prostatitis (CBP).

Table 2: Studies of fosfomycin for chronic bacterial prostatitis

Study	Design	Organism	Fosfomycin Dose	Outcomes
Karaiskos et al., 2019	44 patients w/CBP No alternative drug due to resistance, adverse events or prior failure Most previously treated for CBP	*E.coli* (n=29) *K.pneumonaie* (n=3) *K.oxytoca* (n=3) *P.mirabilis* (n=2) *P.aeruginosa* (n=1) *E.faecalis* (n=6)	3g daily x 1 week, then 3g q48h for 6 weeks (prolonged to 12 weeks if prostate calcifications)	Clinical cure at EOT: 84% Microbiologic cure: 86% Failure was 6/29 with *E.coli,* 1/3 with *K.pneumoniae* and the 1 *P.aeruginosa* patient 4 of 5 fosfomycin resistant organisms at relapse were *K.pneumoniae*
Bouiller et al., 2022	17 episodes CBP in 12 patients All 12 patients had urologic disorders and many other	*E.coli* (n=12 episodes in 9 patients) *K.pneumoniae* (n=5 episodes in 3 patients)	3g daily x 3wks (n=4) As above, then 3g q48h for 3 wks. (n=13)	Clinical/microbiologic cure in 16/17 (94%) episodes in 11/12 patients 7 patients had recurrence by 6 months and 3 had a new UTI at 6 months

	comorbidities **Fever in 6/17 episodes**			By pathogen recurrence: *E.*coli: 4 patients in 4/12 episodes (33%) *K.pneumoniae*: all 3 patients in 3/5 episodes (60%)
Los Arcos et al., 2016	15 patients with difficult to treat CBP, with failure of prolonged treatment and no option of fluoroquinolone or TMP/SMX	*E.coli* (n=14) – 4 were ESBL producers, 1 AmpC producer *K.oxytoca* (n=1)	3g q72h x 6 wks. (n=13) 3g q48h x 6 wks. (n=2)	Clinical cure in 47% at median 20 months follow up Microbiologic cure 53% at 6 mos. Failure was 1 persistent infection and 6 relapses and 1/6 had fosfomycin resistance identified

- **Prophylaxis pre-biopsy:**
  - A recent meta-analysis (Pilatz et al.) evaluating antibiotic prophylaxis for prostate biopsy compared efficacy of fluoroquinolones with other drug classes, including fosfomycin.
  - Dosing in all studies was a single 3-gram oral dose prior to prostate biopsy.
  - Based on 3 studies involving 643 patients who received fosfomycin vs. 596 who received fluoroquinolones, fosfomycin was associated with a reduced number of infection events 17/643 (2.6%) vs. fluoroquinolones, 33/596 (5.5%), with a RR of 0.49 (95% CI 0.27 to 0.87)
  - The high infection rate with fluoroquinolones has been frequently due to the high rate of carriage of fluoroquinolone resistant enteric gram-negative rods.

Adverse Events (Safety Data)

- Adverse events report in the prescribing information for fosfomycin (as a single dose in acute cystitis) include diarrhea (9%), vaginitis (5.5%), nausea (4%), headache (3.9%), dizziness (1.3%), asthenia (1.1%) and dyspepsia (1.1%). Other than diarrhea, other adverse events occurred with similar or lower frequency to comparator drugs (nitrofurantoin, TMP/SMX or ciprofloxacin).
- In case series involving longer treatment durations, diarrhea was most commonly reported and sometimes resulted in discontinuation of treatment. In the case series of 44 patients with chronic prostatitis, diarrhea was reported in 18%, four (11%) had their dosage interval increased to 72 hour and one patient discontinued treatment due to diarrhea. Diarrhea subsided with prolongation of the dose interval or dietary modification. Similarly, in the study of 12 patients by Bouiller et al., diarrhea was seen in 6/21 treatment episodes (male UTI and CBP), minor in 4, and moderate in 2 (requiring symptomatic treatment). The series by Veve et al identified one patient who developed *C.difficile* infection after treatment with fosfomycin. No other study or series noted *C.difficile* infection.
- In the RCT vs. cipro- probably related AEs in 52% of fosfo and 44% of ciprofloxacin patients. Diarrhea occurred in 46% of fosfo and 9% of cipro patients with abdominal

cramping in 15% and 4% of ciprofloxacin. Two on fosfomycin patients redeveloped fever and had to be switched to intravenous antibiotics. An additional patient complained of shortness of breath immediately after the fosfomycin dose and used an epi-pen.

Place in Therapy

- Recent data from across the VA shows increasing resistance in *E.coli* including 30% resistance for fluoroquinolones, 25-30% for TMP/SMX. While rates of resistance are low for nitrofurantoin, some patients may not be able to tolerate nitrofurantoin due to poor kidney function or previous failure. In cases where other oral agents are not available due to resistance, failure or intolerance, alternative therapy often would require admission to the hospital or outpatient parenteral antibiotic therapy.
- The data for fosfomycin for infections other than uncomplicated cystitis in women is limited to a few randomized trials, along with many small case series. Most evaluated fosfomycin for urinary tract infections due to multi-drug resistant pathogens, especially *E.coli* which possesses extended spectrum beta-lactamases.
- Of note, most studies in UTI excluded patients with fever, leukocytosis and symptoms of upper tract infection. There are a few case series that included patients with fever and other signs of pyelonephritis, with some successes, but concerns were also noted due to patients with recurrent fevers on fosfomycin necessitating a return to intravenous antibiotics. Pharmacokinetic data does not support efficacy for systemic infections or those involving the upper urinary tract infection with the currently available formulation.
- While some data supports use in complicated lower UTI in males, most studies did not analyze outcomes by gender and often had a female predominance. At least one identified male sex as an independent risk factor for failure.
- Retrospective series suggest a role for treatment of chronic bacterial prostatitis due to resistant organisms, where other oral options are not available. It is not clear whether outcomes with fosfomycin differ significantly to other treatment options as recurrence is common in this complicated infection.
- Finally, there are a few studies examining a potential role of fosfomycin as prophylaxis prior to transrectal prostate biopsies in situations where resistance is high for fluoroquinolones or when prior screening documents resistance to other potential agents.
- The ideal place in therapy would be as treatment of lower urinary tract infection (e.g. cystitis), without signs of upper tract infection or systemic signs (e.g. fever, leukocytosis) in an ESBL producing *E.coli* resistant to other oral options as a means to prevent a hospital admission or intravenous antibiotic therapy at home.
- Of note, guidance from the Infectious Diseases Society of America (IDSA) suggests limiting oral fosfomycin to *E.coli* cystitis as the fosA gene is intrinsic to several other gram-negative organisms, including organisms at moderate to high risk of AmpC production, which may lead to clinical failure

- Unfortunately, susceptibilities are often not available at the time therapy is started and few VA labs routinely test for fosfomycin susceptibility. Still, epidemiologic studies in the U.S. and other locations show a high rate of susceptibility to Fosfomycin. In the VA ASTF/MedSAFE MUE, only 40 isolates out of 1287 were tested and 38 were found to be susceptible.
- There currently are not established breakpoints in the U.S. for organisms other than *E. coli or E faecalis*, and although fosfomycin may possess significant in vitro activity, clinical data suggests worse outcomes with non-*E.coli* gram negative organisms, including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
- Use of fosfomycin requires a good understanding of the points above as indiscriminate use may have adverse outcomes, including failure to treat resistant organisms, adverse events (especially diarrhea) and emergence of resistance with overuse, indicating a role to limit use to specific situations.

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