Stony Brook Medicine

Antimicrobial Stewardship Program

Drug Name	**Fosfomycin**
Brand Name(s)	Monurol®
Drug Class	Inhibits bacterial cell wall synthesis by inactivating UDP-N-acetylglucosamine-3-enolpyruvyltransferase. Bactericidal.
Restriction level	**ID consult required**
Accepted Indications	- Oral management of urinary tract infections (uncomplicated and complicated) due to multidrug resistant gram negative bacteria (i.e. *Enterobacteriaceae, Enterococcus faecalis*). - **Recommend testing for fosfomycin susceptibility before use**
Unacceptable Uses	- Infections outside of the GU system
Side Effects	- Diarrhea - Headache - Eosinophilia - Nausea - Hypokalemia
Pregnancy Class	B
Dosing	Uncomplicated UTI - 3g po x 1 dose (adult) - 2g po x 1 dose (children) Complicated UTI - 3g po q48-72 hours x 3 doses Prostatitis - 3g po q48-72 hours x 7 days
Lab monitoring	Susceptibility testing must be requested from the Microbiology lab

Questions to ask prior to approval:

- Are there other acceptable alternative agents (i.e. fluoroquinolones)?
- Is fosfomycin susceptibility data available?
- Does the case match one of the Accepted Indications?

Answer of “no” to any of the above questions should prompt evaluation for an alternative therapy.

Formal consultation with Infectious Diseases required.

Susceptibility testing must be requested from the microbiology lab.

Background:

While an old drug, fosfomycin has seen a resurgence with the growing problem of antibiotic resistance. Fosfomycin is a bactericidal cell wall synthesis inhibitor that has a broad antibacterial spectrum. Its mechanism of action involves the inactivation of enolpyruvyl transferase, which irreversibly blocks the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate, one of the first steps in bacterial cell wall synthesis. Fosfomycin has also been shown to have immunomodulating properties and to reduce adherence of bacteria to uroepithelial cells.

In vitro it is effective against a number of gram positive and gram negative bacterial species, including *Enterococcus, E.coli, Proteus,* and *Citrobacter*, including those that are resistant to beta-lactam antibiotics and fluoroquinolones. Clinical experience suggest that fosfomycin is more active against *E.coli* compared to other *Enterobacteriaceae* (*E.coli* 82-100%, *Klebsiella pneumoniae* 15-100%). There is no significant cross resistance seen with other classes of antimicrobials.

Fosfomycin achieves high urinary levels and distributes well into the kidneys, bladder wall, prostate, and seminal vesicles. As such, fosfomycin can be useful for treating multidrug resistant gram negative urinary tract infections (UTIs), and it may be the only orally available option for treatment.

Resistance to fosfomycin has already been demonstrated. Some bacteria species such as *Pseudomonas* and *Acinetobacter* are reported to have intrinsic resistance to fosfomycin. For other bacteria such as *E.coli*, multiple resistance mechanisms have been discovered, including decreased uptake of the antibiotic and the production of fosfomycin modifying enzymes. Concerning about fosfomycin is the *in vitro* association with the rapid development of resistance. While widespread resistance has not been reported in clinical practice, decreasing susceptibility over time has been reported with increased use. One study from Spain noted that over a five year period, a 50% increase in fosfomycin use resulted in an increase of fosfomycin-resistant extended-spectrum beta-lactamase producing *E.coli* strains from 2.2% to 21.7%. As the prevalence of fosfomycin resistance is unclear, it is recommended that susceptibility testing be done prior to use. Regarding this, it should be noted that the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have different breakpoints for fosfomycin susceptibility to select bacteria (see table below).

In the United States, only the oral formulation is available. (An intravenous formulation has been used in other countries, often in combination therapy with carbapenems for multidrug resistant gram negative infections.) The oral formulation should not be taken in its dry form; it should be dissolved in 3-4 ounces of water.

This oral antibiotic is indicated *only* for the management of UTIs. For uncomplicated UTIs, a single dose treatment of 3g is recommended. For complicated UTIs, many guides recommended dosing fosfomycin every 72 hours; however, urinary levels drop significantly when measured at 72 hours, suggesting that an every 48 hour dosing may be more appropriate.

No dose adjustments are recommended for oral fosfomycin in patients with renal impairment. The antibiotic itself is not known to have significant interactions with other drugs. Caution is advised is patients on gastrointestinal promotility agents as it may lower the amount of drug absorbed.

In summary, fosfomycin is a potent, bactericidal, oral, broad spectrum antibiotic in the management of both uncomplicated and complicated UTIs, particularly those due to multidrug resistant *E.coli* and *Enterococcus faecalis*. Fosfomycin has a benign safety profile with few significant adverse drug related events and few drug interactions. Given the concerns about the rapid emergence of resistance associated with increased use, susceptibility testing is advised prior to initiating.

TABLE 1 Available fosfomycin MICs and zone diameter breakpoints according to the latest EUCAST and CLSI criteria[a]

		MIC (mg/liter)			Zone diameter (mm)		
Criteria[b]	Organism(s) and delivery route	S	I	R	S	I	R
EUCAST	*Enterobacteriaceae*						
	Intravenous	≤32		>32	NR		NR
	Oral[c]	≤32		>32	NR		NR
	Pseudomonas spp.						
	Intravenous[d]						
	Oral	NR		NR	NR		NR
	Staphylococcus spp.						
	Intravenous	≤32		>32	—[e]		—
	Oral	NR		NR	NR		NR
CLSI[f]	*E. coli*[g]	≤64	128	≥256	≥16	13–15	≤12
	E. faecalis[h]	≤64	128	≥256	≥16	13–15	≤12

[a] S, susceptible, I, intermediate, R, resistant; NR, not reported.
[b] EUCAST criteria are from version 5.0, 2015 (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf); CLSI criteria are from 2015 (48).
[c] For uncomplicated urinary tract infections.
[d] Epidemiological cutoff for wild-type isolates, ≤128 mg/liter.
[e] —, MICs are recommended.
[f] *Pseudomonas* spp., *Acinetobacter* spp., *B. cepacia* complex, *S. maltophilia*, *S. saprophyticus*, and *S. capitis* are considered to have intrinsic resistance, defined as inherent or innate (not acquired) antimicrobial resistance, which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary.
[g] Testing and reporting only for *E. coli* urinary isolates.
[h] Testing and reporting only for *E. faecalis* urinary isolates.

From Falagas et al. *Clin Micro Review* 2016; 29(2): 321

References:

1. Gilbert D *et al., Sanford Guide to Antimicrobial Therapy*
2. Cosgrove SE *et al. John Hopkins Antibiotic Guidelines*
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050717s005lbl.pdf
4. *Falagas* et al. *Clin Micro Review* 2016; 29(2): 321-347