PMMC Executive Summary

Title: fosfomycin oral sachet (Monurol®), Forest Pharmaceuticals, Inc.

Formulary Recommendation: Fosfomycin was added to the DUHS formulary on August 5, 2013; with restrictions to be determined by each hospital P&T Committee. DUH use is restricted to ID telephone approval for all inpatient areas, including the ED. A 6-month follow-up, system-wide MUE will be conducted to review use.

The following points were considered for this recommendation[1-6]:

1. Efficacy information
    a. A multicenter, doubled-blind, randomized trial (N= 749) compared single-dose fosfomycin tromethamine with a 7-day course of nitrofurantoin for the treatment of acute uncomplicated lower urinary tract infection (UTI) in female patients in the outpatients clinics. Eligible patients were randomly assigned to receive a single dose 3g dose of fosfomycin tromethamine plus 7 days of placebo capsules or a single dose of placebo (3g packet) plus 7 days of nitrofurantoin monohydrate/macrocrystal 100mg capsules. Bacterial cure rate was no different between the fosfomycin group and the nitrofurantoin group. Relapse occurred in 17 patients in the fosfomycin group and 33 patients in the nitrofurantoin group (p =0.02).
    b. A randomized, single-blind, single site study (N=260) evaluated the clinical effectiveness and cure rate of fosfomycin trometamol compared to ciprofloxacin in females with uncomplicated UTIs in the outpatient setting. 3g single dose fosfomycin trometamol was administered to one-half of the study population, and ciprofloxacin was administered at a dose of 500mg twice a day for 5 days to the other half of the patients. No significant difference was found between the cure rates for fosfomycin trometamol and ciprofloxacin therapy, but percentage of susceptible *E.coli* strains were 59% for ciprofloxacin and 94% for fosfomycin, respectively.
    c. A randomized, multicenter, comparative study (N=547) assessed the microbiological and clinical efficacy of a single 3g oral dose of fosfomycin trometamol compared with a 5-day course of an oral dose of trimethoprim (TMP) 200mg twice daily in the treatment of uncomplicated urinary tract infection in female patients in the outpatient setting. The total microbiological cure rates were similar for both trimethoprim and fosfomycin. Persistence of infection was seen in 14 (16.6%) TMP treated patients and 30 (16.9%) in the fosfomycin trometamol treated group. Reinfection with new organism was seen in 5 (5.9%) TMP treated patients and 18 (10.3%) of the fosfomycin trometamol treated group.
    d. A retrospective chart review of adult hospitalized patients in a single site treated with fosfomycin for a multidrug resistant (MDR) urinary pathogen from January 2006 to December 2010 (N=41). Microbiological cure occurred in 59% (24/41) of patients with a UTI due to an MDR pathogen. For *Klebsiella pneumoniae*, the microbiological cure rate was 46%. Overall, microbiological failure occurred in 41% (n=17) of patients due to relapse (n=10) and reinfection (n=7) within 30 days. Microbiological cure rates varied by fosfomycin susceptibility: 60% (21/35) for isolates with MICs of $\leq$ 64µg/mL, 100% (3/3) for isolates with MICs of 128 µg/mL, and 0% (0/3) for isolates with MICs of $\geq$ 256µg/mL.
    e. IDSA Guidelines states that fosfomycin trometamol (3g in a single dose) is appropriate choice for therapy where it is available due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with standard short-course regimens according to data submitted to FDA. However, several *in vitro* studies examined the activity of fosfomycin against multidrug-resistant pathogens, and these demonstrated that fosfomycin is active against vancomycin-resistant enterococci (VRE), methicillin-resistant *S. aureus* (MRSA), and extended-spectrum β-lactamase (ESBL)-producing gram-negative rods. Although clinical outcomes are not yet reported from randomized, controlled studies, as resistance

among uropathogens causing community-acquired uncomplicated cystitis increases, fosfomycin may become more useful.

2. Safety information:
    a. Studies evaluated have noted common side effects related to fosfomycin treatment, such as diarrhea, vaginitis, nausea, headaches, rash, and lethargy.
    b. Rates of common side effects: diarrhea (9% to 10%), headache (4% to 10%), vaginitis (6% to 8%), rhinitis (5%), nausea (4% to 5%), dysmenorrhea (3%), back pain (3%), pharyngitis (3%), abdominal pain (2%), dizziness (1% to 2%), rash (1%), dyspepsia (1% to 2%), weakness (1% to 2%).
    c. <1%: Anorexia, constipation, dysuria, ear disorder, fever, flatulence, flu-like syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, SGPT increased, skin disorder, somnolence, stools abnormal, vomiting, xerostomia
    d. Postmarketing and/or case reports have noted: anaphylaxis, angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, hearing loss, hepatic necrosis, toxic megacolon.
    e. Monitor CBC, fever, and symptomatic improvement
3. No REMS (Risk Evaluation and Mitigation Strategies) is required for this medication.
4. There is no Black Box Warning for this medication.
5. Education Plan / Level: Level 1
6. Research conducted at Duke: none
7. At DUH, fosfomycin will be restricted to ID telephone approval for all inpatient areas, including the ED. A 6-month follow-up MUE will be conducted to review use.
8. Susceptibility testing – The DUH microbiology lab will only be able to test for fosfomycin susceptibility for *E. coli* and *E. faecalis.*

Formulary products(s) with similar therapeutic actions:

Medication Name	Brand Name	Manufacturer	Formulary Status		
			DUH	DRaH	DRH
Cefuroxime	Ceftin®, Zinacef®	GlaxoSmithKline (generic available)	Y	Y	
Nitrofurantoin	Furadantin®	Shionogi Pharma, Inc. (generic available)	Y	Y	
Ciprofloxacin	Cipro®	Bayer Pharmaceuticals (generic available)	Y	Y	
TMP/SMX DS	Septra® DS	Monarch Pharmaceuticals (generic available)	Y	Y	

FDA Labeled Indication[1]:
Fosfomycin is indicated only for the 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.

Pharmacology[1]:
As a phosphoric acid derivative, fosfomycin inhibits bacterial wall synthesis (bactericidal) by inactivating the enzyme, pyruvyl transferase, which is critical in the synthesis of cell walls by bacteria.

Fosfomycin has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic microorganisms which are associated with uncomplicated urinary tract infections. There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents such as beta-lactams and aminoglycosides.

Resistance is primarily chromosomally-mediated and the mutations interfere with transport into the cell.[11,12]

Fosfomycin tromethamine is rapidly absorbed following oral administration and converted to the free acid, fosfomycin. Absolute oral bioavailability under fasting conditions is 37%. The oral bioavailability of fosfomycin is reduced to 30% with food.

Fosfomycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections

Aerobic gram-positive microorganisms

Enterococcus faecalis

Aerobic gram-negative microorganisms

Escherichia coli

The following *in vitro* data are available, but their clinical significance is unknown.

Fosfomycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 64 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of fosfomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms

Enterococcus faecium

Staphylococcus aureus (including MRSA)

Aerobic gram-negative microorganisms

Citrobacter diversus

Citrobacter freundii

Enterobacter aerogenes

Klebsiella oxytoca

Klebsiella pneuomoniae

Proteus mirabilis

Proteus vulgaris

Pseudomonas aeruginosa

Serratia marcescens

Nursing Implications[1,7]:

- **Drug Administration:**
  - **Adult dosing:**
    - In women 18 years and older: single 3 g dose mixed in 3 to 4 oz of water administered orally with or without food
    - Complicated UTI (unlabeled): Males: Oral: 3 g every 2-3 days for 3 doses
    - Prostatitis (unlabeled): Males: Oral: 3 g every 3 days for a total of 21 days
  - **Pediatric dosing**
    - Safety and effectiveness in children age 12 years and under have not been established in adequate and well-controlled studies.
    - Product labeling does not provide dosing recommendations for age 13-17 years.
  - **Geriatric dosing**
    - Similar to adult dosing

        - Clinical studies of fosfomycin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
    - **Renal and Hepatic dosing:** No dosage adjustment provided in manufacturer's labeling
        - In 5 anuric patients undergoing hemodialysis, the $t_{1/2}$ of fosfomycin during hemodialysis was 40 hours. In patients with varying degrees of renal impairment (creatinine clearances varying from 54 mL/min to 7 mL/min), the $t_{1/2}$ of fosfomycin increased from 11 hours to 50 hours. The percent of fosfomycin recovered in urine decreased from 32% to 11% indicating that renal impairment significantly decreased the excretion of fosfomycin.
- **Hazardous drug to be prepared in a Biologic Safety Cabinet (BSC):** No
- **Common Adverse Reactions:**
    - **1%-10%:** Headache, pain, dizziness, rash, dysmenorrheal, diarrhea, nausea, abdominal pain, dyspepsia, vaginitis, back pain, weakness, rhinitis, pharyngitis
    - **<1%:** Anorexia, constipation, dysuria, ear disorder, fever, flatulence, flu-like syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, SGPT increased, skin disorder, somnolence, stools abnormal, vomiting, xerostomia
- **Contraindications:**
    - Fosfomycin is contraindicated in patients with known hypersensitivity to the drug
- **Precautions:** Risk of *Clostridium difficile*-associated diarrhea, using more than one dose per acute cystitis episode (increased risk of adverse events)
- **Monitoring Parameters:** CBC, fever, symptomatic improvement
- **Drug Interactions:**
    - Metoclopramide: When coadministered with fosfomycin, metoclopramide, a drug which increases gastrointestinal motility, lowers the serum concentration and urinary excretion of fosfomycin. Other drugs that increase gastrointestinal motility may produce similar effects.
- **Pregnancy Category:** B
- **Lactation:** It is not known whether fosfomycin tromethamine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fosfomycin, a decision should be made whether to discontinue nursing or to not administer the drug, taking into account the importance of the drug to the mother.
- **Distinctive Information:**
    - Pour sachet contents into 3 to 4 ounces of water and stir; do not use hot water
    - Administer immediately after dissolving in water
    - Patient symptoms should improve in two to three days after taking fosfomycin
    - Diarrhea is a common problem (studies up to 10% for fosfomycin according to studies) caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Summary data for non-FDA approved uses[5,8]:

Neuner EA, Sekeres J, Hall GS, et al. Experience with Fosfomycin for Treatment of Urinary Tract Infections Due to Multidrug-Resistant Organisms. *Antimicrobial Agents and Chemotherapy*. 2012;56(11):5744-5748.

- **Study Design:** Retrospective chart review of adult hospitalized patients in a single site treated with fosfomycin for a multidrug resistant (MDR) urinary pathogen from January 2006 to December 2010 (N=41)
- **Study Purpose or Objective:** To describe the microbiological outcomes and to determine rate of microbiological cure of UTIs due to MDR pathogens treated with fosfomycin.

- **Inclusion Criteria:** Patients were included if they received at least one dose of fosfomycin in the hospital and had a urine culture with an MDR pathogen tested for fosfomycin susceptibility. Patients were determined to have UTI if corresponding urinalysis was abnormal (presence of leukocytes esterase or >5 white blood cells) and/or documentation of symptoms (dysuria, frequency, urgency, suprapubic tenderness, and/or hematuria). Multidrug resistance was defined as resistance to at least one agent in three or more antimicrobial classes.
- **Exclusion Criteria:** None provided
- **Results:** 41 patients had 44 MDR pathogens as shown in the table below. The 4 others were *Actinetobacter baumannii, Enterobacter cloacae, E. faecalis, and Proteus mirabilis.*

TABLE 1 *In vitro* susceptibilities to fosfomycin

Organism (n^a)[b]	MIC (μg/ml) 50%	90%	% susceptible
CR-Kp (13)	32	64	92
P. aeruginosa (8)	8	256	75
VRE (7)	64	64	86
ESBL (7)	1	16	100
E. coli (5)	1	128	80
Other (4)			75

[a] *n*, no. of isolates.
[b] VRE, vancomycin-resistant *E. faecium*; ESBL, extended-spectrum beta-lactamase-producing *E. coli* and *K. pneumoniae*; Other, carbapenem-resistant *A. baumannii* (MIC = 128 μg/ml), *E. cloacae* (MIC = 4 μg/ml), *E. faecalis* (MIC = 64 μg/ml), and *P. mirabilis* (MIC = 1 μg/ml).

Microbiological cure occurred in 59% (24/41) of patients with a UTI due to an MDR pathogen. The most common MDR pathogens were *Klebsiella pneumoniae, P. aeruginosa,* ESBL producers, and VRE. Cure rates by pathogen are shown in the graph below.

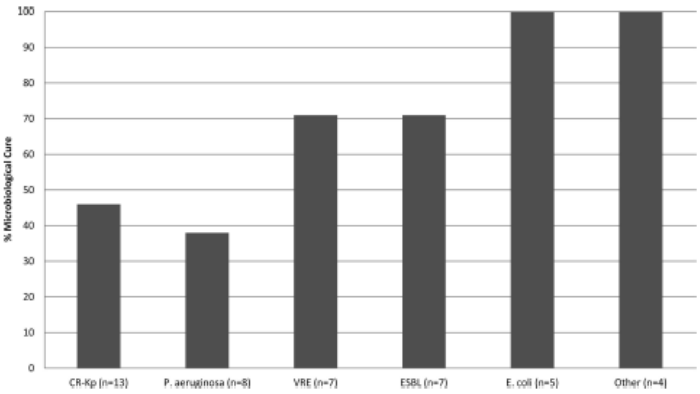

FIG 1 Microbiological cure rates by pathogen. VRE, vancomycin-resistant *E. faecium*; ESBL, extended-spectrum beta lactamase-producing *E. coli* and *K. pneumoniae*; Other, carbapenem-resistant *A. baumannii*, *E. cloacae*, *E. faecalis*, and *P. mirabilis*.

There were no differences between microbiological cure or failure groups in baseline characteristics, including age, gender, or race. The 41 patients received a total of 120 doses of fosfomycin. The average number of doses per treatment course was not different between groups, 3.3±1.9 in the microbiological cure group and 2.4±1.5 in the microbiological failure group. Combination therapy was utilized in 27% (n=11) of the overall population. Agents utilized with fosfomycin were tigecycline (n=5), aminoglycosides (n=2), colistin (n=1), piperacillin-tazobactam (n=1), imipenem (n=1), and daptomycin (n=1). *P. aeruginosa* isolates generally demonstrated higher rates of resistance to fosfomycin *in vitro* than *Enterobacteriaceae*. This cohort had 8 *P. aeruginosa* isolates with a fosfomycin MIC_{50} of 8μg/mL and MIC_{90} of 256μg/m and these had the lowest rate of microbiological cure (38%, 3/8).

Evaluation of Literature for FDA approved uses[2,3,4]:

Comparison of Single-Dose Fosfomycin and a 7-Day Course of Nitrofurantoin in Female Patients with Uncomplicated Urinary Tract Infection. *Clinical Therapeutics*. 1999;21(11):1864-1872.

- **Study Design:** Multicenter, doubled-blind, randomized, Phase III clinical trial (N=749)
- **Study Purpose or Objective:** To compare single-dose fosfomycin tromethamine with a 7-day course of nitrofurantoin for the treatment of acute uncomplicated lower urinary tract infection (UTI) in female patients in the outpatient clinics.
- **Inclusion Criteria:** Healthy females aged ≥ 12 years with symptoms of acute uncomplicated UTI (dysuria, frequency, or urgency) and with onset of symptoms of ≤ 96 hours were eligible for study enrollment. Diagnosis of UTI was defined as symptoms of infection and the presence of $\geq 10^5$ colony-forming units (CFU) per milliliter of an uropathogen in a patient collected clean voided midstream urine sample.
- **Exclusion Criteria:** Those patients with evidence of pyelonephritis (temperature ≥ 101°F, flank pain, or chills), who were pregnant or lactating, with known hypersensitivity to nitrofurantoin, with structural for functional abnormalities of the urinary tract, with a history of recurrent UTIs (>3 during the past year), with renal or hepatic dysfunction, or who had received antibiotics within the prior 2 days were excluded from the study.
- **Intervention(s):** Eligible patients were randomly assigned to receive a single dose 3g dose of fosfomycin tromethamine plus 7 days of placebo capsules or a single dose of placebo (3g packet) plus 7 days of nitrofurantoin monohydrate/macrocrystal 100mg capsules. Patients received the 3-g packets of fosfomycin or placebo in the clinic at study entry. Blister cards containing 14 placebo or nitrofurantoin capsules were given to each patient. Patients were instructed to take 1 capsule with food every 12 hours for 7 days, beginning on the day of study entry.
- **Results:**
    - Treatment efficacy was assessed by both bacteriologic and clinical responses at each clinic visit.
        a. Clinical responses: elimination of all pretherapy symptoms (cure), most but not all symptoms improved or absent (improvement), or not improved from initial assessment (failure).
        b. Bacteriologic responses: urine culture with $<10^4$ CFU/mL of uropathogen (cure) or urine cultures $\geq 10^{-4}$ CFU/mL of uropathogen (failure).
        c. Patients were followed up 5 to 11 days after the initial treatment dose (visit 2) and 5 to 11 days (visit 3) and 4 to 6 weeks after last day of medication (visit 4).
    - 749 female patients were enrolled from 26 US centers with equal number in each treatment arm (375-fosfomycin, 374-nitrofurantoin). Baseline characteristics were similar between the two groups. 228 patients were excluded from the study because pretreatment urine cultures did not contain an uropathogen with a colony count $\geq 10^5$ CFU/mL.
    - Bacteriologic Response
        a. A statistical higher failure rate was observed with fosfomycin at visit 2. However, patients receiving nitrofurantoin were receiving active medication during the first 7 days of this follow-up whereas the patients in the fosfomycin group were taking placebo. A more direct comparison would be visit 2 for the fosfomycin group and visit 3 for the nitrofurantoin group since patients would have discontinued active therapy for 1 week at these visits.
        b. Bacterial cure rate were 78% (visit 2) for the fosfomycin group and 81% (visit 3) for the nitrofurantoin group (p=0.5).
        c. The predominant pretreatment uropathogen in each group was *E.coli* and the next most common isolates were *Klebsiella pneumoniae* and *Staphylococcus saprophyticus.*
        d. Strains of *E.coli* resistant to fosfomycin were the cause of infection in 2 of the 246 patients treated with fosfomycin (both cured 5 to 11 days after a single dose of fosfomycin) and strains of *P. mirabilis, K. pneumonia, and S. saprophyticus* resistant to fosfomycin were the cause of infection in 10 fosfomycin treated patients (6 were cured and 4 failed treatment with fosfomycin).
        e. Strains of *E.coli* resistant to nitrofurantoin were the cause of infection in 15 of the 219 patients treated with nitrofurantoin (10 were cured and 5 failed treatment 5 to11 days after the last dose). Strains of *P. mirabilis, K. pneumonia, and S. saprophyticus*

resistant to nitrofurantoin were the cause of infection in 11 nitrofurantoin treated patients (7 were cured and 4 failed treatment with nitrofurantoin).

f. Relapse occurred in 17 patients in the fosfomycin group and 33 patients in the nitrofurantoin group (p =0.02).

Table II. Bacteriologic responses* to fosfomycin and nitrofurantoin in patients considered assessable for efficacy.

Follow-up Visit	Fosfomycin	Nitrofurantoin	P†	Confidence Interval (%)
Visit 2‡	n = 246	n = 219		
Cure, no. (%)	192 (78.1)	189 (86.3)	0.02	1.2 to 15.3
Failure, no. (%)	54 (21.9)	30 (13.7)		
Visit 3	n = 168	n = 157		
Cure, no. (%)	146 (86.9)	127 (80.9)	0.17	14.0 to 2.0
Failure, no. (%)	22 (13.1)	30 (19.1)		
Visit 4	n = 125	n = 112		
Cure, no. (%)	120 (96.0)	102 (91.1)	0.18	−11.1 to 1.3
Failure, no. (%)	5 (4.0)	10 (8.9)		

*See text for definition of cure and failure.
†*P* values were based on the 2-sided Fisher exact test.
‡Patients may still have been receiving nitrofurantoin at this visit (through day 7).

- Clinical Efficacy: clinical cure rate was similar for both treatment groups at each clinic visit.

Table III. Clinical outcomes.*

Follow-up Visit	Fosfomycin	Nitrofurantoin	P†	Confidence Interval (%)
Visit 2‡	n = 263	n = 245		
Cure, no. (%)	216 (82.1)	206 (84.1)	0.3	−4.6 to 8.5
Improvement, no. (%)	24 (9.1)	26 (10.6)		
Failure, no. (%)	23 (8.7)	13 (5.3)		
Visit 3	n = 229	n = 217		
Cure, no. (%)	207 (90.4)	193 (88.9)	0.3	−7.1 to 4.2
Improvement, no. (%)	10 (4.4)	6 (2.8)		
Failure, no. (%)	12 (5.2)	18 (8.3)		
Visit 4	n = 202	n = 180		
Cure, no. (%)	184 (91.1)	165 (91.7)	0.91	−5.1 to 6.2
Improvement, no. (%)	5 (2.5)	3 (1.7)		
Failure, no. (%)	13 (6.4)	12 (7.3)		

*See text for definition of cure, improvement, and failure.
†*P* values were based on the 2-sided Fisher exact test.
‡Patients may still have been receiving nitrofurantoin at this visit (through day 7).

- **Safety:**
  - The adverse event profiles of fosfomycin and nitrofurantoin were similar.
    a. 22 patients (5.3%): fosfomycin arm; 21 patients (5.6%): nitrofurantoin arm
  - Common side effects related to fosfomycin treatment were diarrhea (2.4%), vaginitis (1.8%), and nausea (0.8%)
  - Common side effects related to nitrofurantoin treatment were nausea (1.6%), vaginitis (1.6%), dizziness (0.8%), and diarrhea (0.8%).
  - 7 patients (1.9%) in the fosfomycin arm and 16 patients (4.3%) in the nitrofurantoin group were removed from the study by the investigator because of an untoward event, but these events were not medically severe and none of these patients were hospitalized.

A randomized comparative study of single-dose fosfomycin and 5-day ciprofloxacin in female patients with uncomplicated lower urinary tract infections. *Journal of Infection and Chemotherapy.* 2010;16:424-430.

- **Study Design:** Randomized, single-blind, single site clinical trial (N=260)
- **Study Purpose or Objective:** To evaluate the clinical effectiveness and cure rate of fosfomycin trometamol compared to ciprofloxacin in females with uncomplicated UTIs in the outpatient setting.
- **Inclusion Criteria**: Females between 18-65 years of age diagnosed with uncomplicated UTIs (dysuria and urgency for <1 week plus pyuria and bacteriuria).
- **Exclusion Criteria:** Patients with symptoms and signs suggestive of complicated UTIs or systemic infections (fever, flank pain, leukocytosis), pregnancy or lactation, predisposition to infection resulting from urinary system abnormalities, or obstruction or renal parenchymal disease, recurrent UTIs (>3

per year), administration of antibiotic therapy within the past 15 days, chronic diseases, and administration of immunosuppressive treatment.

- **Intervention(s):** 3g single dose fosfomycin trometamol was administered to one-half of the study population, and ciprofloxacin was administered at a dose of 500mg twice a day for 5 days to the other half of the patients. Patients were evaluated on days 7-10 for clinical signs, and their urine sediments and cultures were repeated.
- **Results:**
    - 260 patients fulfilled the inclusion criteria and were randomized 1:1 to each treatment group, but only 142 patients completed the study (118 patients were excluded due to no follow-up, could not obtain urine sediment, no bacterial growth, and growth of more than two species of microorganisms).
    - No significant difference was found between the cure rates for fosfomycin trometamol and ciprofloxacin therapy. In the fosfomycin trometamol group, both clinical and bacteriological cure were achieved in 64 (83.1%) patients. In the ciprofloxacin group, clinical and bacteriological cure were obtained in 53 (81%) and 51 (78.4%) patients, respectively, at the first follow-up visit on day 7 (Table 3).
    - Among the patients in which fosfomycin trometamol treatment failed, the pathogen was *E.coli* in 8 patients, *Enterobacter spp.* in 3 patients, *Proteus mirabilis* in 1 patient, and *Staphylococcus saprophyticus* in 1 patient. This was due to high MIC values. Treatment failed in 12 patients in the ciprofloxacin group. The pathogen was *E.coli* in 10 patients and *Enterobacter spp.* in 2 patients. All these microorganisms were ciprofloxacin resistant by the disk diffusion method (Table 4).

Table 3 A comparison of the two groups on day 7

	FMT ($n = 77$) n (%)	Ciprofloxacin ($n = 65$) n (%)
Clinical remission	64/77 (83.1)	53/65 (81)
Improvement of urinary findings	62/77 (80.5)	52/65 (80)
Bacterial eradication	64/77 (83.1)	51/65 (78.4)

FMT fosfomycin trometamol

Table 4 Isolated microorganisms and treatment results

Isolated bacteria	n	FMT		Ciprofloxacin	
		Success	Failure	Success	Failure
Escherichia coli	117	53	8	46	10
Enterobacter sp.	12	4	3	3	2
Proteus sp.	4	2	1	1	
Other gram-negative bacteria	4	2		2	
S. saprophyticus	3	1	1	1	
Enterococcus sp.	2	2			

FMT fosfomycin trometamol

    - In the present study, 59% and 94% of *E.coli* strains were susceptible to ciprofloxacin and fosfmomycin, respectively.

- **Safety:** Side effects, such as gastrointestinal system complaints (diarrhea), rash, headaches, lethargy, and vaginitis were reported. Gastric complains were observed in 3 of 77 (3.9%) patients using fosfomycin and 2 of 65 (3.07%) patients using ciprofloxacin.

A comparison between single-dose fosfomycin trometamol and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. *International Journal of Antimicrobial Agents.* 1998;10:39-47.

- **Study Design:** Randomized, multicenter, comparative study (N=547)
- **Study Purpose or Objective:** To assess the microbiological and clinical efficacy of a single 3g oral dose of fosfomycin trometamol compared with a conventional 5-day course of an oral dose of trimethoprim (TMP) 200mg twice daily in the outpatient setting.
- **Inclusion Criteria:** Females of any race, aged 18-65 years of age with uncomplicated lower urinary tract infection based on symptoms (dysuria, frequency, urgency) and a microbiologically significant count ($\geq 10^5$ colony forming units in urine). The symptoms had to be present for less than 48 hours before entering the trial.
- **Exclusion Criteria:** Patients with signs and symptoms of upper urinary tract infection (loin pain, fever >38.5°C, rigor, and vomiting), pregnant or lactating, presence of urinary tract abnormalities that can predispose to infection and or presence of calculi, intravenous drug users, on antibacterial therapy in the previous 2 weeks or steroids, chronic gastro-intestinal disorders, renal impairment, folate

deficiency or megaloplastic anemia, malignancies, HIV infection, hypersensitivity towards agents being tested, and any condition requiring treatment with any agent that could interact with the study drugs (i.e. antibacterials, antineoplastic drugs, sulfasalazine, metoclopramide, oral therapy for vaginitis).

- **Intervention(s):** Two-thirds of subjects received a single 3g dose of fosfomycin trometamol and one-third received a 5 day course of trimethoprim 200mg twice daily.
- **Results:**
  - Female patients (N=547) were recruited into the study and 300 patients met criteria for randomization (204 patients were treated with fosfomycin trometamol and 96 patients were treated with TMP). A total of 261 patients were evaluable for analysis (177 with fosfomycin and 84 with TMP).
  - Both treatment groups were homogenous regarding age, height, weight, and race
  - Total microbiological cure rates were similar for both trimethoprim and fosfomycin (83% and 83%, respectively).
  - Persistence of infection was seen in 14 (16.6%) TMP treated patients and 30 (16.9%) in the fosfomycin trometamol treated group and reinfection with new organism was seen in 5 (5.9%) TMP treated patients and 18 (10.3%) of the fosfomycin trometamol treated group.
  - *E. coli* was the most common pathogen comprising 235 (77.8%) of the strains. Other strains included *S. saprophyticus*, *Proteus mirabilis*, *Klebsiella* spp., *E. faecalis*, and *Citrobacter* spp.
  - In this study, results suggest that fosfomycin trometamol is more efficacious than TMP in the treatment of *E.coli* UTIs. MIC data indicated that TMP has higher activity than fosfomycin with S*. saprophyticus* and *E. faecalis*.
- **Safety:** Safety outcomes were not noted in this study.

Table 1
Microbiological evaluation of outcome of treatment as judged by urine culture of the first follow up visit at day 7–9

Patient treatment group	Significant bactiuria day 0	Microbiological evaluation of the first follow up visit at day 7–9							
		Exclusion			Evaluable samples	Eradication rate		Persistence	
	Number	Sample not received	Unsatisfactory sample	Total	Number	Number	%	Number	%
FMT	(204)	(19)	(8)	(27)	(177)	(147)	(83)	(30)	(16.9)
	195	*19*	*8*	*27*	*168*	*139*	*82.7*	*29*	*17.3*
TMP	(96)	(7)	(5)	(12)	(84)	(70)	(83.3)	(14)	(16.6)
	96	*9*	*5*	*14*	*82*	*69*	*84.1*	*13*	*15.9*
Total	(300)	(26)	(13)	(39)	(261)	(217)	(83.1)	(44)	(16.9)
	291	*28*	*13*	*41*	*250*	*208*	*83.2*	*42*	*16.8*

The data in brackets refer to patients with microbiological evaluation (300 pts) of outcome of treatment as judged by urine culture of the first follow up visit at day 7–9.
The data in italics referred to the subset of patients with both microbiological and clinical evaluation (291 pts).

Pharmacogenomic Testing Recommended: No

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