

Fosfomycin (CONTEPO) in Complicated Urinary Tract Infection

National Drug Monograph

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VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description/MOA	Fosfomycin is an epoxide antibacterial drug that disrupts bacterial cell wall synthesis. It acts by covalently binding and inhibiting phosphoenolpyruvate transferase (MurA), thereby blocking the synthesis of peptidoglycan. It is bactericidal against Enterobacterales.	
Indication Under Review	Treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), caused by susceptible isolates of <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> in patients 18 years of age and older.	
Dosage Regimen	6 grams (g) administered every 8 hours by intravenous (IV) infusion over 1 hour in adults with estimated creatinine clearance (CrCl) greater than 50 mL/min. Duration of therapy is up to 14 days and should be guided by the severity of the infection and clinical status.	
Dosage Forms Under Review	For injection: 6 g sterile powder in single dose vial for reconstitution and further dilution. Each vial contains 1,980 mg of sodium.	
Pretreatment Procedures	<div>☐ Assess previous hypersensitivity reactions to oral or parenteral fosfomycin.</div> <div>☐ A low-sodium diet is recommended during treatment due to the high sodium load.</div>	
Treatment Monitoring	<div>☐ Serum electrolytes (Na, K, Ca, Mg, P)</div> <div>☐ Fluid status</div> <div>☐ Hepatic enzymes (ALT, AST)</div> <div>☐ QT prolongation</div>	<div>☐ CBC (for neutropenia)</div> <div>☐ Estimated CrCl to adjust dosage, as needed</div> <div>☐ Evaluate patients if diarrhea occurs to rule out <i>Clostridioides difficile</i>-associated diarrhea.</div>

EFFICACY CONSIDERATIONS

Trial	ZEUS Trial (NCT 02753946)²
Design	Phase 2/3, multinational, multicenter, randomized, parallel-group, double-blind, noninferiority trial. <ul style="list-style-type: none">Participants were randomized 1:1 to intervention:comparator, respectively.
Population	<p>N= 362 (microbiologic-mITT). Individuals at least 18 years of age, requiring hospitalization for suspected or confirmed cUTI or acute pyelonephritis with a baseline urine culture within 48 hours of randomization.</p> <p>Definition of cUTI: At least 2 signs/symptoms [chills, rigors, or warmth associated with fever; nausea or vomiting within 24 hours of screening; dysuria, increased urinary frequency, or urinary urgency; lower abdominal or pelvic pain], urine specimen with evidence of pyuria, and at least 1 additional associated risk(s): use of intermittent bladder catheterization or presence of an indwelling catheter, current known function or anatomical abnormality of the urogenital tract, complete or partial obstructive uropathy expected to be treated during study, azotemia (BUN >20 mg/dL, blood urea >42.8 mg/dL, or Scr >1.4 mg/dL), chronic urinary retention in men.</p> <p>Definition of AP: At least 2 signs/symptoms [chills, rigors, or warmth associated with fever; nausea or vomiting within 24 hours of screening; dysuria, increased urinary frequency, or urinary urgency; acute flank pain within 7 days of randomization, costovertebral angle tenderness on physical examination], urine specimen with evidence of pyuria.</p> <p>Key Exclusions: CrCl <20 mL/min, renal transplantation/ESRD, known or suspected resistance to study drugs, acute bacterial prostatitis/orchitis/epididymitis, chronic bacterial prostatitis, gross hematuria requiring intervention other than administration of study drug or removal/exchange of urinary catheter, severe sepsis, pregnancy/breastfeeding, immunosuppression, significant hepatic disease, use of effective systemic antibiotic against Gram-negative urinary pathogens within 72 hours of randomization, need for additional systemic antimicrobial therapy other than study drug during treatment, HIV-positive with CD4 <200, ANC <1000, PLT <50,000, QT >480 ms.</p> <p>Demographics: 36% male, 100% White, mean age: 50.6 years, 9% bacteremia at baseline. More than 90% of patients in both groups had a monomicrobial Gram-negative infection at baseline. Most common pathogens were <i>E. Coli</i> and <i>K. pneumoniae</i>.</p>
Intervention	6 g fosfomycin IV q8h x 7 days (no oral switch); patients with concomitant bacteremia could receive up to 14 days.
Comparator	4.5 g pip-tazo IV q8h x 7 days (no oral switch); patients with concomitant bacteremia could receive up to 14 days.
Results	<ul style="list-style-type: none">Overall Success: clinical cure plus microbiological eradication at test of cure (TOC, day 19-21).Clinical Cure: complete resolution or significant improvement of signs/symptoms, no further antimicrobial therapy indicated.Microbiological Eradication: Pathogen reduced to <10⁴ CFU/mL on urine culture (and negative on repeat blood culture, if applicable).Non-inferiority met if lower limit of the 95% CI for treatment difference above -15%.

Primary and Key Secondary Efficacy Outcomes

Outcome	IV FOS (n/N)	PTX (n/N)	Treatment Difference (95% CI)
Overall Success*	64.7% (119/184)	54.5% (97/178)	10.2% (-0.4, 20.8)
Clinical Cure [^]	90.8% (167/184)	91.6% (163/178)	-0.8% (-7.2, 5.6)
Microbiological Eradication*	65.8% (121/184)	56.2% (100/178)	9.6% (-1.0, 20.1)

*: Primary endpoint; ^: Secondary endpoints

Amongst resistant isolates, cure rates were similar in both groups; however, eradication rates numerically favored fosfomycin IV.

Trial	FOREST Trial³
Design	Multicenter, randomized, open-label, noninferiority trial conducted at 22 hospitals in Spain. <ul style="list-style-type: none"> Participants were randomized 1:1 to intervention:comparator, respectively.
Population	<p>N = 143 (mITT). Individuals at least 18 years of age hospitalized with bacteremic UTI due to MDR <i>E. coli</i> (isolates must be sensitive to study drugs). Urinary origin of infection requires at least one clinical PLUS one analytical criterion:</p> <p><u>Clinical criteria:</u> LUTS (dysuria, frequency, urgency, pain, tenesmus), lumbar pain, positive renal fist percussion, cognitive impairment in patients >70 years of age in the absence of another cause, bacteremia that occurs in the absence of signs/symptoms from another source of infection.</p> <p><u>Analytical criteria:</u> presence of pyuria, positive urine culture for same pathogen isolated in blood.</p> <p><u>Key exclusions:</u> polymicrobial bacteremia, septic shock, undrained kidney abscess, unresolved urinary tract obstruction, polycystic kidney disease, renal transplantation, allergy/hypersensitivity to study drugs, CHF (NYHA Grade I to IV), liver cirrhosis, renal failure/hemodialysis, untreated arrhythmias, active empiric treatment >72 hours at time of randomization, pregnancy/breastfeeding.</p> <p><u>Demographics:</u> 49% male, median age of 72 years.</p>
Intervention	4g IV fosfomycin disodium q6h x 10-14 days (option to switch to oral fosfomycin after 4 days of IV)
Comparator	1g IV ceftriaxone (CTX) q24h OR 1g IV meropenem (MER) q8h (if CTX-resistant) x10-14 days (option to switch to susceptible oral agent after 4 days of IV)
Results	<ul style="list-style-type: none"> Clinical cure: resolution of all new signs and symptoms of infection at test of cure (TOC, 5-7 days after treatment completion). Microbiological cure: no isolation of <i>E. coli</i> in blood cultures from Day 5 onwards or in urine culture at TOC. Non-inferiority margin set at -7%. The lower bound of the CI exceeded this threshold so fosfomycin did not meet the pre-specified non-inferiority criteria.

Primary Outcome

Outcome	IV FOS (n/N)	CTX or MER (n/N)	Treatment Difference (1-sided 95% CI)
Clinical and Microbiological Cure (CMC)	68.6% (48/70)	78.1% (57/73)	-9.4% (-21.5, ∞); p = .10
CTX-susceptible isolates	80.6% (25/31)	87% (27/31)	-6.4% (-21.7, ∞); p = .24
CTX-resistant isolates	59% (23/39)	71.4% (30/42)	-12.4% (-29.8, ∞); p = .12
Clinical or microbiological failure	14.3% (10/70)	19.7% (14/73)	-5.4% (-∞, 4.9); p = .19

- Failure was numerically lower in the fosfomycin IV group; decreased CMC rates for IV fosfomycin affected by higher number of withdrawals due to adverse events (n= 6) versus comparator group (n = 0). Reasons for withdrawal included heart failure, cholecystitis, and persistence of fever.

Secondary Endpoints

Endpoint	IV FOS (n/N)	CTX or MER (n/N)	Treatment Difference (1-sided 95% CI)
Clinical Cure in CEP	96.7% (59/61)	90.1% (64/71)	6.6% (-0.2, ∞); p = .05
Microbiological Cure in MEP	82.8% (48/58)	85.5% (59/69)	-2.7% (-13.3, ∞); p = .33

CEP: Clinically Evaluable Population – All patients evaluated at TOC or who had a previous failure

MEP: Microbiologically Evaluable Population – All patients with urine cultures at TOC

SAFETY CONSIDERATIONS^{1,2}

Boxed Warnings	None
Contraindications	Known serious hypersensitivity to fosfomycin or any of the excipients.
Other Warnings	<p>Serum electrolyte abnormalities: High sodium load (1980 mg/vial) may cause hypernatremia, hypokalemia, hypocalcemia, and hypophosphatemia. QT prolongation: Avoid in patients with known prolongation or ventricular arrhythmias as fosfomycin can prolong the QT interval. Increased Transaminases: Reversible elevations in ALT and AST have been reported.</p> <p>Neutropenia/Agranulocytosis: Monitor CBC and discontinue if neutropenia occurs. <i>Clostridioides difficile</i> associated diarrhea (CDAD).</p>
Top AEs	Transaminase elevations (10.3%), hypokalemia (9.9%), neutropenia (6.4%), nausea (4.3%), diarrhea (3.9%).
Drug Interactions	Avoid co-administration with drugs known to prolong the QT interval, including Class IA or Class III antiarrhythmics, tricyclic antidepressants, macrolides, and antipsychotics.
Pregnancy	Insufficient data in humans. Animal data showed no evidence of malformations after administration of fosfomycin IV but evidence of fetotoxicity was observed.
Lactation	Breastfeeding is not recommended during treatment and for 24 hours after the last dose. Fosfomycin is present in human milk; however, no data on the effects of fosfomycin on the lactating child.
Renal Impairment	Dosage adjustment is required for patients with estimated CrCl of 50 mL/min or less. Refer to US Prescribing Information ¹ for recommendations. In patients requiring hemodialysis, fosfomycin IV should be administered after hemodialysis on hemodialysis days.
Hepatic Impairment	Monitor patients with severe hepatic impairment closely for fluid overload and electrolyte abnormalities.

THERAPEUTIC ALTERNATIVES ^{4,5}			
DRUG [#]	VANF	Dosing [*]	Clinical Guidance
Fosfomycin inj	TBD	6g IV q8h	
Cephalosporins			
Cefepime inj [^]	Yes	1-2g IV q8-12h	4 th generation cephalosporin; MIC 4-8 mcg/mL: 2g IV q8h
Cefiderocol inj	PA-F	2g IV q8h	Reserve for use in limited/no alternatives
Ceftazidime inj [^]	Yes	1-2g IV q8h	3 rd -generation cephalosporin
Ceftriaxone inj [^]	Yes	1-2g IV daily	3 rd -generation cephalosporin
B-Lactam/β-Lactamase Inhibitors			
Amoxicillin-clavulanate tab	Yes	875mg PO q8-12h	Dosing based on amoxicillin component
Ceftazidime-avibactam inj	PA-F	2.5g IV q8h	
Ceftolozane-tazobactam inj	PA-F	1.5g IV q8h	
Imipenem-cilastatin-relebactam inj	PA-F	1.25g IV q6h	Reserve for use in limited/no alternatives
Meropenem-vaborbactam inj	PA-F	4g IV q8h	
Piperacillin-tazobactam inj [^]	Yes	4.5g IV q8h	Alternative dosing: 3.375g IV q6h
Fluoroquinolones (IV)			
Ciprofloxacin inj [^]	Yes	400mg IV q12h	Avoid if patient has prior exposure to FQ in prior 12 months
Levofloxacin inj [^]	Yes	500-750mg IV q24h	Cipro: 400mg IV q8h for resistant gram-negatives Levo: 750mg IV q24h for resistant gram-negatives
Fluoroquinolones (PO)			
Ciprofloxacin tab [^]	Yes	500-750mg PO q12h	Avoid if patient has prior exposure to FQ in prior 12 months
Levofloxacin tab [^]	Yes	500-750mg PO q24h	Cipro: 750mg PO q12h for resistant gram-negatives Levo: 750mg PO q24h for resistant gram-negatives
Sulfonamides			
Sulfamethoxazole-trimethoprim tab [^]	Yes	1 DS tab PO q12h	
Carbapenems			
Ertapenem inj	Yes	1g IV daily	
Imipenem-cilastatin inj	Yes	1g IV q8h	500mg IV q6h for resistant gram-negatives Dosing based on imipenem component
Meropenem inj	Yes	1g IV q8h	2g IV q8h for resistant gram-negatives
Aminoglycosides			
Amikacin inj	Yes	15mg/kg IV x1, then PK dosing	
Gentamicin inj	Yes	5-7mg/kg IV x1, then PK dosing	
Plazomicin inj	No	15mg/kg IV x1, then PK dosing	
Tobramycin inj	Yes	5-7mg/kg IV x1, then PK dosing	

[#]Empiric agents for cUTI per IDSA ^{*}Dosing used in clinical trials in patients with normal renal function [^]: Preferred empiric agents PK: pharmacokinetic

~Prime Vendor pricing as of 06.03.2026 for 7-day course

Empiric antibiotic therapy should be guided by patient-specific factors (including history of resistant pathogens, risk of allergic reaction, contraindications, drug-drug interactions, etc). Antibiotic therapy should be further de-escalated and targeted based on urine culture and susceptibility results.

POTENTIAL PLACE IN THERAPY

1. Surveillance data published in 2021 demonstrated a 7% increase in *E. coli* urinary isolate resistance to 3rd-generation cephalosporins, compared to 2009 – 2018. Fluoroquinolone and sulfamethoxazole-trimethoprim resistance to *E. coli* remained steady but was upwards of 30% and 25%, respectively, over the 10-year observation period.⁶
2. The 2025 IDSA cUTI guidelines positions IV fosfomycin as an alternative (not first-line) empiric agent for cUTI, citing concerns regarding sodium overload, hypokalemia, susceptibility testing and limited availability (at the time of publishing, fosfomycin IV had not yet gained FDA approval in the United States). Recommended first-line empiric agents are 3rd/4th generation cephalosporins, piperacillin-tazobactam, fluoroquinolones, and carbapenems (if sepsis present). Novel beta-lactam/beta-lactamase inhibitor combinations and cefiderocol should be reserved for MDR/carbapenem-resistant pathogens to promote antimicrobial stewardship.⁵
3. In the ZEUS trial, fosfomycin IV was shown to be noninferior to piperacillin-tazobactam for cUTI/acute pyelonephritis; results were similar in the subgroup analysis of ESBL-producing pathogens.²
4. Fosfomycin IV did not meet inferiority criteria versus comparators in the FOREST trial (possibly due to higher withdrawal rates due to adverse effects). However, in subgroup analyses of patients with CTX-resistant isolates who were able to be evaluated at TOC, fosfomycin IV was clinically noninferior to meropenem in both clinical and microbiological endpoints.³
5. Fosfomycin IV may be an alternative antibiotic for patients with suspected or confirmed cUTI caused by ESBL-producing *Enterobacterales* when other agents are not viable options due to resistance or contraindications, particularly in patients who are hemodynamically stable and can tolerate the high sodium load of fosfomycin IV.⁷

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