Fosfomycin activity when tested against Gram-positive and Gram-negative US isolates collected by the SENTRY Antimicrobial Surveillance Program

RK Flamm[1], D. Shortridge[1], PR Rhomberg[1], K Sweeney[2], EJ Ellis-Grosse[2], HS Sader[1]

[1]JMI Laboratories, North Liberty, Iowa, USA

[2]Zavante Therapeutics, Inc. San Diego, California, USA

Background: ZTI-01 (fosfomycin, FOS, for injection) is under US development to treat complicated urinary tract infections. FOS is unique compared to other antimicrobials in that it inhibits an early step in cell wall synthesis via covalent binding to MurA. FOS demonstrates broad *in vitro* activity against Gram-negative (GN) and -positive (GP) bacteria, including multidrug-resistant (MDR) organisms.

Methods: FOS was tested against over 1,400 GN and 800 GP clinical isolates collected in US medical centers from the SENTRY Antimicrobial Surveillance Program (96% of isolates from 2015) and a selection of 29 GN and 20 GP anaerobes. Isolates were susceptibility (S) tested against FOS and comparators by reference agar dilution (25 µg/mL glucose-6-phosphate supplementation) using existing FDA breakpoints of the oral formulation for comparative assessments.

Results: FOS was very active against selected Enterobacteriaceae ($MIC_{50/90}$, 4/16 µg/mL). For randomly selected *Escherichia coli,*100.0% were S to FOS ($MIC_{50/90}$, 0.5/1 µg/mL), and for *Klebsiella pneumoniae* the FOS $MIC_{50/90}$ was 4/16 µg/mL (97.0% ≤64 µg/mL). The FOS $MIC_{50/90}$ for randomly selected *Enterobacter aerogenes*, *E. cloacae* complex, *Serratia marcescens*, *Proteus mirabilis*, *Citrobacter koseri*, *and C. freundii* complex was 8/16, 8/64, 8/16, 1/8, 1/1, and 0.5/1 µg/mL, respectively. For *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* complex, higher FOS $MIC_{50/90}$ were observed, 64/128 µg/mL and 128/256 µg/mL, respectively. FOS activity was limited against *Prevotella* and *Porphyromonas* spp. ($MIC_{50/90}$,>256 µg/mL) with variable MICs for the *Bacteroides fragilis* group. FOS was very active against *Staphylococcus aureus* ($MIC_{50/90}$, 4/8 µg/mL) and against coagulase-negative staphylococci excluding *S. saprophyticus (*$MIC_{50/90,}$ 8/64 µg/mL). For *S. saprophyticus* the FOS $MIC_{50/90}$ were 128/>256 µg/mL. No *E. faecalis* isolates were resistant to FOS (99.0%S; 1.0% intermediate). *E. faecium* MICs were generally higher to various antimicrobials including one FOS isolate (19.2% intermediate; 79.8%S). FOS was active against β-haemolytic streptococci (*S. pyogenes;* $MIC_{50/90}$, 32/64 µg/mL; *S. agalactiae*; $MIC_{50/90}$, 8/64 µg/mL) and GP anaerobes.

Conclusions: FOS demonstrated broad spectrum activity against a large collection of GN and GP bacteria. FOS merits further study in infections where resistant GN and GP may occur. Potential introduction of an IV form will warrant a re-assessment of FDA breakpoints, given the bioavailability limitations of the current oral formulation.

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Key words: fosfomycin, Enterobacteriaceae, *Staphylococcus aureus*

Track AAD01 Antibacterial resistance: Surveillance, typing and clinical and molecular epidemiology