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Testimony Before the FDA's Antimicrobial Drugs Advisory Committee Meeting about Sulopenem Etzadroxil/Probenecid for Uncomplicated Urinary Tract Infection

N. Jia Ahmad, MD, MPH
Public Citizen's Health Research Group
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I'm Jia Ahmad, a Research Fellow at Public Citizen's Health Research Group. We have no financial conflicts of interest.

The committee today is tasked with discussing the benefits and risks of the use of the oral drug sulopenem etzadroxil/probenecid for uncomplicated UTIs (uUTIs) in adult women.

Increasing rates of antimicrobial resistance in many US communities highlight the need for novel therapies to treat urinary tract infections. From the data presented, including trials 301 and 310, oral sulopenem seems to have efficacy in treating uUTIs when a urinary isolate is susceptible.

However, the potential for broad application of this medication for empiric treatment of uUTIs comes with a significant risk of increasing antimicrobial resistance. Although antimicrobial resistance is on the rise, it is relatively rare that urinary isolates for community acquired infections are resistant to all existing first line treatments for uUTIs. In a retrospective analysis by Kaye et al, researchers found that while the US resistance rate to fluoroquinolones and trimethoprim-sulfamethoxazole was significant (21.1% and 25.4%, respectively); the resistance rate to nitrofurantoin was only 3.8%.[1] Furthermore, in this sample that evaluated over 1.5 million E. Coli urinary isolates from outpatients between 2011 and 2019, only 3.8% of the isolates were resistant to all three first line agents or were extended spectrum beta-lactamase (ESBL) producers.[2] In other words, if clinicians work in communities where urinary isolates are often resistant to one class of medication, it is likely that a different class of oral medication will have efficacy. Given their cross-reactivity with carbapenems, usage of oral penems for uUTIs holds the risk of furthering antimicrobial resistance to an important class of medications that is a mainstay of treatment for multi drug resistant organisms.

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[1] Kaye KS, Gupta V, Mulgirigama A, Joshi AV, Scangarella-Oman NE, Yu K, Ye G, Mitrani-Gold FS. Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. Clin Infect Dis. 2021 Dec 6;73(11):1992-1999. doi: 10.1093/cid/ciab560. PMID: 34143881; PMCID: PMC8664433.

[2] Ibid.

Furthermore, there is insufficient evidence that oral sulopenem is superior to existing first line therapies uUTI. In trial 301 oral sulopenem failed to demonstrate noninferiority to ciprofloxacin in populations that were sensitive to ciprofloxacin. Although in trial 310 sulopenem was successfully compared to amoxicillin/clavalulanate, amoxicillin/clavalulanate is not a first line medication for the treatment of uUTIs and in metanalyses has demonstrated inferiority to therapies such as ciprofloxacin and trimethoprim/sulfamethoxazole.[3]

If sulopenem is approved for the treatment of uUTI, there is a considerable risk that it will be used to treat uUTIs that could be successfully treated with other drugs and that it will be used off-label either as a first-line treatment for complicated UTIs or as stepdown therapy following intravenous therapy of complicated UTIs.

The applicant suggested during this meeting that insurance prior authorization may be an adequate barrier to widespread usage of the drug. However, we are concerned that this strategy, even in combination with language in the labeling of the drug and communications with prescribers, is insufficient to mitigate the risk of increasing antimicrobial resistance. Furthermore, judicious regulation that would prevent overutilization or inappropriate use of this drug is the purview of the FDA, not insurance companies.

If this drug is approved, we urge the committee to advise the FDA to require post-market studies to assess the frequency of off-label use of sulopenem, the frequency of its use to treat uUTIs infections that could be successfully treated with other drugs, and any changes in the antimicrobial resistance patterns for uUTIs in communities where oral sulopenem may be widely prescribed. If post-market studies demonstrate the need for additional and more robust risk-management strategies, such strategies should be promptly implemented.

[3] Knottnerus BJ, Grigoryan L, Geerlings SE, Moll van Charante EP, Verheij TJ, Kessels AG, ter Riet G. Comparative effectiveness of antibiotics for uncomplicated urinary tract infections: network meta-analysis of randomized trials. Fam Pract. 2012 Dec;29(6):659-70. doi: 10.1093/fampra/cms029. Epub 2012 Apr 19. PMID: 22516128.